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Research Article

# Revisiting Resistin: A Novel Signaling Molecule in the Development of Inflammation, Insulin Resistance, and Type 2 Diabetes Mellitus

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## Abstract

Resistin has a role in the development of insulin resistance, occurring through the pathways of glucose regulation, inflammation, and dyslipidemia. The aim of this study was to revisit the topic of resistin and uncover the latest research on this novel molecule. Additionally, another aim was to create a molecular diagram detailing how resistin contributes to the development of insulin resistance in humans through these pathways. This resulting diagram demonstrates that resistin may play an integral role in the development of insulin resistance. Further in vivo studies are needed to investigate the action of resistin within humans. Further research in this area could potentially lead to the development of pharmaceutical therapies that target resistin to treat insulin resistance.

**Key words:** type 2 diabetes mellitus; resistin; insulin; inflammation; glucose uptake; dyslipidemia

## List of Abbreviations

| | |
|---|---|
| T2DM | Type 2 Diabetes Mellitus |
| PCSK9 | Proprotein Convertase Subtilisin/Kexin type 9 |
| ROR1 | Tyrosine Kinase-like Orphan Receptor 1 |
| CAP1 | Adenylyl Cyclase Assocated Protein 1 |
| TLR4 | Toll-Like Receptor 4 |
| cAMP | Cyclic AMP |
| RSTN | Resistin |
| GLUT | Glucose Transporter |
| RELM | Resistin Like Molecule |
| TNF - α | Tumor Necrosis Factor Alpha |
| KR | Kringle Domain |
| FZZ | Frizzled-like Domain |
| SIRT1 | Sirtuin 1 |

## Introduction

T2DM continues to be a growing health concern in the United States that disproportionately affects minorities including non-Hispanic Black Americans [1]. The underlying molecular pathology leading to the development of T2DM is still being studied and the study of adipokines such as resistin has become an emerging avenue of research. Human studies have shown that severe insulin resistance is associated with higher resistin levels compared to those with normal insulin function [2].

Resistin, is a 12.5 KDa, polycysteine hormone. Also referred to as Adipocyte-specific secretory factor (ADSF), Fizz3, RSTN, or cysteine-rich protein 1 (XCP1) [5].

The role of resistin in the development of insulin resistance has been a subject of debate. First discovered and studied in mice, initial murine models focused on its association with insulin resistance, and a significant correlation was shown [4]. Numerous studies looking at serum resistin levels in humans have found a similar correlation [12]. Other studies have shown that elevated serum resistin levels are found in diabetic patients, and there is a correlation between body mass index (BMI) and serum resistin in both non-diabetic and diabetic obese patients [16]. Furthermore, circulating resistin levels are significantly elevated and positively correlated with glucose and lipids [17]. Others have failed to find a correlation between resistin and insulin resistance [13, 14]. A meta-analysis of resistin and insulin resistance showed that in patients with hyperresistenemia, resistin, and insulin resistance are positively correlated, particularly in those with type 2 diabetes and obesity [3]. This information taken together indicates that current research seems to support resistin levels being correlated with insulin resistance and T2DM. This supports resistin having a role in the development of insulin resistance.

Resistin levels in the setting of interventions meant to treat T2DM also support its role in the development of insulin resistance. Studies in Lepob/ob mice have shown that both resistin mRNA expression and protein levels are suppressed by leptin treatment in parallel with reductions in glucose and insulin [47]. In 3T3-L1 adipocytes, resistin expression was significantly upregulated by high glucose concentrations and was suppressed by insulin.

Treatment with troglitazone, an antihyperglycemic agent, or Tumor Necrosis Factor – Alpha (TNF- A) suppressed mouse resistin expression by 80% [48]. The nutritional regulation of resistin and changes in resistin gene expression and circulating levels in obesity are mediated, at least in part, through insulin and glucose [47]. This oppositional relationship to insulin also supports its role in the development of insulin resistance.

Although the mechanism underlying the relationship between resistin and insulin resistance is still being investigated, it has been found that resistin does not have a direct effect on the transcription of the insulin receptor promoter [15]. Rather, it may influence insulin resistance through its role in glucose uptake, inflammation, and dyslipidemia by binding to various body receptors.

