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Insulin Resistance: A Chicken That Has Come to Roost

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ABSTRACT

Insulin-mediated glucose disposal varies approximately 10-fold in apparently healthy human beings. Insulin (I)-resistant individuals can remain glucose tolerant if the pancreas compensates for this defect by secreting large amounts of I. Type 2 diabetes develops when I-resistant persons cannot sustain this state of compensatory hyperinsulinemia (↑ I). However, the ability of ↑ I to prevent decompensation of glucose tolerance is a mixed blessing, and the combination of I resistance and ↑ I predisposes such individuals to develop a series of abnormalities that increase risk of coronary heart disease (CHD). Given the health-related consequences of I resistance and ↑ I, it has been suggested that a "thrifty" genotype exists that favored evolutionary survival by enhancing I secretion and thereby promoting energy accumulation. An alternative view is that conservation of muscle mass was necessary for survival, and that muscle I resistance was the "thrifty"

genotype. This latter hypothesis is more consistent with current data, and there is evidence of a genetic basis for I resistance. In either case, there is little question as to the importance of I resistance and related abnormalities in diseases of Western civilization. However, the strength of the association between I resistance and its consequences varies in magnitude, and it is necessary to emphasize that development of a clinical end-point will vary as a function of (1) degree of I resistance; (2) "closeness" of I resistance to the end-point; and (3) the ability to compensate for the effects of I resistance. I resistance is a physiological characteristic, genetically determined, that helped primitive humans to survive. It is greatly aggravated by obesity and physical inactivity, and represents a modern scourge.

INTRODUCTION

The ability of insulin to mediate glucose disposal varies widely from person to person. [1,2] It has become increasingly obvious that insulin resistance, and the efforts made by the organism to compensate for this defect, play a vital role in the pathogenesis and clinical course of what are often designated as diseases of Western civilization. [3,4] In this presentation, I will (1) briefly summarize the major pathological consequences of insulin resistance; (2) present a hypothesis to explain why health-related consequences of insulin resistance have become so overwhelming; and (3) question the utility of establishing a rigorous definition of what clinical conditions are, and are not, related to insulin resistance, based on a statistical, not a pathophysiological, approach.

WHAT ARE THE MAJOR PATHOPHYSIOLOGICAL CONSEQUENCES ASSOCIATED WITH INSULIN RESISTANCE?

Type 2 Diabetes

The physiological response to insulin resistance is an increase in insulin secretion, and the greater the magnitude of the pancreatic ß-cell response, the more likely an individual will be able to maintain normal oral glucose tolerance. However, even within a group of healthy volunteers, with normal glucose tolerance, the more

insulin resistant the individual, the higher the plasma glucose response. [2] The less able the pancreas is to compensate for insulin resistance, the more likely gross decompensation of glucose homeostasis will occur. This hypothesis was first advanced more than 30 years ago on the basis of cross-sectional measures of plasma insulin and glucose concentration in individuals with varying degrees of glucose tolerance. [5] Evidence was published subsequently, confirming the view that patients with Type 2 diabetes were insulin resistant. [6,7] More recently, results of several longitudinal studies have shown that insulin resistance and/or hyperinsulinemia precede the development of Type 2 diabetes, [8-11] and frank hyperglycemia develops when the pancreatic ß-cell is no longer able to sustain the degree of hyperinsulinemia necessary to maintain normal glucose tolerance. Controversy no longer exists as to the role of insulin resistance in the pathogenesis of Type 2 diabetes, and it is clear that a defect is present in the vast majority of patients with this syndrome. However, what is not as well recognized is that only a relatively minor proportion of insulin-resistant individuals develop Type 2 diabetes. The vast majority of insulin-resistant individuals are able to compensate for this defect by continuing to secrete large amounts of insulin. However, this is, at best, a Pyrrhic victory, as will be emphasized in the remainder of this section.

