Large meals and large arteries: Is resistin the link?

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See article by Jung et al. [11] (pages 76–85) in this issue.

“'To lengthen thy Life, lessen thy Meals.'”

Benjamin Franklin, Poor Richard’s Almanack, 1733

The burden of chronic diseases is on the rise on all continents, and the predictions for its detrimental effects on the individual and society resemble the warnings of a hurricane approaching land [1]. Most of the storm settles on complications of cardiovascular disease, the risk of which is increased by a factor of two to three even by the clustering of “prestages” of traditional cardiovascular factors, referred to as the “metabolic syndrome” and related to insulin resistance ever since Reaven’s seminal work in 1987 [2]. Five different major sets of criteria are currently in place for the diagnosis of the metabolic syndrome, with the entire concept being very critically appraised by representatives of American and European diabetes societies, yet again endorsed by the American Heart Association, and with a worldwide definition by the International Diabetes Federation appearing on the horizon [3,4]. The most apparent underlying risk factor for the metabolic syndrome is truncal or visceral obesity and hence waist circumference or waist-to-hip ratio are better clinical parameters than body mass index [3]. Hence, as society is “supersizing” so is the risk of cardiovascular diseases and the call to the cardiovascular practice and research community.

Once considered to serve no other purpose than to store energy, adipose tissue has been increasingly recognized as an active endocrine organ, capable of synthesizing and secreting so-called adipokines. One of the 21st century editions of these substances is resistin, a 12.5-kDa, 114-amino acid polypeptide, rich in cysteine residues, that can form dimers and hexamers in the new family of resistin-like molecules [5,6]. The name “resistin” is derived from its discovery in the search for a molecular target for thiazolidinediones, linking insulin resistance and obesity in rodents. Obese mice were noted to have higher circulating resistin levels, likely related to higher expression in adipose tissue as reported in microarray analyses, which gave rise to the alternate name adipose secretory factor (ADSF). Finally, it was realized that resistin or ADSF was also FIZZ3, a sequence tag related to a protein “found in inflammatory zone 1” of murine lungs, which constituted the first link of this molecule with inflammation.

The human gene and protein structures of resistin differ from their rodent counterparts, and of note, resistin is predominantly expressed in the bone marrow, circulating monocytes, and tissue macrophages, but only at low levels in adipose tissue in humans [5]. Polymorphisms of the resistin gene on chromosome 19 and circulating levels of resistin have not been conclusively associated with insulin resistance, and resistin plasma concentrations have not been consistently linked with obesity, truncal adiposity, or percentage body fat [5,6]. Instead, it has been recognized that circulating resistin levels correlate with heart disease in patients with end-stage renal disease, with coronary artery calcification in patients with a family history of premature coronary artery disease (CAD), with multivessel CAD in patients undergoing coronary angiography, and with CAD by any clinical definition in a Saudi Arabian population [7–10]. The pathophysiology underlying this interplay, however, remains incompletely characterized.

In the current issue of Cardiovascular Research, Jung et al. [11] aim to fill this void of knowledge by demonstrating the expression of resistin in the transition zone and center area of aortic abdominal aneurysms (AAA) that were
histologically characterized by inflammation, thrombus, and atheromatous plaque. Although not expressed in quantitative terms by immunohistochemistry and immunofluorescence for different tissue regions, the expression of resistin did seem to be higher in the center area in co-localization with cells of monocytes/macrophages lineage. Applying real-time PCR, the authors noted that resistin mRNA was expressed minimally in peripheral (varicose) vein samples but significantly in aortic aneurysm samples. As for cell types, mRNA was also expressed minimally in commercially obtained human umbilical vein endothelial cells (HUVEC) and vascular smooth muscle cells (VSMC) from gastroepiploic arteries of patients undergoing gastric surgery but significantly in peripheral blood mononuclear cells (PBMC) from healthy volunteers. In additional cell cultures experiments, resistin stimulated the expression of PAI-1 and ET-1 in HUVEC and the migration of cultured VSMC in a scratched wound assay. Based on these findings, the authors concluded: “Resistin is secreted from macrophages within atheroma and promotes atherosclerosis,” as stated in the title of their manuscript.

On the endothelial cell level, Verma et al. [12] and Kawanami et al. [13] previously showed that resistin stimulates the expression of ET-1, VCAM-1, ICAM-1, MCP-1, and downregulates TRAF-3, an inhibitor of CD40 signaling. Furthermore, Kougias et al. [14] showed that incubation of porcine coronary artery rings with resistin for 24 h impairs endothelium-dependent vasorelaxation along with an increase in oxidative stress and a decrease in eNOS expression. In addition to the potential, indirect way that resistin can stimulate VSMC proliferation via reduced NO bioavailability, Calabro et al. [15] demonstrated that resistin can stimulate VSMC proliferation directly, and the current work adds the dimension of VSMC migration to these previous studies. Jung et al. [11] did not study the effects of resistin on macrophages, but Silswal et al. [16] showed just recently that incubation of murine and human macrophages with recombinant human resistin resulted in enhanced secretion of pro-inflammatory cytokines such as TNF-α, similar to the action of endotoxin. Vice versa, Lehrke et al. [17] showed that incubation of human macrophages with endotoxin or TNF-α stimulated resistin gene expression. Finally, Bokarewa et al. [18] recently confirmed a positive reciprocal interaction between IL-1β, IL-6, and TNF-α and resistin, linked to the NFκB pathway, in PBMC. Of note, in morbidly obese patients, resistin mRNA was undetectable in endothelial cells and VSMC but was readily detectable in circulating mononuclear cells [19]. In addition, Ghanim et al. [20] noted circulating mononuclear cells of obese patients to be in a proinflammatory state, characterized by an activated NFκB pathway. Taken together, these data support the concept that mononuclear/macrophage cells are the primary source of resistin within the vascular wall and identify resistin as a proinflammatory cytokine capable of contributing to endothelial cell dysfunction and VSMC transformation.

