EDITORIAL

Insulin resistance: looking back, looking forward[†]

Understanding the role of insulin resistance in diabetes has followed a fascinating path, with more than 20 000 matches in in the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) database having "insulin resistance" as a title term, increasing progressively from the early 1940s (Figure 1).

The first such reference, a commentary in the *British Medical Journal*, stated, "the most characteristic action of insulin is its ability to increase the rate at which the peripheral tissues remove sugar from the blood,"[1] an observation as applicable today as 60 years ago. The insulin resistance typically recognized in clinical practice at that time was associated with the impure insulin preparations then available, with administration of serum from patients with insulin resistance shown to prevent the glucose-lowering effect of insulin in mice, a phenomenon taken as evidence of a relationship to the presence of antibodies to insulin,[2] as was the typical pattern of glucose-lowering with insulin requiring extremely high doses, with the insulin resistance appearing in some cases to be transient.[3] Resistance to administered insulin could also be seen with insulin injection into areas of lipodystrophy.[4]
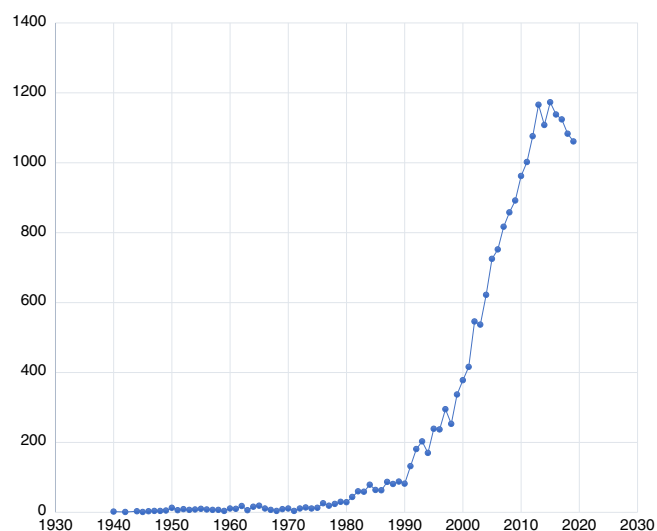

FIGURE 1   PubMed title phrase search for "insulin resistance," number of results per year

Our modern understanding of the nature of insulin resistance began with the development by Yalow and Berson of the technique of radioimmunoassay and its application to the measurement of insulin levels in blood, allowing recognition of the elevated circulating insulin levels seen in many persons with diabetes.[5] This tool led to the understanding that obesity itself is associated with elevation in circulating insulin levels, described by Rabinowitz and Zierler as "a link in the chain of evidence incriminating simple obesity as a precursor of maturity onset stable diabetes."[6] Subsequent work by many groups allowed more precise characterization of the phenomenon of insulin resistance in prediabetes[7] and in obesity,[8] with Reaven integrating what had become a large body of evidence into the recognition that hyperinsulinemia and insulin resistance are associated with a variety of conditions including not only diabetes but also dyslipidemia and hypertension, which he called "syndrome X,"[9] leading to the recognition of what is now described as the metabolic syndrome.[10] Although we can readily recognize the syndrome, determining useful approaches to quantitation of insulin resistance for clinical practice has been elusive - despite the long history of studies such as those from Reaven's group showing that markers such as the steady state plasma glucose after intravenous insulin and glucose can be estimated either from the serum insulin or from the triglyceride level or triglyceride to high-density lipoprotein (HDL) cholesterol ratio.[11] Higher insulin (and triglyceride) levels are predictive of diabetes risk several decades subsequently.[12] As a further example of the potential of such an approach, in a meta-analysis of the use of rosiglitazone, risk of myocardial infarction appeared greater with rosiglitazone treatment in groups with triglyceride levels below 150 mg/dL, whereas rosiglitazone appeared to be associated with reduction in myocardial infarction in those with higher triglyceride levels, who presumably had greater degrees of insulin resistance and hence greater benefit from the insulin sensitizing effect of the thiazolidinedione.[13]

What of current studies of insulin resistance? More than one thousand studies per year have "insulin resistance" as a title term beginning in 2011, so any review of the topic is necessarily limited. Both the Homeostatic

Model for Insulin Resistance (HOMA-IR), calculated from the product of serum insulin and glucose levels, and a triglyceride-based measure were found to be associated with the presence of coronary artery disease (CAD) on computerized tomographic angiography in persons not having diabetes, and HOMA-IR was also associated with CAD among persons with diabetes.[14] Among more than 20 000 persons evaluated in the National Health and Nutrition Examination Survey (NHANES) population-based survey, HOMA-IR, adjusted for a variety of measures including the degree of obesity, was associated with general health condition, with the triglyceride and triglyceride-HDL ratio, with hepatic enzymes, with all the parameters of the complete blood count, and (inversely) with levels of vitamins B6, C, D, and folic acid;[15] interestingly, among nondiabetic but not diabetic persons in NHANES, HOMA-IR was associated with diabetic retinopathy.[16] Insulin resistance has been shown to be associated with abnormal macrophage function, leading to decreased bactericidal response in a peritonitis model.[17] Insulin resistance has also been demonstrated in animal models in cutaneous tissue, in association with impaired barrier function, with increased transepidermal water loss and altered keratin and cell cycle regulatory molecule expression, as well as with increased subcutaneous adipose tissue monocyte chemoattractant protein-1 and with macrophage infiltration of the subcutaneous tissue.[18] Strikingly, insulin resistance is associated with worsening of cognitive function. In a study of persons with serum insulin measurement at age 55, elevated HOMA-IR was associated with decreased executive function and cognitive processing speed at age 70.[19] This and many similar studies have led to the concept that insulin resistance may be an important explanatory factor in the development of Alzheimer's disease,[20] with much evidence pointing to the hippocampus as an insulin responsive tissue playing a major role in memory and involved in age- and diabetes-related cognitive issues.[21] In this regard, it is fascinating that insulin resistance may have epigenetic effects on expression of brain-derived neurotrophic factor, with the potential for multigenerational impairment of memory mechanisms being caused by the insulin resistant state.[22]

The relationship of insulin resistance to obesity has been well demonstrated, and in this regard the progressive increase in obesity prevalence is of great concern.[23] New approaches to insulin sensitization involving leptin,[24] perhaps involving non-thiazolidinedione agents directed at targets such as the PPARγ inhibitor transcriptional co-activator with PDZ-binding (TAZ),[25] or involving metabolomic abnormalities associated with insulin resistance such as branched chain amino acids[26] and bioactive lipids,[27] may ultimately allow us to address this complex and far-reaching set of metabolic disturbances.

Zachary Bloomgarden[1,2]

[1]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York
[2]Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, New York

Correspondence
Zachary Bloomgarden, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029.
Email: zbloom@gmail.com

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