## Methods

Methods: A systematic review was conducted on papers from 2000 - 2023 focused on the role ofresistin in pathways leading to the development of insulin resistance. A PubMed database searchwas conducted on papers using the following keywords: “Resistin”, “Insulin Resistance”, “Type2 Diabetes Mellitus”

### Structure of Resistin and Implications for Function

Understanding the structure of resistin is important for understanding its function. Studies of mouse resistin have revealed a unique structure. Chromatographic analysis of the structure of mouse resistin revealed an unusual multimeric structure. Each protomer comprises a C- terminal disulfide-rich -sandwich “head” domain, an N-terminal -helical “tail” segment, and a middle variable domain. The alpha-helical segments associate to form three-stranded coiled coils, and surface-exposed interchain disulfide linkages mediate the formation of tail-to-tail hexamers at the N-terminal. The head domain adopts a six-stranded jelly-roll topology made of two three- stranded antiparallel β sheets [19]. This jelly-roll topology is notably also found in TNF - α. The head domain rich in cysteine residues is the main domain for receptor binding.[19]. The presence of cysteine residues in the main receptor binding site may influence which receptors resistin binds to throughout the body.

The structure of human resistin has also been characterized. In comparison to mouse resistin, it has 2 domains: an N-terminal domain alpha-helical tail and a C-terminal globular domain. The N-terminal contains cysteine residues critical for oligomerization [8, 19]. Human resistin also shows a concentration-dependent secondary structural transition from alpha-helical to beta-sheet structure due to increased oligomerization as concentration increases [11].

The oligomerized form of resistin is more potent at inducing the release of pro-inflammatory cytokines from macrophages than the trimer form [20]. Additionally, in order for resistin to reduce glucose uptake in certain tissues such as cardiac myocytes, it requires oligomerization [54]. This information implies that resistin can act on most tissues in its circulating state without processing.

While mouse resistin exists primarily in hexamer and trimer forms, human resistin exists primarily as an oligomer or trimer in vitro with the prevailing form being oligomer [20]. As previously mentioned, the oligomerized form of human resistin has greater effects on pro-inflammatory cytokine release and glucose uptake. The prevalence of oligomerized human resistin supports the idea that its role in insulin resistance is heavily related to its role in glucose uptake and inflammation.

There are resistin homologs that form a multigene family, the resistin-like molecule (RELM) family, along with resistin. The only subtype expressed in humans is RELM - β. This protein contains three domains: a signal sequence N-terminal, a middle variable region, and a highly conserved C-terminal domain. The least homologous domain is the variable domain which shares 24% homology with human resistin, the most homologous domain is the C-terminal domain containing the cysteine residues which are highly conserved among RELMs. In mice, it was found to be secreted from goblet cells mostly in the proximal and distal colon [4]. RELM - β has been found to have multiple functions, pertinently in mice it was found to suppress insulin signaling in cultured hepatocytes by reducing the expression of insulin receptor substrates. In the same study, transgenic mice overexpressing RELM - β developed increased hyperglycemia, hyperlipidemia, and islet cell enlargement when fed a high-fat diet [49]. Mouse and human RELM - β are highly conserved (Steppan et al., 2001), so it stands to reason that human RELM - β may have similar effects [4].

There are notable differences between human and mice resistin. Human resistin shares 64% mRNA homology with mouse resistin with the cysteine residues being highly conserved. At the genomic level, differences notably include a lack of an intron in 3’ UTR in human resistin. In mice resistin, this intron contains a PPAR/RXR heterodimer binding site that may affect its function [8]. It is interesting to note that human resistin lacks a PPAR/RXR heterodimer binding site but PPAR agonists such as Rosiglitazone have been shown to decrease resistin expression in human monocytes/macrophages (L. Patel et al., 2003). Instead, a possible mechanism exists as PPARγ has been shown to interact with Sp1 transcription factors and thus decrease resistin expression in these cells [17]. Additionally, human resistin is primarily secreted by peripheral-blood mononuclear cells while in mice it is mainly secreted by white adipocytes. These PBMCs have also been demonstrated to be the primary targets of resistin’s pro-inflammatory effects which have been shown to be associated with obesity and insulin resistance [12]. The initial step leading to hyperrestinemia in both species is still being researched, there is evidence that hyperresistinemia correlates with hyperinsulinemia and hyperglycemia in mice [47]. On the other hand, it has been found that resistin expression in human monocytes/macrophages is upregulated by pro-inflammatory cytokines such as TNF-α and IL-6. The source of these initial cytokines may be adipose tissue in the case of obesity [38].

