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Mechanisms by which Elevated Resistin Levels Accelerate Atherosclerotic Cardiovascular Disease

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Abstract

The global epidemic of obesity and its strong association to Atherosclerotic Cardiovascular Diseases (ASCVD), including coronary heart disease, has lead to extensive research into the causes of obesity mediated ASCVD. Currently, there is a great deal of interest on the role of adipose tissue derived adipokines as obesity induced ASCVD risk factors. The present review focuses on the current state of knowledge of the recently discovered adipokine, resistin, and the role of resistin as an emerging ASCVD risk factor. Studies investigating the relationship between elevated serum resistin levels, which is characteristic of obese individuals, and atherosclerosis progression and clinical ASCVD events are discussed. Investigations on the actions of resistin as a direct cellular mediator of pro-atherosclerotic processes in the arterial wall are summarized. We further examine the evidence for resistin in inducing the atherogenic dyslipidemia, a major ASCVD risk factor in obesity. The novel role of human resistin in stimulating hepatic dysregulation of Low-Density Lipoprotein (LDL) and Very-Low Density Lipoprotein (VLDL) metabolism, two key pro-atherogenic components of the atherogenic dyslipidemia are featured. The important therapeutic implications of the pathophysiological effects of human resistin on LDL and VLDL metabolism are delineated. Finally, the overall potential of resistin as an ASCVD risk factor and therapeutic target in mitigating ASCVD in human obesity is examined.

Keywords: Resistin; Atherosclerosis; LDL; VLDL; Cholesterol; Statin; Cardiovascular diseases

Obesity as a Major Cardiovascular Risk Factor

Obesity is a growing global epidemic, with more than 1 billion individuals worldwide characterized as being overweight or obese [1]. In North America alone, 1 in 3 adults are obese [2]. This is a problem because the consequences of obesity are dire [3]. Obese individuals are at greatly elevated risk for developing atherosclerotic Cardiovascular Diseases (ASCVD) because it accelerates the initiation and progression of atherosclerosis, the leading cause of morbidity and mortality in North America [4].

Obesity is defined as a chronic condition in which there is an excess accumulation of body fat to an extent that can compromise an individual's health [4]. It is more specifically defined as having 25% or more total body fat in men and 35% or more in women [3]. Obesity occurs when caloric intake exceeds energy expenditure, resulting in a positive caloric balance [5]. Commonly, obesity is identified by simple anthropometric measurements, such as Body Mass Index (BMI) ≥ 30 kg/m^2, waist circumference >102 cm in men and >88 cm in women, or waist-to-hip ratio >0.95 in men and >0.80 in women [3].

In the landmark INTERHEART study, the presence of obesity was identified as a major ASCVD risk factor globally. INTERHEART was a randomized, case-control trial which investigated clinical parameters that could potentially increase the risk of heart attacks in 27,000 patients in 52 countries globally [6]. The trial findings showed that abdominal obesity accounted for a marked 24% of the global population burden of myocardial infarction [6]. Consistent with this, the Framingham Heart Study [7] and the Third National Health and Nutrition Examination Survey [8] have shown marked and significant increases in the lifetime risk of coronary artery disease in the presence of obesity.

Why are obese individuals so predisposed to developing ASCVD? Obesity, especially of the central or visceral abdominal type, is a major underlying risk factor for ASCVD through its association with other major established and emerging ASCVD risk factors. Obesity is associated with the following established ASCVD risk factors: hypertension, dyslipidemia, insulin resistance, type 2 diabetes and

prothrombotic and proinflammatory clinical states [3]. Moreover, currently, there is a strong interest in identifying novel emerging risk factors linking obesity to ASCVD. Recent attempts at identifying such novel obesity ASCVD risk factors have focused on the secretory products of adipose tissue in obesity.

Adipose tissue synthesizes and secretes biologically active molecules, termed adipokines that may either modulate ASCVD risk factors or potentially act as pro-atherogenic or anti-atherogenic factors on their own. Some of the key adipokines that have been identified include adiponectin, resistin, leptin, plasminogen activator inhibitor-1, tumor necrosis factor-alpha, and interleukins-6, 8 and 10 [5]. With the adipose tissue expansion that occurs in obesity there are changes in the levels of synthesis and secretion of these adipokines [5] that can then potentially modulate ASCVD risk in obesity.

