

# Obesity and Type II Diabetes Mellitus: Is Resistin the Link?

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## Abstract

There has been much effort recently to explore the role of adipocytokines in the interaction between adipose tissue, inflammation, and immunity. Tumor necrosis factor- $\alpha$ , interleukin-6, resistin, and many other adipocytokines are the soluble mediators derived mainly from adipocytes (fat cells). They are known to influence insulin sensitivity and glucose metabolism profoundly, thus providing a molecular link between increased adiposity and insulin resistance (IR). Resistin, an adipocytokine, is a member of a class of cysteine-rich proteins, collectively termed resistin-like molecules. They were initially discovered in rodents. It is present in gross visceral fat deposits and is released by adipocytes in humans. Owing to the regional variation in the expression of resistin mRNA and protein levels in humans, the highest levels have been noted in the abdominal depot. It is interesting to note that resistin also gets released from infiltrating white blood cells subsequent to subclinical chronic low-grade inflammatory response, accompanying obesity. This convergence of adipocyte and macrophage function in obese Type II diabetics has paved its role in molecular linkage of obesity, inflammation and metabolic syndrome (MetS) risk. Resistin, being a pro-inflammatory adipokine, contributes to atherosclerosis. High serum resistin levels have been found, although with some inconsistencies, in cardiovascular patients, labeling it as a cardiovascular disease (CVD) marker, to predict incident cardiovascular events. Both IR and inflammation are the pathogenic factors contributing to increased risk of CVD, associated with diabetes, thus tagging resistin as a potential MetS marker. In conclusion, resistin is a fascinating new hormone awaiting further research in the obesity – IR – diabetes – MetS link.

**Keywords:** Adipocytokines, diabetes, obesity, resistin

## INTRODUCTION

With a rapid increase in the incidence and prevalence of obesity and with more than half of the world's population being considered overweight, obesity has become the most frequently encountered metabolic disease worldwide. In 1995, the worldwide obese population was estimated to be approximately 200 million. Seven years later, this figure increased to 315 million. This vertiginous rise in obesity has triggered a parallel upward swing in diabetes mellitus (DM) statistics too.<sup>[1]</sup>

Type II DM (T2DM) usually affects people aged over 40 years. This metabolic disorder is characterized by target-tissue resistance to insulin, is epidemic in industrialized societies, and is strongly associated with obesity.<sup>[2,3]</sup>

Thus, obesity is generally considered to be a strong risk for the later development of T2DM, and at times, they frequently occur together. Statistics show that 60%–90% of all patients with T2DM are or have been obese.<sup>[4]</sup> The relative risk for a given obese patient to develop T2DM is 10-fold for women and 11.2-fold for men.<sup>[5]</sup>

The World Health Organization has termed the increased prevalence of obesity and diabetes as a “21<sup>st</sup> century epidemic.” With increase in body mass index (BMI), a paralleling increase has been observed in the prevalence of T2DM.<sup>[6]</sup> Thus, the term “diabesity” has been coined to represent obesity-associated diabetes.<sup>[7]</sup>

This close relationship between obesity and T2DM raises questions that apart from obesity being a risk factor for T2DM, was there any underlying mechanism by which increased adiposity caused insulin resistance (IR) in T2DM?<sup>[5]</sup>

With a high percentage of genes expressed within visceral white adipose tissue, about 30% are attributed to secretory proteins.<sup>[8]</sup> The secretory nature of this adipose tissue allows cellular regulation through a complex network of signaling which incorporates endocrine, autocrine, and paracrine

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signaling. This secretome comprises a complex array of proteins termed adipokines or “adipocytokines.”<sup>[9]</sup> These include several cytokines, chemokines, and hormone-like factors that participate in the regulation of physiological and pathological processes such as metabolism, immunity, and inflammation.<sup>[10]</sup> Four categories have been recognized: the metabolic adipokines, pro-inflammatory adipokines, extracellular matrix adipokines, and pro-mitogenic and pro-angiogenic adipokines.<sup>[11]</sup>