Resistin has involvement in a wide array of disease processes. It has been shown to play a role in multiple disease processes including sepsis, rheumatoid arthritis, and cardiovascular diseases through its pro-inflammatory properties [10]. This may be due to resistin’s ability tobind to

multiple receptors throughout the body, this variety in receptors leads to a variety in the effects of resistin on insulin resistance. Resistin has been shown to exert its effects through multiple receptors:

- ROR1: ROR1, located in preadipocytes, has been shown to have an inhibitor effect on adipogenesis and modulates the expression of Glut1/Glut4 on cells. Resistin has been shown to have an inhibitory effect on ROR1 through the down-regulation of the ROR1 receptor [22].
- CAP1: Human resistin directly binds to CAP1 in monocytes and upregulates cyclic AMP (cAMP) concentration, protein kinase A (PKA) activity, and NF-κB-related transcription of pro-inflammatory cytokines such as TNF-α (28), leading to their increased release from these cells [23].
- Decorin: Decorin is a small leucine-rich proteoglycan that is secreted as a protein from adipose tissue, mostly visceral. Decorin expression in adipose tissue is markedly upregulated in the obese state. Circulating Decorin levels were shown to be elevated in T2DM patients and correlated with waist-to-hip ratio. Resistin is an endogenous ligand of Decorin in white adipose tissue [24, 25].
- TLR4: Resistin competes with LPS for binding of TLR-4, an interaction occurring possibly through the C-terminal loops [26]. Direct binding of resistin to TLR-4 in the hypothalamus promotes inflammation through activation of Jun NH-2 terminal kinase (JNK) and P38 mitogen-activated protein-kinase signaling pathways and increases insulin resistance in adipose and skeletal muscle tissue [29]. Additionally, central resistin promotes FGF21 resistance and impairs adiponectin signaling via the TLR-4 pathway [28].

As previously stated, resistin does not interact directly with insulin receptors, but in humans may indirectly mediate the development of insulin resistance. Resistin's binding to these receptors stimulates multiple downstream signaling pathways that affect glucose homeostasis, inflammation, and dyslipidemia. All these pathways can lead to the development of insulin resistance, the mechanisms by which will be expanded upon.

## Resistin and Glucose Uptake

Hyperglycemia plays an important role in the development of insulin resistance. An increase in plasma glucose concentration stimulates insulin release from pancreatic beta cells. Combined hyperinsulinemia and hyperglycemia stimulate glucose uptake by peripheral and hepatic tissues and suppresses endogenous glucose production, both resulting in glucose disposal (Solis-Herrera et al., 2000). Resistin's involvement in glucose disposal centers around its effects on glucose uptake as will be shown.

There is debate among prior reviews and studies about the correlation between resistin and fasting blood glucose, the significance of which has previously been found to be inconsistent [17, 52]. These discrepancies may partially be due to different sample sizes or genetic groups, gender, and from experimental studies. However, more recent studies have continued to find a significant correlation between resistin and fasting blood glucose, as well as other measures of metabolic syndrome, specifically in elderly individuals without T2DM [51].

As previously mentioned, mouse resistin acts as an inhibitor ligand for the ROR1 receptor. ROR1, located in preadipocytes, has been shown to have an inhibitor effect on adipogenesis and modulates the expression of Glut1/Glut4 on cells. Resistin interaction with the KR and FZZ extracellular domains of the ROR1 receptor results in the inhibition of ROR1 phosphorylation. Suppressed ROR1 activity leads to downregulated GLUT1/GLUT4 expression on the surface of 3T3-L1 preadipocytes and thus decreased glucose uptake by these cells [22]. Additionally, resistin has been shown to affect adipogenesis, driving human adipose- derived mesenchymal stem cells (hADSC) to differentiate into hypertrophic adipocytes and abnormal osteocytes that are both insulin resistant [63]. This insulin resistance may have been driven in part by the downregulation of SIRT1, a histone deacetylase that diminishes the inflammatory profile and promotes insulin sensitivity in adipose tissue among other tissues [62]. To this author's knowledge, no studies have been conducted using human resistin with ROR1, however, the existence of these mechanisms in mouse studies is a possible explanation for the effects of resistin on fasting blood glucose.