As such, we have focused our recent research efforts on the adipokine, resistin, and its novel role in promoting ASCVD in obesity. Prior to our recent studies, the mechanisms by which resistin stimulates ASCVD were not entirely understood. In the current review, we summarize the current state of knowledge of resistin and its link to ASCVD, our findings on the causal relationship between elevated resistin levels in obesity and the promotion of ASCVD risk factors and their therapeutic implications.

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Resistin Emerges as a Novel Risk Factor for Atherosclerotic Cardiovascular Diseases (ASCVD)

Resistin is a 12.5 kDa sized C-terminal cysteine-rich signaling peptide [9,10]. It is a member of a class of cysteine-rich proteins, collectively termed resistin-like molecules, which have differential tissue distribution [9,10]. Resistin is secreted predominantly by adipose tissue in humans and rodents [9,10]. In particular, it is secreted from adipocytes in both species and also by macrophages within adipose tissue in humans [9,10]. It exists in three forms: a trimer, a hexamer and a monomer, with the lower molecular weight form being the most active [11]. Recently, a functional receptor for resistin has been identified, named decorin [12]. Decorin was identified on the surface of adipose tissue progenitor cells and isoforms of decorin may act as receptors to resistin in other peripheral tissues [12].

Since its discovery in 2001, there has been controversy regarding the role of resistin in humans. There has been strong rodent data on the pathophysiological effects of resistin in mediating a multitude of metabolic impairments, including insulin resistance and type 2 diabetes [13]. Unfortunately, these findings have not been necessarily translatable to humans. One reason may be the relatively low homology between rodent and human resistin – only 53% homology between the two species [9].

A clear finding that has emerged regarding resistin physiology in humans is that resistin adipose tissue expression and resistin serum levels are increased in obese subjects [14-16]. Consistent with this, there are strong positive correlations between plasma resistin levels and increases in both BMI and the quantity of abdominal visceral adipose tissue, the most metabolically adverse type of fat, in humans [14,17-20].

Furthermore, and highlighting its clinical importance, is the observation that elevated serum resistin levels in humans correlate strongly with ASCVD and has therefore been identified as a link between obesity and the resulting accelerated development of cardiovascular diseases in obese individuals. High serum levels of resistin were not only found to correlate positively with established surrogate markers of atherosclerosis development and progression, including coronary artery calcification [21,22], but they also predicted the occurrence of major adverse cardiovascular events. The prognostic value of resistin as an independent predictor of cardiovascular events, including myocardial infarction, extended both to patients with stable coronary artery disease [23,24] and to healthy primary prevention populations [25]. Moreover, in patients with more severe ASCVD, including those with acute coronary syndrome and individuals with atherothrombotic ischemic stroke, elevated resistin was independently associated with a poor prognosis, including the occurrence of future cardiovascular events and increased mortality [26,27]. With the accumulating body of evidence of the strong association between resistin and ASCVD, resistin has thus emerged as a novel risk factor and strong potential biomarker for ASCVD.

Adverse Effects of Resistin at the Arterial Wall

The finding that resistin immunoreactivity is increased in atherosclerotic regions of the human vasculature [28] seemed to indicate that at least part of the mechanism of action of resistin in promoting ASCVD involved stimulation of the atherosclerosis process directly at the arterial wall. Consistent with this, studies have shown that resistin is involved in pathophysiological pro-atherogenic processes in multiple cell types in the arterial wall. More specifically, resistin has been found to promote endothelial cell dysfunction, smooth muscle cell migration and proliferation and monocyte and macrophage activation and transformation.

To begin with, in several different cell systems, including human coronary artery endothelial cells, resistin has been reported to induce endothelial dysfunction, one of the earliest impairments at the vascular wall in the atherosclerosis process. Resistin was shown to mediate endothelial cell dysfunction via downregulation of cellular eNOS mRNA and protein levels [29]. Resistin, thereby, potentially impairs endothelial-dependent vasorelaxation. The mechanisms through which resistin mediates a reduction in endothelial cell eNOS levels in humans is not known but has been investigated in other species, including in porcine and rodent endothelial cells. These studies indicated that resistin induced eNOS downregulation occurs via increased production of pro-oxidant Reactive Oxygen Species (ROS) and through reduced eNOS phosphorylation [29].

Next, resistin has been found to induce aberrant activity of human vascular smooth muscle cells. In a recent report, human aortic smooth muscle cells were induced to proliferate in response to resistin treatment, an effect mediated by ERK 1/2 and Akt signaling systems [30]. In addition, resistin was shown to stimulate the pro-atherogenic vessel process of vascular smooth muscle cell migration [31,32].