Hypertension

In 1966, it was noted that patients with high blood pressure had significantly higher plasma insulin concentrations, before and after an oral glucose challenge. [12] Although this observation suggested that insulin resistance may be associated with essential hypertension, it received relatively little attention until recently. Within the past few years, several papers have been published [13-16] showing that this is the case, and there now appears to be widespread agreement that insulin resistance and compensatory hyperinsulinemia are characteristic of patients with essential hypertension.

Although insulin resistance and/or hyperinsulinemia are commonly seen in patients with hypertension, not all patients with high blood pressure are insulin resistant. [17] Thus, arguments continue as to whether or not insulin resistance and/or compensatory hyperinsulinemia play a role in the regulation of blood pressure. Perhaps the simplest answer to this question is that insulin resistance and compensatory hyperinsulinemia are neither necessary nor sufficient for essential hypertension to develop. In this regard, the situation closely resembles the role of insulin resistance in the development of Type 2 diabetes. Hyperglycemia develops in insulin-resistant individuals when they no longer are able to secrete the large amount of insulin necessary to overcome the insulin resistance. In a similar fashion, it seems likely that hypertension only develops when some unknown compensatory response (or responses) is no longer able to overcome the metabolic changes associated with insulin resistance and compensatory hyperinsulinemia that favor an increase in blood pressure.

The evidence in favor of the notion that insulin-resistant subjects are at increased risk to develop hypertension as compared to insulin-sensitive individuals can be summarized as follows.

1. Patients with high blood pressure, as a group, have been shown to be insulin resistant as compared

to normotensive individuals when matched for all relevant confounding variables. [13-16] In addition, a large number of cross-sectional studies have demonstrated that blood pressure and insulin resistance and/or compensatory hyperinsulinemia are significantly correlated. [16,18-23] In the population at large, the most persuasive evidence can be seen in the study published by the European Group for the Study of Insulin Resistance. [23] These investigators examined the relationship between a specific measure of insulin resistance, fasting insulin concentration, and blood pressure in 333 normotensive individuals, evaluated in 20 different clinical research centers. The results indicated that blood pressure was directly related to both insulin resistance and insulin concentration. Furthermore, these relationships were independent of differences in age, gender, and degree of obesity.

2. Insulin resistance does not develop in patients with secondary forms of hypertension. [24,25] Thus, it cannot be argued that high blood pressure, per se, accounts for the association between insulin resistance and essential hyperteusion.
3. Insulin resistance and compensatory hyperinsulinemia are observed in normotensive first-degree relatives of patients with essential hypertension when compared to individuals without a family history of hypertension. [26-30] Furthermore, this difference is independent of variations in age, gender, and either generalized or localized obesity.
4. Four large prospective studies have been published indicating that the presence of hyperinsulinemia, as a surrogate measure of insulin resistance, is a risk factor for the development of hypertension. [31-34] This was true both in adults and children, and the relationship appeared to be independent of differences in gender and both overall and regional obesity. Furthermore, hyperinsulinemia also predicted the development of the dyslipidemia characteristic of insulin-resistant individuals.

In summary, considerable evidence exists in support of a strong relationship between insulin resistance and essential hypertension. That not all patients with essential hypertension are insulin resistant simply emphasizes the fact that this is a complex syndrome, and it should not be surprising that blood pressure may increase for any one of several reasons. However, once this is acknowledged, it is even more important to accept the notion that insulin-resistant individuals are clearly at increased risk to develop essential hypertension.

Coronary Heart Disease

Coronary heart disease (CHD) is the major cause of morbidity and mortality in patients with Type 2 diabetes or hypertension. Given the importance of insulin resistance in the pathogenesis of these two syndromes, it is obvious that it also plays a central role in the etiology of CHD. In addition to Type 2 diabetes and hypertension, insulin resistance is associated with a cluster of risk factors for CHD, [3,4] including relatively higher plasma glucose concentrations, a dyslipidemia characterized by higher triglyceride and lower HDL-cholesterol concentrations, smaller, denser LDL particles, an accentuated degree of postprandial lipemia, and increased concentrations of plasminogen activator inhibitor-1 (PAI-1). Any one, or combination of them, would be viewed as increasing risk of CHD. In addition, two

reports have recently been published [35,36] showing a significant relationship between insulin resistance and ultrasound evidence of carotid artery thickening. These studies have been interpreted as evidence that insulin resistance, per se, may lead to enhanced atherogenesis. In this context, we have recently published evidence from a prospective study that insulin resistance was a significant predictor of CHD in a group of healthy volunteers. [37]