These “adipocytokines” or “adipokines” also play a central role in the control of energy homeostasis, regulating lipid and glucose metabolism, influencing insulin secretion and action, and regulating blood pressure and cardiovascular changes, including angiogenesis and coagulation processes.<sup>[12]</sup> Release of resistin from adipose tissue was noted to be influenced by diet and visceral fat levels which increased circulating levels of resistin.<sup>[3]</sup> It is noted that the production of these proteins by adipose tissue and by macrophages within adipose tissue is increased in obesity, T2DM, and associated pathological conditions characterized by the presence of IR.<sup>[12]</sup>

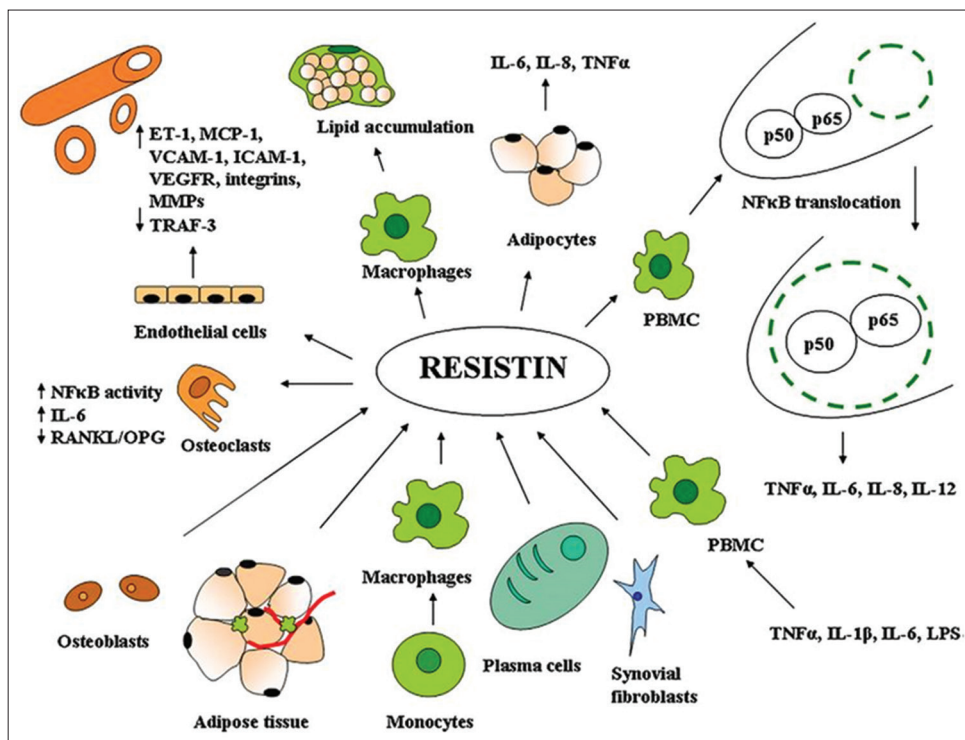
### Molecular and cellular biology of resistin

Resistin was discovered in 2001, by a team headed by Dr. Mitchell A. Lazar, from the University of Pennsylvania School of Medicine.<sup>[3]</sup> An attempt to screen for genes that are induced during fat cell differentiation but downregulated in mature adipocytes exposed to thiazolidinediones (TZDs) led to the discovery of a polypeptide, the investigators named