Finally, resistin has been shown to have pathophysiological effects on human monocytes and macrophages. The migration and recruitment of circulating monocytes and macrophages into the subendothelial space is a critical component of the initiation of the chronic inflammatory component of atherosclerosis [33]. Resistin was shown to increase the expression in human endothelial cells of proinflammatory cytokines that promote monocyte/macrophage recruitment and adhesion to endothelial cells, including MCP-1, ICAM-1 and VCAM-1 [34-36]. Resistin increased MCP-1 production by endothelial cells both through CD40 ligand-induced MCP-1 expression and by downregulation of Tumor Necrosis Factor Receptor-Associated Factor-3 (TRAF3), an inhibitor of CD40 signaling [34]. Furthermore, increased monocyte adhesion to endothelial cells by resistin was dependent on resistin-mediated increases in endothelial cell ICAM-1 and VCAM-1 levels [34,35]. The resistin induced stimulation of monocyte-endothelial cell adhesion by ICAM-1 and VCAM-1 occurred through the activation of a p38MAPK-dependent pathway [35].

Resistin has been further shown to promote monocyte and macrophage morphological transformation into lipid-filled foam cells, which constitute the major cellular component of the fatty streaks characteristic of atherosclerotic plaques. Resistin-induced transformation of human monocytes and macrophages into lipid-abundant foam cells was through the upregulation of the macrophage CD36 and SR-A receptors and a consequent increase in cellular uptake of oxidized LDL particles [37,38]. Resistin further downregulated macrophage expression of the ABCA1 transporter, the rate-limiting protein in cellular cholesterol efflux [38], potentially enhancing macrophage retention of intracellular cholesterol.

In vivo, resistin gene transfer into atherosclerotic plaques of rabbits increased the macrophage and lipid contents of their plaques, and because of these effects, increased not only atherosclerotic plaque size and progression, but also plaque destabilization and vulnerability [39]. If the same effect of resistin in inducing atherosclerotic plaque instability holds true in humans, once tested, it would explain the increase in cardiovascular events, including myocardial infarction and the poor prognosis observed in patients with elevated serum resistin levels.

Overall, it should be noted that the above vascular cell pro-atherosclerotic effects of resistin, while broad, have only been demonstrated in humans at the *in vitro* level in cell culture. A direct causal effect of resistin in promoting the development and advancement of the atherosclerosis process in the human vasculature has not been shown. Nonetheless, in light of the strong association between elevated resistin and clinical ASCVD outcomes, the question then remained if resistin mediates direct pro-atherogenic effects in humans through its actions outside the vasculature to increase ASCVD risk factors in obesity.

Resistin as a Potent Metabolic Generator of the Atherogenic Dyslipidemia

As indicated above, obesity is associated with several established ASCVD risk factors. One of the earliest metabolic defects to appear in obese individuals, which is central to the pathway of ASCVD is, dyslipidemia [40,41]. Dyslipidemia is also one of the most prevalent metabolic impairments in obesity, occurring in almost 60% of abdominally obese subjects, and also one of the strongest ASCVD risk factors in obesity [6,40-42]. The characteristic dyslipidemia of obesity is the atherogenic dyslipidemia, which is a triad of lipoprotein disorders including: elevated serum triglycerides, high serum numbers of pro-atherogenic Low-Density Lipoprotein (LDL) particles, and low concentrations of athero-protective High-Density Lipoprotein Cholesterol (HDL-C) [40-43]. We recently identified a novel role of resistin in directly increasing the levels of the pro-atherogenic lipid and lipoprotein components of the atherogenic dyslipidemia in humans – that is, elevated triglycerides and increased LDL particle concentration [44,45].

In terms of serum triglycerides, a recent large population-based Framingham study found a highly significant positive association between circulating resistin levels and serum triglycerides [46]. No studies, however had investigated whether the association between resistin and triglycerides in humans was a cause-and-effect relationship until our recent studies on the topic.

The major carrier of triglycerides in human serum is the circulating triglyceride-rich Very-Low Density Lipoprotein (VLDL) particles, which is, thereby, a key determinant of serum triglyceride levels. Serum VLDL levels in humans are primarily determined by the extent of liver VLDL production [43,47]. We therefore initially wished to determine if resistin plays a role in liver VLDL production in a human setting.

