Nutrition Vol. 13, No. 1, 1997

Only the man who is familiar with the art and science of the past is competent to aid in its progress in the future.

—Theodore Billroth

CLASSICS EDITOR:
DONALD McLAREN, MD, PHD

West Sussex, United Kingdom

Role of Insulin Resistance in Human Disease

GERALD M. REAVEN

Reprinted with permission from Diabetes 1988;37:1595

...PROSPECTIVE OVERVIEW

Is Insulin Resistance Becoming a Global Epidemic?

DONALD S. McLAREN, MD, PHD, FRCP

International Centre for Eye Health, Institute of Ophthalmology, London, United Kingdom

When trying to choose for Classic Overview a publication to honor adequately a contribution to nutrition/metabolism knowledge that will fittingly represent the work in question, one is frequently faced with a real dilemma. Not surprisingly, early papers often do little more than skim the surface of the subject and it may be years before the real breakthrough comes, or before an opportunity arises for painstaking research to be synthesized and some unifying concept to emerge.

For at least a quarter of a century experimental animal and clinical studies from the group led by Gerald Reaven, Professor of Medicine at Stanford University School of Medicine in Palo Alto, California, have been reporting steadily on the possible implications of insulin resistance. In 1988 Reaven was honored by the American Diabetes Association and invited to give the Banting Lecture for that year. The published form of this important lecture is the classic cited here.

Reaven paid tribute to Harold Himsworth, Secretary of the Medical Research Council in the UK for many years, for his work that more than 50 y ago differentiated between insulin-dependent and noninsulin-dependent diabetes mellitus (IDDM and NIDDM, respectively). The Stanford researchers have shown that resistance to insulin-stimulated glucose uptake is not only present in nearly all patients with impaired glucose tolerance and NIDDM, but occurs even in about 25% of non-obese individuals with normal oral glucose tolerance. In this paper Reaven developed the concept of what he termed "Syndrome X." Others have subsequently called it Reaven's Syndrome and in a modified form it has been called Metabolic Syndrome.[1] In its original form Syndrome X includes (*1*) resistance to insulin-stimulated glucose uptake; (*2*) glucose intolerance; (*3*) hyperinsulinemia; (*4*) increased very-low-density lipoprotein (VLDL) triglyceride; (*5*) decreased high-density lipoprotein (HDL) cholesterol; and (*6*) hypertension. In addition

(*Continued on page 66*)

Nutrition 13:64–66, 1997

ELSEVIER

0899-9007/97/$17.00
PII: S0899-9007(96)00380-2

Banting Lecture 1988

Role of Insulin Resistance in Human Disease

GERALD M. REAVEN

Resistance to insulin-stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in ~25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the β-cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot be achieved, gross decompensation of glucose homeostasis occurs. The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free-fatty acid (FFA) concentration. Patients with NIDDM are also resistant to insulin suppression of plasma FFA concentration, but plasma FFA concentrations can be reduced by relatively small increments in insulin concentration. Consequently, elevations of circulating plasma FFA concentration can be prevented if large amounts of insulin can be secreted. If hyperinsulinemia cannot be maintained, plasma FFA concentration will not be suppressed normally, and the resulting increase in plasma FFA concentration will lead to increased hepatic glucose production. Because these events take place in individuals who are quite resistant to insulin-stimulated glucose uptake, it is apparent that even small increases in hepatic glucose production are likely to lead to significant fasting hyperglycemia under these conditions. Although hyperinsulinemia may prevent frank decompensation of glucose homeostasis in insulin-resistant individuals, this compensatory response of the endocrine pancreas is not without its price. Patients with hypertension, treated or untreated, are insulin resistant, hyperglycemic, and hyperinsulinemic. In addition, a direct relationship between plasma insulin concentration and blood pressure has been noted. Hypertension can also be produced in normal rats when they are fed a fructose-enriched diet, an intervention that also leads to the development of insulin resistance and hyperinsulinemia. The development of hypertension in normal rats by an experimental manipulation known to induce insulin resistance and hyperinsulinemia provides further support for the view that the relationship between the three variables may be a causal one. However, even if insulin resistance and hyperinsulinemia are not involved in the etiology of hypertension, it is likely that the increased risk of coronary artery disease (CAD) in patients with hypertension and the fact that this risk if not reduced with antihypertensive treatment are due to the clustering of risk factors for CAD, in addition to high blood pressure, associated with insulin resistance. These include hyperinsulinemia, IGT, increased plasma triglyceride concentration, and decreased high-density lipoprotein cholesterol concentration, all of which are associated with increased risk for CAD. It is likely that the same risk factors play a significant role in the genesis of CAD in the population as a whole. Based on these considerations the possibility is raised that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of three major related diseases—NIDDM, hypertension, and CAD. *Diabetes* 37:1595–607, 1988

From the Department of Medicine, Stanford University Medical Center; and the Geriatric Research, Education and Clinical Center, Veterans Administration Medical Center, Palo Alto, California.

Address correspondence and reprint requests to G.M. Reaven, MD, GRECC (182-B), VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

Received for publication 27 June 1988 and accepted in revised form 11 July 1988.