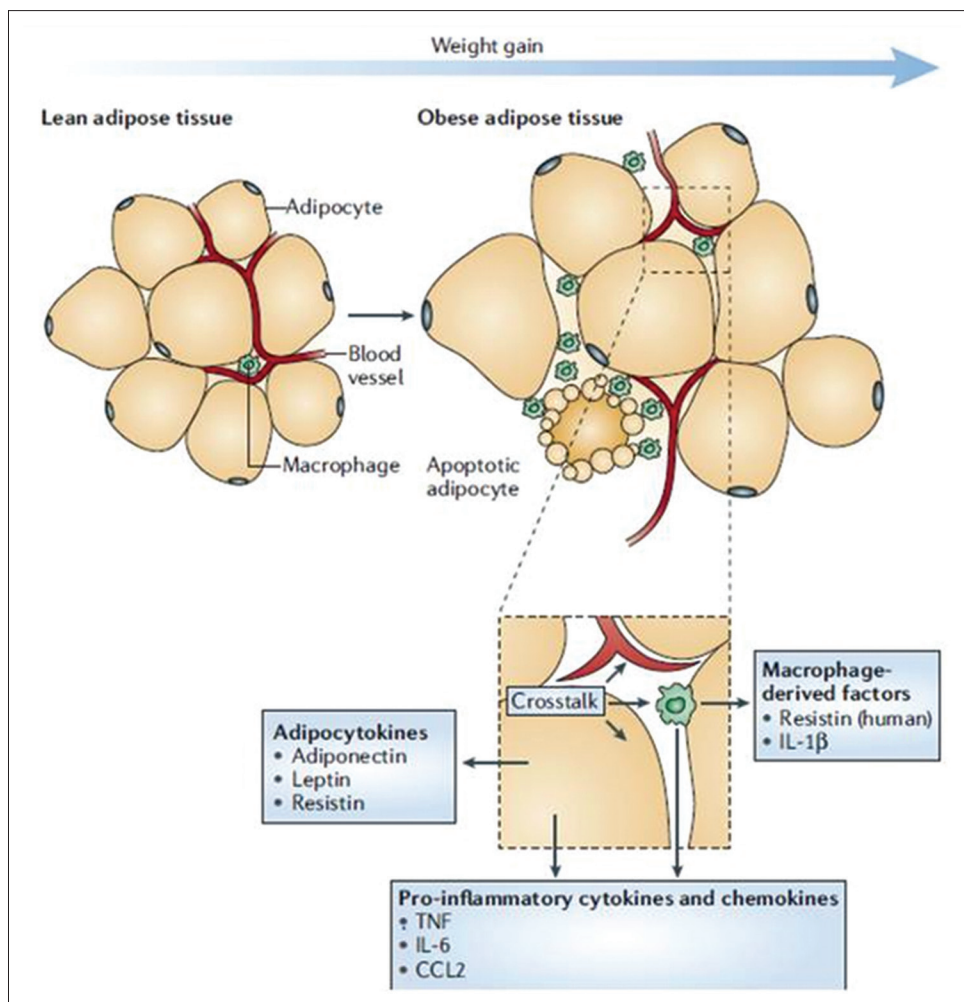
resistin (for the observed resistance to insulin in mice, when injected with insulin and thus leading to the postulation that resistin caused resistance to insulin).<sup>[4]</sup>

Further, this was found to be produced and released from white adipose tissue into the circulation. It was observed that it is expressed at very low levels in preadipocytes, endothelial cells, and vascular smooth muscle cells but is abundantly expressed in the peripheral mononuclear cells and bone marrow.<sup>[13]</sup> It was also observed that it is expressed in high levels in female gonadal adipose tissue [Figure 1].<sup>[3]</sup>

Resistin, known as resistin-like molecules (RELMS), one among a family of three proteins, shared a conserved pattern of 11 cysteine residues at the C-terminal end of the structure.<sup>[3]</sup> A 12.5 kDa cysteine-rich peptide resistin consists of 108 amino acids in humans and 114 amino acids in mice with a mature sequence, which includes a 17-amino acid signal peptide, a variable region of 37 amino acids, and a conserved C terminus.<sup>[3,14]</sup> The mouse resistin gene is situated on chromosome 8, while the human resistin gene (*Retn*) is found on chromosome 19 [Figure 2]; both share 46.7% homology at the genomic DNA level, 64.4% sequence resemblance at the mRNA levels, and 59% identity at the amino acids levels.<sup>[14]</sup> Oligomerized resistin molecules in several different low molecular weight and high molecular weight isoforms circulate in the human peripheral blood.<sup>[15]</sup> Both the oligomeric and dimeric forms of resistin are able to activate tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-12 (IL-12) in