Considering the origin of the tissue samples, the question arises whether the findings presented by Jung et al. suggest a role for resistin in the development of aortic occlusive disease (AOD) and/or AAA. Although AAs are invariably associated with atherosclerotic plaque formation, there is no convincing evidence that aortic atherosclerosis inevitably causes AAA, justifying the term “nonspecific” over “atherosclerotic” aneurysm [21,22]. Indeed, hyperlipidemia in rabbits will produce aortic atherosclerosis but not aortic aneurysms unless combined with additional local irritants [23]. Vice versa, aneurysm formation preceded atherosclerotic lesions formation in apoe−/− mice treated with angiotensin-II [24]. Of note, in these mice, AAA formation started as a disease of the media whereas atherosclerosis classically starts as a disease of the intima. In the clinical arena, the significance of genetic susceptibility for AAA formation has long been recognized, and a number but not all studies in the field highlighted cardinal differences in risk factor profiles between AAA and AOD. In this regard, smoking has been considered the single most important exogenous risk factor for AAA formation; in fact, chronic smokers are three and nearly five times more likely to develop AAA than coronary artery and cerebrovascular disease, respectively. On the contrary, diabetes mellitus has been recognized as a coronary heart disease equivalent but as a negative risk factor for AAA formation [22]. Interestingly enough, aortic aneurysmal disease is associated with higher tissue levels of the inflammatory cytokines TNF-α and IL-6 and lower levels of the protease inhibitors TIMP-2 and PAI-1 than aortic occlusive disease [25,26]. Hence, atherogenesis and aneurysm formation cannot be used synonymously, and the current findings should only be interpreted according to the way they were obtained and within their histological diagnoses. A series of different stages of atherosclerotic or aneurismal lesions may have provided a better way to identify a temporal and potentially pathophysiological relationship between resistin expression in the arterial wall and atherogenesis and/or aneurysm formation. Furthermore, normal arteries may have been a better control tissue than varicose veins. Support for the current findings, though, comes from the very recently published results by Burnett et al. [27] showing that carotid endarterectomy samples but not nondiseased internal mammary artery stained positive for resistin. In addition, this group found that the gene coding for resistin was one of the most strongly upregulated genes in the aorta of apoe−/− mice in the course of aortic atherogenesis and was associated with an increase in resistin mRNA and protein levels in the aorta and resistin concentrations in the serum. Taken together, these findings support an association between resistin and atherosclerosis, whereas its association with AAA awaits further confirmation.

As for the precise pathophysiological role of resistin in degenerative arterial disease, the answer will have to be provided by future studies. One approach would be to inhibit resistin signaling pathway(s), although, in this
regard, it is important to note that the receptor for resistin has not yet been identified. Also, PPAR-γ agonists, known to downregulate resistin in rodents, have not been unani-
mously confirmed to exert the same effect in humans, but remain an important study object as the potential next big wave in cardiovascular therapeutics following HMG-CoA inhibitors in view of the recent PROACTIVE study results [19,28,29]. Of note, HMG-CoA inhibitor therapy has been shown to reduce circulating levels of resistin in humans [30]. This may relate to their inhibitory action on NFκB activation and anti-inflammatory effects rather than specific and selective effects on resistin signaling. Indeed, systemic resistin levels and systemic C-reactive protein levels seem to be closely related, and hence hyperresistinemia may simply be a reflection of inflammation in general and not be specifically related to degenerative arterial disease. In this context, it is important to point out the very recent findings by Bokarewa et al. [18] showing that resistin also accumulates in the inflamed joints of patients with rheumatoid arthritis and correlates with the intra-articular white blood cell count and IL-6 levels. Furthermore, intra-articular injection of resistin in a murine model induced synovitis with pannus formation and cartilage destruction within 4 days [18]. It would be intriguing to similarly study the effects of local resistin overexpression on the vascular wall. These approaches will be important to extend currently available data, which do not yet justify statements of a causal link between resistin and degenerative arterial disease.

At this point, even though resistin may resist a direct link with insulin resistance and the metabolic syndrome, it is tempting to view resistin as part of the low-grade inflammatory state that accompanies visceral obesity and has been linked to cardiovascular diseases (Fig. 1). Hence, in the end, large meals may lead to large arteries, and in this sequence of potentially fatal events resistin may be one but not the only link.

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References