We found an extremely potent effect of resistin treatment in directly stimulating VLDL production by human liver hepatocytes [44]. At physiological levels of resistin characteristic of human obesity, recombinant human resistin induced a highly significant 10-fold increase in human hepatocyte VLDL production. The physiological relevance of the findings were further established by the demonstration that treatment of the hepatocytes with serum from obese humans with elevated resistin levels caused a greater stimulatory effect on VLDL production than serum from lean individuals with lower resistin levels. We then determined the quantitative importance of the resistin effect in human serum in inducing VLDL production. This was shown by the substantial reduction of the stimulatory effect of obese and lean human serum on hepatocyte VLDL production when resistin was specifically removed from the serum (via antibody immunoprecipition) prior to serum stimulation of the hepatocytes.

We thereafter examined the mechanisms through which human resistin induced hepatocyte VLDL overproduction [44] and found that resistin induced a stimulatory effect on the hepatic synthesis of both the major protein and lipid components of VLDL particles – apolipoprotein B (apoB) and triglycerides and cholesteryl esters, respectively. Moreover, resistin increased the activity of Microsomal Triglyceride Transfer Protein (MTP), the rate-limiting enzyme in hepatic VLDL assembly. Finally, resistin downregulated the expression and activity of several key proteins in the insulin signalling pathway, a pathway which when activated, reduces hepatic VLDL production. Overall, resistin mediated its potent enhancement on VLDL production in a human setting both by increasing the stimulatory signals on VLDL production and decreasing the inhibitory signals, thereby inducing a synergistic effect on VLDL production. In this way, resistin elevates serum triglycerides in humans.

Our next objective was to investigate if resistin plays a role in generating the other pro-atherogenic component of the atherogenic dyslipidemia in humans – increased LDL particle concentration [45]. Since VLDL particles are the precursor particles to LDL particles in the circulation, we already demonstrated through our VLDL studies above a mechanism by which resistin increases LDL particle levels in humans – that is, via VLDL overproduction. However, the primary determinant of LDL levels in humans is the rate of LDL particle uptake and clearance by the liver. The rate of liver LDL uptake and clearance is, moreover, regulated primarily by hepatocyte cell surface LDL receptors. We, therefore, wished to investigate if resistin affects human hepatocyte LDL receptor regulation.

Our results showed that resistin, at the levels characteristic of human obesity, causes a substantial 40% downregulation of LDL receptor protein levels in human hepatocytes [45]. The effect of resistin in reducing LDL receptor expression was dose-responsive and occurred in both cultured human HepG2 hepatocytes and primary hepatocytes freshly isolated from human livers. The resistin-mediated decrease in LDL receptor levels was seen both when the hepatocytes were treated with recombinant human resistin and with obese human serum with elevated resistin levels. Thus, the results were applicable physiologically to humans.

At present, LDL receptor concentrations are thought to be regulated essentially by a dual mechanism. In one direction, the cellular transcription factor, SREBP2, induces an increase in LDL receptor gene expression [48]. On the opposite end, PCSK9, the recently discovered protein of high current interest, functions to direct intracellular degradation of the LDL receptor [48,49]. Unfortunately, few factors have been indentified that regulate SREBP2 or PCSK9 levels. We identified a novel and important effect of resistin in raising cellular levels of PCSK9, thereby accounting for part (approximately 50%) of the resistin effect in decreasing cellular LDL receptor concentrations [45]. The rest of the resistin-mediated effect on hepatic LDL receptors may be through other as-of-yet unidentified pathways altered by resistin and/or a direct effect of resistin on LDL receptors.

Therapeutic Implications of the Resistin-Mediated Dysregulation of Human VLDL and LDL Metabolism

The results of our studies above on the adverse effects of human resistin on VLDL and LDL regulation have important therapeutic implications on ASCVD risk and development in human obesity (Figure 1). Both VLDL and LDL are intimately involved in and stimulate pro-atherosclerotic events in ASCVD. Both lipoprotein particles are taken up by macrophages and other cells in the arterial wall and are well known to induce processes in the vascular wall leading to atherothrombotic plaques [50,51]. In fact, elevated serum LDL is both necessary and sufficient for atherosclerosis initiation and