**Figure 1:** Resistin as a potential regulator of inflammation. A schematic representation of key pathophysiological signaling pathways that are mediated by resistin in immune and resident tissue cells is depicted. Resistin can target several human cells, thereby enhancing inflammatory and autoimmune processes. Together with a glucose-dependent increase in triglyceride and cholesterol cellular mass in macrophages, it can contribute to the process of atherosclerosis and its related complications. (Courtesy: M. Filkova *et al.* Clinical Immunology (2009) 133,157-170)



**Figure 2:** Adipose tissue: cellular components and molecules synthesized. Expansion of the adipose tissue during weight gain leads to the recruitment of macrophages through various signals, which might include chemokines synthesized by adipocytes, such as CC-chemokine ligand 2. Various mediators synthesized by adipocytes and resident macrophages might contribute to local and systemic inflammation. The overall “adipocytokine–cytokine cocktail” might favor a pro-inflammatory milieu. (Courtesy: Herbert Tilg, *Nature Reviews, Immunology*, 2006, vol. 6)

macrophages and monocytes. On the other hand, the resistin’s inflammatory influence is independent of its conformation.<sup>[16]</sup>

Found in Inflammatory Zone (FIZZ) mediator was identified recently as part of an investigation of molecules associated with allergic inflammation and airway hyperresponsiveness. FIZZ gene family comprises three murine genes and two human homologs (mFIZZ1, mFIZZ2, mFIZZ3, hFIZZ1, and hFIZZ3). mFIZZ3 polypeptide is exclusively expressed in white adipose tissue.<sup>[17]</sup> Resistin was also termed adipose tissue-specific secretory factor (ADSF).<sup>[18]</sup> Thus, ADSF and FIZZ3 are used synonymously along with current nomenclature and refers to the protein resistin.<sup>[3]</sup>

### Regulation of resistin gene expression

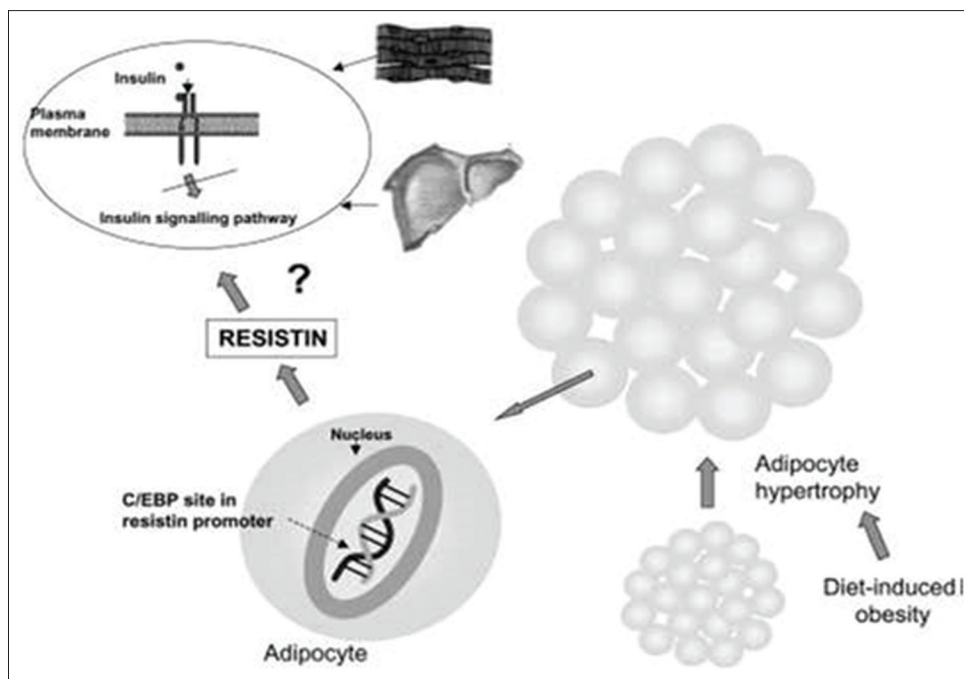
The adipocyte specificity of resistin gene expression is thought to be caused by CCAAT/enhancer-binding protein alpha [Figure 3].<sup>[19]</sup> They are a family of transcription factors that, like the peroxisome proliferator-activated receptor (PPAR) system, have been shown to be important in the regulation

or induction of adipocyte differentiation.<sup>[20,21]</sup> A transcription factor that activates transcription of PPAR-responsive genes in the absence of ligand by fusion of the potent viral transcription activator VP16 to PPAR $\gamma$ 2 (VP16-PPAR $\gamma$ ) was created in a study.<sup>[22]</sup>