Resistance to insulin-stimulated glucose uptake is a common phenomenon and plays a central role in the pathogenesis and clinical course of several important human diseases. The fact that a large number of patients with diabetes are "insulin insensitive" was first demonstrated by Himsworth (1) ~50 yr ago; on the basis of this finding, he suggested that patients with diabetes should be divided into two categories—insulin sensitive and

a significant portion (perhaps 15%) of the variance in insulin resistance in a community is genetically determined.

In a subsequent review publication, Reaven proposed several possible additions to Syndrome X, namely microvascular angina, hyperuricemia, and plasminogen activator inhibitor 1 (PAI-1).[2] Bjorntorp[1] has always placed central emphasis on the etiologic role of obesity (of the abdominal, truncal, or android type), rather than insulin resistance in what he terms Metabolic Syndrome. Reaven has never accepted this and repeatedly points out that all the elements of Syndrome X as defined above can occur in nonobese individuals. He acknowledges that obesity, per se, can lead to a decrease in insulin-mediated glucose uptake, and weight loss in obese individuals is associated with enhanced in vivo insulin action.[3] He goes on to emphasize that obesity is only one of many environmental influences that modify insulin sensitivity. Habitual physical activity is even more potent.[4] Reaven's hypothesis has been criticized and even refuted,[5] but the consensus seems to be that the ramifications of insulin resistance in some of the common diseases of the 20th century are probably as great as Reaven proposes.

The underlying mechanisms in the interrelated disease processes of Metabolic Syndrome are not fully understood. Until they are, it is unlikely that real progress can be made in controlling and eventually preventing the diseases. Free fatty acids are known to cause insulin resistance in muscle and liver, to increase hepatic gluconeogenesis and lipoprotein production, and perhaps to decrease hepatic clearance of insulin. The capacity of the beta cells of the pancreatic islets to respond in the presence of insulin resistance probably determines whether euglycemia can be maintained despite the onset of early impairment of glucose tolerance, or whether hyperinsulinemia or frank diabetes of the noninsulin type supervenes. Hyperinsulinemia is considered to predispose to hypertension by causing an increase in renal sodium/water reabsorption, sympathetic nervous system activation, decreased sodium/potassium/ATPase activity, increased sodium/hydrogen pump activity, and increased intracellular calcium accumulation. The atherogenic effect of insulin may result from enhanced uptake of cholesterol by atheromatous plaques, increased platelet aggregation, and increased levels of coagulation factors such as fibrinogen and PAI.

In recent years a series of studies by the MRC Environmental Epidemiology Unit at the University of Southampton, U.K., has provided convincing evidence that adverse influences of some kind, possibly nutritional, during intrauterine life resulting in poor growth tend to be associated with a high incidence of the very diseases that have been brought together in Syndrome X.[6]

Other epidemiologic studies among communities that during the past century or so have been undergoing very rapid and radical social changes have shown that NIDDM and some of the other components of Syndrome X have been increasing at an alarming rate during this period. For example, the Pima Indians of Arizona now have the highest reported NIDDM prevalence in the world, about 50% of adults over 35 y of age.[7] In the Pacific island community of Micronesian Nauruans, a decline in the incidence of epidemic glucose intolerance has been reported in recent years.[8] This has been attributed to the death of a high proportion of genetically susceptible individuals.

These are small communities, but it is becoming evident that the same phenomenon is occurring among much larger groups, such as the more than 1.5 million from the Indian subcontinent who have settled in Britain.[9] Their much greater risk of coronary heart disease than the indigenous white population is not explained by the usual risk factors: total cholesterol, hypertension, and smoking. However, insulin resistance, NIDDM, and other components of Syndrome X, such as high plasma triglyceride and very-low-density lipoproteins, and low high-density lipoproteins, are common associations.

REFERENCES

1. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132
2. Reaven GM. Role of insulin resistance in human disease (Syndrome X): an expanded definition. Annu Rev Med 1993;44:121
3. Rosenthal M, Haskell WL, Solomon R, Widstrom A, Reaven GM. Demonstration of a relationship between level of physical training and insulin-stimulated glucose utilization in normal humans. Diabetes 1983;32:408
4. Bogardus C, Lillioja S, Mott DM, Hollenbeck C, Reaven GM. Relationship between degree of obesity and in vivo insulin action in man. Am J Physiol 1985;248:E286
5. Jarrett RJ. In defence of insulin: a critique of syndrome X. Lancet 1992;340:469
6. Barker DJP. (Ed.) *Fetal and infant origins of adult disease.* London: British Medical Association, 1992
7. Wendorf M, Goldfine ID. Archaelogy of NIDDM: excavation of the "thrifty" genotype. Diabetes 1991;40:161
8. Dowse GK, Zimmet PZ, Finch CF, Collins VR. Decline in incidence of epidemic glucose intolerance in Nauruans: implications for the "thrifty genotype." Am J Epidemiol 1991;133:1093
9. Gupta S, de Belder A, Hughes LO. Avoiding premature coronary deaths in Asians in Britain. Br Med J 1995;311:1035