The effect of resistin on glucose uptake in skeletal muscle will be discussed under the inflammation subheading. However, there are other tissues that show effects on glucose uptake through resistin. In vitro, osteoclasts may promote insulin resistance by secreting resistin, which was shown to affect glucose uptake in C2C12 myoblasts, precursors to myocytes [50]. The mechanism by which this occurs was not concurrently investigated, however, the secretion of resistin by pre-osteoclasts may explain why RANKL, a key cytokine in osteoclast differentiation, is an independent risk factor for T2DM. This effect of decreasing glucose uptake has been found in multiple tissues including hippocampal neurons (Cisternas et al., 2019) which may provide a link between obesity and a higher risk of neurological disorders such as Alzheimer's Disease (AD) [53].

## Resistin causes Insulin Resistance through Inflammation

Inflammation has been shown to play a role in the development of insulin resistance. This occurs through pro-inflammatory cytokines such as TNF-a and IL-12. These cytokines contribute to the development of insulin resistance through the downregulation of genes required for normal insulin action, direct effects on insulin signaling, induction of elevated free fatty acids via stimulation of lipolysis, and negative regulation of PPARγ, an important insulin-sensitizing nuclear receptor [30].

To further reinforce that resistin has a role in inflammation, it's important to note that resistin secretion is influenced by inflammation. In human macrophages, resistin gene and protein expression are increased by inflammatory stimuli, indicating their role in inflammation [38]. Resistin has been shown to enhance secretion of pro-inflammatroy cytokines from macrophages. The addition of recombinant human resistin protein (hResistin) to macrophages (both murine and human) resulted in enhanced secretion of pro-inflammatory cytokines, TNF-α, and IL-12 [35]. Resistin increases the production of pro-inflammatory cytokines in macrophages via the TLR4/NF-κB-mediated pathway as well as binding to the CAP1 receptor on monocytes/macrophages. It also induces the expression of cytokines and chemokines in articular chondrocytes through messenger RNA stabilization and transcriptional up-regulation. [35, 39]. This evidence shows that there is significant interplay as inflammation both increases resistin levels and is enhanced by elevated levels of resistin.

The pro-inflammatory cytokines released in response to resistin enhancement affect insulin resistance through JNK and other stress-activated kinases. These can inhibit insulin receptor signaling by inducing serine/threonine phosphorylation of insulin receptor substrates. This causes reduced tyrosine phosphorylation, which attenuates downstream signals [31]. Thus, the tissues affected will have reduced expression of insulin receptors, decreasing the effects of insulin signaling and decreasing glucose uptake.

Lastly, resistin showed a significant BMI-dependent association with insulin resistance and factors linked with obesity and inflammation in patients with type 2 diabetes. Therefore, it may represent a link between obesity and insulin resistance via pro-inflammatory pathways [45]. Chronic stimulation by resistin leads to glucose intolerance and hyperlipidemia associated with impaired insulin signaling, and the activations of the three MAPKs are likely related to the suppression of insulin signaling.

## Resistin causing Insulin Resistance through dyslipidemia

It is generally accepted that obesity leads to the development of insulin resistance. Adipose tissue releases various substances that modulate metabolism, including NEFAs, glycerol, hormones such as leptin and

adiponectin, and proinflammatory cytokines. Additionally, retinol-binding protein-4 (RBP4) induces insulin resistance through a retinol-dependent mechanism, reducing phosphatidylinositol-3-OH kinase (PI(3)K) signaling in muscle and enhancing expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver. The release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) by macrophages and other cells in adipose tissue also plays a role in the development of insulin resistance [40]. By these mechanisms, there is already a body of evidence showing that obesity leads to developing insulin resistance.

More recent studies have also looked at the effects of extracellular vesicles/exosomes released from adipose tissue on hepatocytes [58]. These effects include inhibition of insulin signaling as well as decreasing FGF21 secretion [59]. The content of these exosomes and the role of resistin in these pathways is unclear yet, these studies do however give insight into how increased adipose tissue and dyslipidemia can contribute to insulin resistance.

Resistin is an adipokine that contributes to dyslipidemia. Studies have shown that resistin induces white adipose tissue inflammation, leading to increased lipolysis and accumulation of lipids in muscle, which results in increased Pkcq pathway activity and serine phosphorylation of Irs-1 [41]. This serine phosphorylation of insulin receptors causes reduced expression of insulin receptors in tissues such as muscle.