Many hormones and molecules can regulate resistin gene expression, such as TZDs, insulin, glucose, glucocorticoid, and growth hormone (GH).<sup>[23]</sup>

Since resistin was first identified as a downregulated gene by TZDs, resistin mRNA and protein levels were suppressed by TZDs in 3T3-L1 adipocytes.<sup>[23,24]</sup> Overexpression of PPAR which is strongly activated by TZDs markedly reduced resistin gene expression.<sup>[25]</sup> Rosiglitazone, a TZD, has also been observed to downregulate resistin mRNA levels through activation of PPAR $\gamma$ .<sup>[3]</sup>

Dexamethasone, one of potent synthetic glucocorticoids, increased expression of resistin at both mRNA and protein levels by 2.5–3.5-fold in 3T3-L1 adipocytes and by



**Figure 3:** The adipocyte specificity of resistin gene expression is caused by binding to CCAAT/enhancer-binding protein alpha (Hartman HB 2002) that belongs to a family of ligand-activated nuclear transcription factors (Darlington GJ, 1998). Resistin circulates in the blood and was suggested to impair insulin action in the original proposal by (Steppan *et al.* 2001). However, this view has been challenged by others (Way JM, 2001) (Courtesy: Olavi Ukkola *et al.*, European J of Endocrinology (2002) 147)

approximately 70% in white adipose tissue from mice, which indicates that resistin may be a possible link between Cushing syndrome and IR.<sup>[24,26]</sup>

GH, an important regulator of metabolism, is also a regulator of resistin. Resistin gene expression was significantly suppressed in GH-deficient rats compared with controls. Acute treatment or continuous infusion of recombinant human GH both caused marked increases of resistin gene expression in the white adipose tissue.<sup>[27]</sup> Besides these regulators, other factors have also been reported to regulate resistin gene expression, such as  $\beta$ -adrenoceptor agonist, thyroid hormones, Vitamin A, and epigallocatechin-3-gallate.<sup>[28-30]</sup>

### Involvement of resistin in insulin resistance

Resistin is a peptide hormone that belongs to a family of tissue-specific RELM and serves endocrine functions likely involved in IR by impairing glucose tolerance.<sup>[3,31]</sup> An abundance of evidence has emerged linking resistin to IR.

Some of these polypeptides, such as leptin, TNF- $\alpha$ , adipsin, and Acrp30/adipoQ could affect insulin action in other tissues. Fat cell secretion of free fatty acids could also contribute to IR in the peripheral tissues. Neutralization of systemic resistin by antiresistin antibodies negatively modulates the effects of resistin on blood sugar and insulin action, promoting the uptake of glucose.<sup>[3]</sup>

In mice, neutralization of resistin by antibody improved glucose and insulin action in diet-induced obesity. Administration of

recombinant resistin impaired glucose tolerance and insulin action.<sup>[3]</sup> In an *in vitro* study, L6 myocytes that were stimulated by mouse resistin showed impaired glucose uptake induced by insulin.<sup>[32,33]</sup> Besides glucose metabolism, chronic incubation of L6 myocytes with resistin could inhibit fatty acid uptake and metabolism *via* a pathway involving CD36, fatty acid transport protein 1, acetyl-CoA carboxylase, and AMP-activated protein kinase.<sup>[34]</sup>

