Resistin: Can we resist its role in insulin resistance?

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Adipose tissue has long been considered a merely passive reservoir of energy. This view started to change in the late 1980s when it was demonstrated that adipose tissue is an important site for the metabolism of sex hormones.[1] In 1994, leptin was discovered as a novel hormone expressed and secreted by adipose tissue and acts primarily on the hypothalamus as a signal of energy sufficiency.[2] This was followed by the discovery and characterization of a myriad of other adipose tissue-derived hormones and bioactive peptides, collectively designated as adipokines.[3] These exciting findings over the last decade have conclusively established the role of adipose tissue as an important endocrine organ with a complex network of afferent and efferent metabolic and endocrine signals.[3]

We have known for a long time that obesity is associated with insulin resistance and the development of diabetes mellitus type 2. It is not clear however how obesity induces insulin resistance. Resistin, a newly discovered adipocyte-derived factor, is a 12.5 kDa polypeptide with a cysteine-rich C-terminal domain.[4] It belongs to a new group of small proteins called resistin-like molecules (RLMs).[4] It is expressed in adipose tissue and is much more abundant in visceral than subcutaneous tissue in rodents.[4] Resistin was initially shown to induce insulin resistance in a rodent model and was thought to represent a potential link between obesity and insulin resistance.[5] This was further supported by the fact that resistin is down-regulated by thiazolidiones, a relatively new class of antidiabetic drugs with insulin sensitizing actions.[5] Furthermore, in vivo treatment with recombinant resistin in rodents induces insulin resistance whereas immunoneutralization of resistin has the opposite effect.[5] The resistin knockout mice model showed no change in weight but did show improved glucose homeostasis and a reduction in gluconeogenesis and hepatic glucose output.[6] In humans, initial studies showed a correlation between serum resistin levels and obesity and/or insulin resistance.[4,7-8] However, it was not too long before these exciting findings of the potential role of resistin in insulin resistance were challenged by conflicting and inconsistent results from rodent and human studies.[4,9-10]

In this issue of the Annals, Drs. Al-Harithy and Al-Ghamdi measured fasting resistin levels in 89 Saudi women; 24 lean, 21 overweight or obese non-diabetic, and 44 diabetic women. They showed a progressive increase in resistin levels with the lowest level in the lean women and the highest in the diabetic patients. The increase in overweight and obese non-diabetic women fell in between. The difference in resistin level between these subgroups was significant, indicating an overall correlation between body weight and insulin resistance and the level of resistin. This suggests a pathophysiological link between resistin and insulin resistance. Moreover, resistin levels were significantly correlated with indices of obesity (weight, hip and waist circumferences, BMI) and measures of insulin resistance (glucose, insulin, and HOMA-IR) in the diabetic subgroup, but only with insulin and homeostasis model

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assessment of insulin resistance (HOMA-IR) in obese non-diabetic subjects, suggesting that resistin levels are more a reflection of insulin resistance than obesity per se. This is further supported by the fact that HOMA-IR is significantly higher in diabetic than obese non-diabetic patients.

The study is a good addition to the literature and helps to clarify the relationship between resistin and insulin resistance. It is unique in that it is one of a few studies assessing this new adipocyte-derived hormone in Saudi subjects, a population with a high prevalence of diabetes and obesity. Although the study demonstrates a clear correlation between insulin resistance, assessed by HOMA-IR, and resistin level, this correlation obviously does not establish a causal relationship. Some additional points are noteworthy. The sample size is quite small, especially in the lean and overweight/obese non-diabetic subgroups. The study included women only and whether the same findings would apply to men is not clear. There is also a significant age difference between the three subgroups. Previous studies showed gender and age-related differences in resistin levels with a tendency for women and older subjects to have higher levels.[7,9,11] A relatively accurate but non-standardized method of measuring glucose, the rapid capillary blood glucose system, which may have a 10% to 15% difference under optimal conditions from the standard laboratory method, was used and this also adds to the variability. The HOMA-IR estimate of insulin sensitivity is an indirect method of measuring insulin resistance, and while in general it correlates with insulin clamp technique, a much more standardized method of estimating insulin resistance, it is not clear whether it has the same accuracy in non-diabetic patients or in diabetic patients with extreme values of glucose. HOMA-IR is also likely to be affected by the oral hypoglycemic agents used in the diabetic subgroup since these drugs affect fasting insulin levels. The investigators wisely excluded patients using insulin since HOMA-IR depends on the endogenous insulin and glucose levels and therefore would be inaccurate if the patient is taking exogenous insulin. It is not clear, however, whether patients using thiazolidindiones were also excluded. Thiazolidindiones have been shown to affect the level of resistin and may contribute to a lower resistin level in diabetic patients.[5] Despite these shortcomings, the study is an interesting contribution to a relatively new and exciting area in endocrinology, and as the authors rightfully indicate, is a call for more studies on this and other adipokines in the Saudi population.

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