Furthermore, resistin inhibits LDLR levels by increasing cellular expression of the protease PCSK9, which enhances intracellular LDLR lysosomal degradation. The relative ineffectiveness of statins in selective target populations has also been linked to resistin, as it diminishes statin- mediated up-regulation of the LDLR [42]. The recruitment of M1-polarized macrophages during obesity also leads to increased proinflammatory cytokine secretion, contributing to the development of insulin resistance [43]. The initial adaptive response to a positive energy balance that disrupts energy homeostasis eventually morphs into a maladaptive response, which fails to resolve the initial response to the insult and leads to sustained inflammation [44]. The combination of these effects is to increase accumulation of lipids both in adipose tissue and within muscle. This contributes to dyslipidemia and thus can contribute to insulin resistance. As this review was being written more studies have been published regarding resistin's role in obesity-associated insulin resistance. It has been known that obesity can lead to mitochondrial dysfunction in tissues including skeletal muscle and liver which reduces their glucose tolerance. Human resistin has been shown to induce mitochondrial fission in human myoblasts and hepatocytes both in vivo and in vitro by binding obesity-associated insulin resistance. to CAP1 [60]. This strengthens the idea that resistin has an important role in obesity-associated insulin resistance.

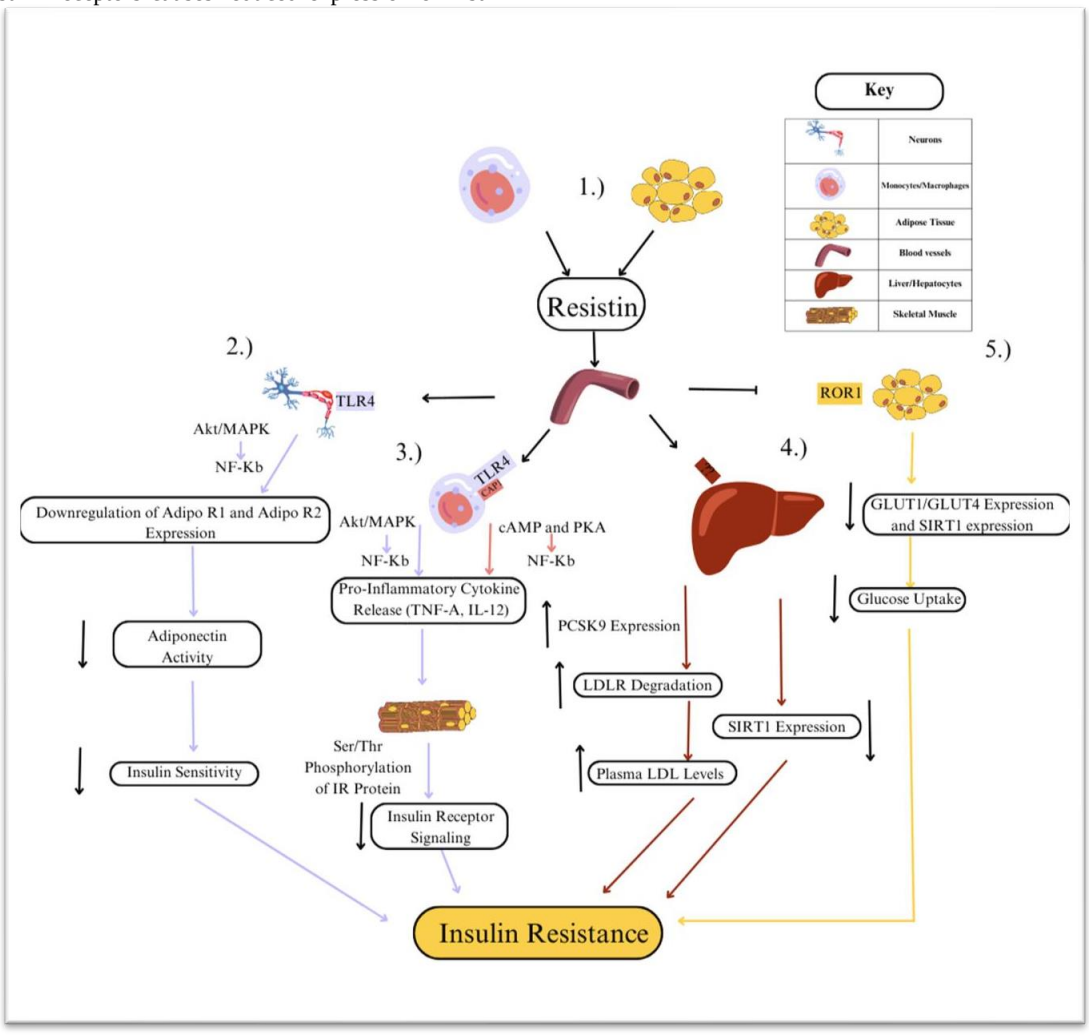


**Figure 1:** Diagram outlining molecular pathways contributing to insulin resistance that involve resistin. 1). Resistin is secreted into the systemic circulation from monocytes and adipocytes in response to inflammatory stimuli. 2). Resistin acts on neurons through the TLR4 receptor, downregulating adiponectin receptor expression on the cell membrane, reducing adiponectin activity which reduces peripheral insulin sensitivity. 3). Resistin acts on

monocytes/macrophages at both the TLR4 and CAP1 receptors, interactions at both sites lead to inflammatory cytokine release. These cytokines act on tissues such as skeletal muscle to reduce insulin receptor (IR) expression and thus reduce whole-body insuliin signaling. 4). The receptor that resistin binds to on hepatocytes is currently unknown, however it's effect is to increase PCSK9 expression thus degrading LDL receptors and increasing plasma LDL levels. It has also been shown to reduce SIRT1 expression in hepatocytes which reduces the insulin sensitivity of these tissues. 5). Finally, Resistin has been shown to act on the ROR1 receptor on adipocytes, inhibiting it's function which reduces GLUT expression and glucose uptake by these cells leading to hyperglycemia. Acting on ROR1 also possibly is the mechanism behind reduced SIRT1 expression which promotes differentiation of insulin resistant adipocytes.