Role of resistin in IR was also investigated in mice engineered to knockdown or overexpress resistin. Knockdown of resistin could completely reverse the hepatic IR in diet-induced IR mice.<sup>[35]</sup> Resistin knockout in mice exhibited low blood glucose levels after fasting, due to reduced hepatic glucose production, and showed dramatically better glucose tolerance when fed a high-fat diet.<sup>[36]</sup> Overexpression of resistin in circulation by adenovirus-mediated gene expression led to glucose intolerance, hyperinsulinemia, and hypertriglyceridemia associated with impaired insulin signaling in the skeletal muscle, liver, and adipose tissue.<sup>[37]</sup> Resistin transgenic mice showed increased adiposity and enlarged adipocyte size. These mice also exhibited improved glucose tolerance and insulin sensitivity either on chow or high-fat diets.<sup>[18]</sup> Resistin gene single nucleotide polymorphisms have been linked to obesity and diabetes.<sup>[38]</sup>

Interestingly, resistin also is expressed within the  $\beta$ -cells of pancreatic islets, co-localizing with insulin.<sup>[39]</sup> In T2DM, a significant increase in resistin expression within the  $\beta$ -cells occurred, which suggested a role for resistin in pancreatic  $\beta$ -cell regulation.<sup>[40]</sup>



Resistin appeared to increase IR in various tissues at least in part by decreasing phosphorylation of AMPK.<sup>[36]</sup> It was suggested that resistin stimulated hepatic gluconeogenesis and inhibited insulin signal transduction in adipocytes by inducing SOCS-3.<sup>[3]</sup>

All of these findings clearly suggest a pivotal role of resistin in IR and Type II diabetes.

### Studies on serum and salivary resistin in diabetes and obesity

The analysis of salivary hormones is a proven and accepted alternative to serum analysis.

It was observed that salivary resistin levels in T2DM patients were significantly higher when compared to nondiabetics. These salivary levels were noted not to be affected by eating activity (i.e. oral glucose load), and although serum levels were higher than salivary levels, it correlated with serum resistin levels at any time point of oral glucose tolerance test. A positive correlation of serum and salivary resistin with BMI and HOMA-IR also was reported. Thus, it was concluded that measurement of salivary resistin was a noninvasive, simple, and easy to multipoint dynamic observation and could serve as an acceptable alternative to serum sampling and further contribute to the elucidation of the physiology and pathological role of resistin in T2DM. Resistin levels in the saliva also could be used as a tool to appraise inflammation/obesity/IR state for T2DM patients.<sup>[41]</sup>

On the other hand, in a study correlating salivary resistin, visfatin, and adiponectin levels, it was observed that neither association between serum and salivary resistin levels existed nor was it linked with either BMI or insulin sensitivity.<sup>[42]</sup>

Serum resistin levels in diabetic Japanese patients were significantly higher than controls in a study, where circulating human resistin levels were assessed by enzyme-linked immunosorbent assay (ELISA) levels and was associated with insulin sensitivity in T2DM patients. The same observations were noted in yet another study of serum resistin concentration in normal subjects versus T2DM, and confirmed a negative correlation between serum resistin and insulin sensitivity.<sup>[43,44]</sup>

With regard to the salivary adipokines, it was noted that the parotid acinar and interstitial tissue of T2DM patients, being rich in lipids, were responsible for the presence of increased adipokines in saliva, secreted by the fat cells.<sup>[45]</sup> It was also noted that salivary adiponectin and resistin levels significantly correlated with their corresponding serum levels, while salivary visfatin levels did not correlate.

Neither any association between serum and salivary resistin levels with age, BMI, or body fat percentage was reported, nor was there any difference between males and females.<sup>[35]</sup> With regard to the relationship between serum resistin, BMI, and body fat, it was further reported that resistin mRNA expression and protein levels were detectable in the subcutaneous and visceral abdominal adipocytes of both lean and obese

individuals.<sup>[46]</sup> Thus, the association between resistin levels, BMI, and body fat remains controversial.<sup>[10,15,47,48]</sup>

Source of resistin in the saliva is not clear to date. It has been thought that the source of saliva resistin in newly diagnosed T2DM was mainly derived from blood resistin by ultrafiltration. Thus, it has been speculated that there is an increase in permeability of the salivary gland basement membrane in diabetes, allowing leakage of the serum proteins into saliva by ultrafiltration.<sup>[49,50]</sup> Peptides either enter the salivary glands by active transport mechanisms or are expressed and secreted by the salivary glands themselves. Thus, concentrations of salivary peptides do not always correlate well with serum concentrations as do concentrations of passively diffused steroids.<sup>[14]</sup>