Figure 1: Pathogenic adipose tissue resistin secretion in obesity-induced dyslipidemia.
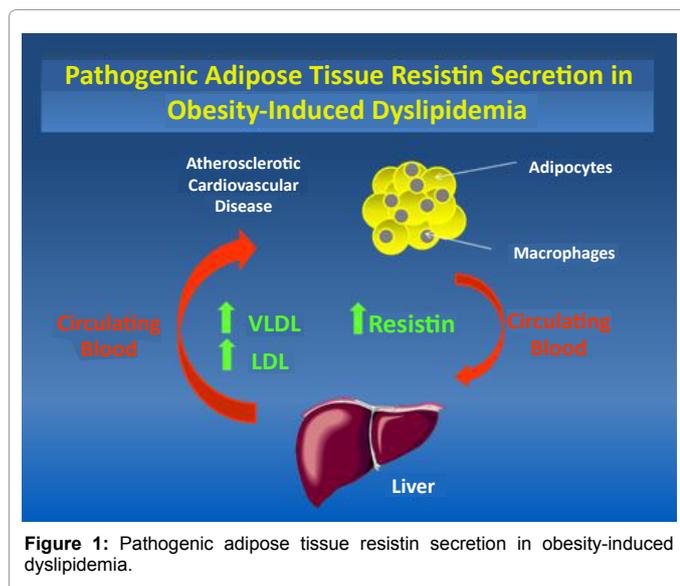
progression [52]. Elevated VLDL and LDL are also amongst the earliest metabolic ASCVD impairments in obesity. Therefore, targeting these particular dyslipidemias in obesity should certainly garner large gains in ASCVD risk reduction.

This premise has already been tested and proved with the substantial reductions in ASCVD progression and risk achieved in randomized clinical trials with the statins [53]. Statins are the major and most successful class of drugs administered to patients with elevated LDL and lower both LDL and VLDL significantly and effectively in a large proportion of patients receiving them [53-55]. Unfortunately, in 30-50% of individuals receiving statins, they are not sufficiently effective to meet recommended patient LDL targets [53,56,57]. Obese individuals, in particular, as a group have been found to respond inadequately to statin LDL lowering effects [58,59]. A cause had not been identified until we reported that human resistin, at the levels seen in obese individuals, almost completely ablates the LDL receptor upregulatory effect of statins, the major mechanism of action of the statins [45]. This implied that elevated resistin markedly reduces statin efficacy in human obesity.

Because of the high potency we observed of the effect of human resistin in inducing adverse effects on VLDL and LDL metabolism [44,45], the development of inhibitors against resistin could potentially produce large reductions in serum VLDL and LDL levels in humans, thereby mitigating clinically significant reductions in ASCVD. This will of course need to be specifically tested clinically. As a start, and as discussed above, we have already shown as a proof of principle that antibody removal of resistin from both obese and lean human serum largely reduces the adverse effects of the serum on VLDL and LDL metabolism [44,45]. Inhibitors of resistin, moreover, may be an effective addendum to statin therapy to lower LDL in the large numbers of individuals resistant to statin therapy, including obese and overweight patients [58,59], and in those intolerant to statin side effects, reported to occur frequently in patients on high dose statin therapy and in certain high ASCVD risk populations.

Conclusions

All in all, the accumulating evidence shows that elevated serum resistin levels, characteristic of overweight and obese individuals, is a significant emerging ASCVD risk factor in predicting ASCVD

progression, events and prognosis. While a multitude of adverse effects have been described of resistin on human arterial wall cell models, these studies will need to be expanded *in vivo* in humans to determine their applicability to the human vasculature at the whole-body level. Established advanced vascular imaging techniques can help in this endeavor.

We further identified a novel role of human resistin in stimulating one of the strongest and earliest metabolic defects and ASCVD risk factors in overweight and obese individuals, the atherogenic dyslipidemia. Resistin strongly impaired the regulation of both pro-atherogenic lipoproteins within this triad of lipoprotein disorders, that is, VLDL and LDL particles. These effects were shown in physiologically relevant human settings. Moreover, we elucidated the key mechanisms responsible for these resistin-mediated pathophysiological effects, which were reduced activity and levels of the key rate-limiting proteins in VLDL and LDL metabolism – MTP and the LDL receptor, respectively.

Finally, we showed the potential for promising therapeutic benefits of inhibitors against resistin. Resistin, we found, reduced the effectiveness of statins on LDL regulation. Antibody-mediated removal of resistin from human serum, moreover, reversed the adverse effects of resistin on hepatic VLDL and LDL metabolism. Future studies should be aimed at expanding our understanding of the pathways and mechanisms of action of resistin and resistin inhibition on dyslipidemia and other established ASCVD risk factors in humans at the cellular and whole-body levels. By doing so, we may mitigate the high risk of ASCVD and the consequent morbidity and mortality in the alarmingly large proportion of individuals globally afflicted with obesity.

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