## Discussion

Limitations of this study include the different reported effects of resistin on adipogenesis and levels of insulin resistance. Might be explained by the different source and bioactivity of the resistin used in the specific assays. Being cysteine-rich molecule, proper resistin folding might be an issue affecting the results. The cellular state and the normal genetic variation of the same cell line cultured in different laboratories could be also an important factor affecting resistin effects on adipogenesis [22]. Future research may be done to further uncover the relationships between resistin and other active molecules throughout the body. For example, Sirtuin 1 is an anti-aging gene that encodes for SIRT 1, a histone deacetylase that diminishes the inflammatory profile [61]. It's anti- inflammatory effects occur partly through decreasing resistin expression by PBMCs and adipocytes (Nakamaru et al. 2009; Mercader et al. 2011) and this relationship has been implicated in the development of other disorders related to inflammation such as aortic stenosis (Samiei et al., 2019) [62, 64]. Defective Sirt 1 associated with glucose dysregulation with inhibition of insulin signaling and acute mitochondrial apoptosis, this function may be related to its relationship with resistin which has similar effects (Edith Cowan University & J Martins, 2017). Thus, there continues to be future areas of research related to insulin and its role in insulin resistance.

## Conclusion

The influence of resistin on insulin resistance is heavily related to its roles in inflammation, glucose uptake, and dyslipidemia. Resistin has the effect of suppressing glucose uptake, contributing to hyperglycemia. Resistin-induced release of pro-inflammatory cytokines inhibits insulin-receptor signaling through downregulation of insulin receptor expression. It also decreases LDL receptor expression, contributing to dyslipidemia which promotes insulin resistance. Current research supports resistin as having a role in the development of insulin resistance. It has current utility as a biomarker to assess insulin resistance status. Further work is needed to understand the secretion of resistin, specifically its regulation and the factors that elevate or decrease circulating resistin levels. Further work uncovering the role of resistin in insulin resistance may drive the development of intervention that specifically targets resistin and therefore, treat insulin resistance at the molecular level.

## Conflict of Interest

All authors declare no conflict of interest

## Author Contributions

This work was conceived by Dr. KG who also edited all the drafts. DE prepared all the drafts including the schematic representation. This manuscript was prepared as a partial requirementfor completion of senior elective. MF and WO edited the final draft.

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