A study on serum resistin levels of obese, lean children, and adolescents noted higher serum resistin levels in obese children and girls compared to boys and also observed that resistin levels in children tended to be higher in girls as in adults.<sup>[15]</sup> A positive correlation with age in both obese and lean children was also noted,<sup>[15]</sup> whereas inconsistent results have been reported in adult male and female population.<sup>[47]</sup> In yet another study, the relationship of serum resistin with age remained controversial, with no such association being reported in middle-aged women.<sup>[48]</sup> Women tended to have higher plasma resistin concentrations,<sup>[51]</sup> but the finding was not supported and not affected by age in adults.<sup>[52]</sup> An increase in serum resistin levels in obese adults when compared to lean groups was reported with a positive correlation between resistin and obesity indices.<sup>[12]</sup> It was concluded that resistin could potentially be a marker in obese children, predicting the risks of transition to T2DM.

Insignificant difference in fasting serum resistin levels was observed between obese adult T2DM and non-diabetic healthy men thereby concluding that T2DM did not affect serum resistin in the presence of obesity.<sup>[53]</sup> In this regard, some previous studies support the direct relationship between resistin levels, obesity, and IR. In other words, resistin probably plays a major role in the relationship between obesity and IR in people with diabetes through pro-inflammatory pathways.<sup>[54]</sup>

The impact of changes in plasma resistin levels in the development of T2DM in obese individuals with an emphasis on the higher levels of serum resistin in T2DM as compared with healthy controls was observed.<sup>[55]</sup> Few other studies also supported the role of resistin in visceral obesity, obesity-induced IR, and incidence of T2DM.<sup>[56,57]</sup>

Despite the above observations and conclusions, it was noted that the serum resistin levels were not associated with insulin sensitivity, lipid profile, and BMI in T2DM. In other words, serum resistin levels in T2DM were similar to healthy subjects.<sup>[58]</sup> Thus, it appeared that circulating resistin levels did not play an important role in IR or metabolic syndrome (MetS) in humans.<sup>[59]</sup> Although serum resistin levels are increased in diabetics, this increase was neither related to body fat nor related to IR determinant symptoms.<sup>[60]</sup>

Subsequently, it was found that obesity affected the serum resistin levels in obese individuals and not in diabetics, as compared with those with normal body weight. According to the results of this study on obese individuals, serum resistin levels were not affected by the presence of diabetes.<sup>[53]</sup>

Although resistin is not closely associated with global metabolic dysfunction, it is a marker of fat distribution because it is specifically associated with abdominal fat depots. Its correlation with central obesity could also be a link between the function of resistin in obesity and inflammation, mediated by macrophages. The elevated plasma resistin levels observed in children with central obesity, a known determinant of IR development in adults, could also be the indirect link between resistin and IR as the children mature to adults. The nature of the direct link between IR metabolism and resistin in humans, if there is any, remains unclear.<sup>[61]</sup>

The levels of resistin hormone in patients with chronic hepatitis C virus (HCV) and T2DM patients and its possible relation to IR and severity of liver diseases in HCV patients were studied. It was observed that serum resistin was significantly higher among T2DM patients with decompensated liver disease. It was concluded that resistin levels are increased in IR cases, such as T2DM and HCV patients, and were related to the severity of liver disease too.<sup>[62]</sup>

The role of serum resistin in coronary artery disease, major cardiovascular events, and all complications which were the cause of mortality in T2DM was assessed. Serum resistin in nondiabetic controls was lower than diabetic patients. Amongst complications, nephropathy had higher whereas hyperlipidemia showed lower levels of resistin than other complications. The high levels of blood urea nitrogen and hypercreatinemia in renal dysfunction correlated with resistin levels which was possibly indicative of its role as a proinflammatory mediator in causing kidney dysfunction. Although not deemed significant, the increase in serum resistin levels in diabetic patients could indicate the presence of pro-inflammation in diabetic patients prone to develop cardiovascular diseases.<sup>[63]</sup>

It was observed that the levels of resistin were upregulated locally in the salivary glands and corresponded to the intensity of lymphocytic inflammation in patients with Sjogren's syndrome, which suggested resistin, expressed in the salivary glands, could be a driving factor of local inflammation in such patients.<sup>[49]</sup>

### The role of resistin in inflammation

Release of human resistin is mediated by inflammatory events, such as stimulation with lipopolysaccharide or the cytokines, IL-1, IL-6, and TNF- $\alpha$ .<sup>[64]</sup> *In vivo* resistin aggravated atherosclerosis through the stimulation of monocytes to induce vascular inflammation. Systemic resistin was also shown to increase the expression of cell adhesion molecules on endothelial cells. Increased levels of intercellular adhesion molecule 1, monocyte chemoattractant protein-1, and vascular cell adhesion molecule-1 antagonized the effects of the

adipokine, adiponectin, and increased the production of IL-12 and TNF- $\alpha$ .<sup>[64,65]</sup> This along with resistin's ability to promote the formation of foam cells attributed to resistin's role in the initiation of atherosclerosis.<sup>[66]</sup>

Increased levels of resistin correlated with an increase in pro-inflammatory cytokines, particularly in patients with MetS.<sup>[67]</sup> Several studies have also reported that increased resistin levels correlated with increased C-reactive protein levels and TNF- $\alpha$ . All these data led to the conclusion that increased levels of resistin were related to increased inflammation.<sup>[68]</sup>

### Role of resistin in other diseases

Recently, resistin has been implicated as a biomarker in cancer development and potential area for therapeutic interventions. Elevated levels of resistin, in certain forms of cancer, such as gastroesophageal, gastric, colorectal, endometrial, and postmenopausal breast cancer, have been reported by many studies. Elevated resistin levels are proposed to initiate further production of inflammatory cytokines, through activation of the p38 mitogen-activated protein kinase (MAPK) – nuclear factor-kappa B (NF- $\kappa$ B) pathway, a pathway already known to be involved in the contribution of chronic inflammation to cancer.<sup>[24]</sup> Transcription through the p38 MAPK – NF- $\kappa$ B pathway – produces stromal cell-derived factor-1, IL-1, IL-6, and TNF $\alpha$ . These cytokines further act to stimulate angiogenesis and metastasis, cell proliferation, and cell differentiation. The upregulation of resistin in these cancers consequently promotes a vicious cycle of synthesis and release of inflammatory cytokines further promoting tumor cell progression.<sup>[69]</sup>

Colon cancer patients with positive Resistin-like molecule (RELM) beta (RELM $\beta$ ) expression were observed to have a significantly longer survival rate than those with negative RELM $\beta$  expression, which implicated that resistin had a potential therapeutic approach in colon cancer. Thus, its utilization as a biomarker and prognostic tool in colon cancer also was considered.<sup>[70]</sup>

Decreased levels of resistin, observed in myelodysplasia (MDS) patients, were speculated as a compensatory response to the upregulation of other inflammatory factors etiologically linked to MDS. Decreased levels of resistin in patients with multiple myeloma and colorectal cancer patients were also reported.<sup>[71,72]</sup> By contrast, elevated levels of resistin were observed in patients with gastric cancer, considering it as a biomarker.<sup>[73]</sup> Resistin levels gradually increased with tumor stage progression, in cases of squamous cell carcinoma of the esophagus (SCCE), which implied that resistin acted as a biomarker in the progression of SCCE, rather than as a risk factor in its carcinogenesis.<sup>[74]</sup>

### CONCLUSION

Adipokines, released mainly from the white adipose tissue play a key role in lipid and glucose metabolism and also exert

regulatory influences on the cardiovascular system. Resistin (RELMs) is one such adipokine, which is profoundly linked with visceral obesity, obesity induced insulin resistance, cardiovascular complications, inflammatory processes and also has been implicated in cancer development. Though, few studies imply a controversial role in T2DM and obesity, a clear perception and its possible role in obesity induced T2DM and in other disease processes is awaited.

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### Conflicts of interest

There are no conflicts of interest.

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