In light of the above evidence, it is apparent that the risk of CHD is drastically increased in insulin-resistant individuals. Whether this relationship is due primarily to insulin resistance, or to one or another of its manifestations, does not seem to be a particularly fruitful issue to focus on at this time. A much more useful approach would be to acknowledge the importance of insulin resistance *and* its related manifestations, and begin educating both the public and health care professionals that hypercholesterolemia is not the only issue to address in efforts to prevent CHD.

WHY HAVE THE HEALTH-RELATED CONSEQUENCES OF INSULIN RESISTANCE BECOME SO OVERWHELMING?

In 1962, when addressing the question of why the prevalence of Type 2 diabetes was increasing at such an alarming rate, Neel proposed that the diabetic genotype must have been of survival benefit to primitive human beings. [38] Phenotypically, the "thrifty" genotype was postulated to involve a "quick insulin trigger," minimizing urinary glucose loss when fasting was replaced by feasting, helping primitive man survive fasting by storing energy more efficiently.

Another view as to how primitive man survived famine was proposed by Cahill and associates, [39-42] who postulated that the crucial element necessary to withstand famine was the ability to conserve as much muscle protein as possible. By so doing, the individual was able to hunt successfully at the first opportunity, as well as protect himself when preyed upon. A major impediment to human beings of accomplishing this goal was the presence of a nervous system which was relatively hypertrophied compared to other animals and which required a constant supply of substrate throughout the period of deprivation.

The difference between these two hypotheses as to how primitive man survived famine is substantial.

Neel believed the essential attribute to be a "quick insulin trigger" leading to more efficient accumulation of energy, thus permitting primitive man to survive a fast longer. The alternative view, based upon the work of Cahill and colleagues, states that the more efficient one is in conserving muscle protein, the better the chances of survival. One theory focuses on energy storage, the other on maintaining muscle mass. In light of available data, it seems most likely that the phenotype Neel was searching for was muscle insulin resistance, and the view of muscle insulin resistance as the thrifty gene offers the most likely explanation of the emerging epidemic Type 2 diabetes, hypertension, and CHD.

Enhanced Energy Storage versus Maintenance of Muscle Mass

The left side of Figure 1 displays the "thrifty gene" helping primitive man survive famine as described by Neel. When feasting, the "quick insulin trigger" and ensuing hyperinsulinemia decrease urinary loss of glucose, and lead to enhanced energy storage. The consequences of a quick insulin trigger for modern man, faced with a longer life span, obesity, and decreased physical activity, are outlined in the right portion of Figure 1. As formulated by Neel, the hyperinsulinemia associated with the quick insulin trigger in modern man leads to a state of *secondary* insulin resistance, followed by ß-cell failure, and Type 2 diabetes.

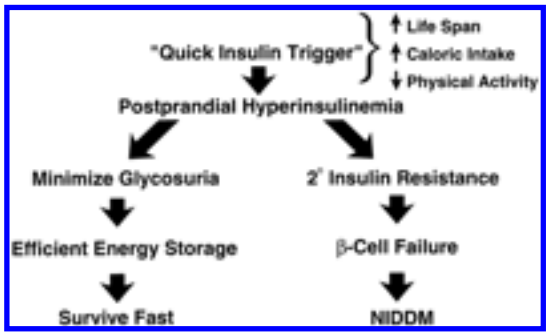

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FIGURE 1. "Thrifty" genotype: the advantages of a "quick insulin trigger" to primitive man as suggested by Neel are seen on the left. The disadvantages of this phenotype to modern man, and how it leads to Type 2 diabetes, are depicted on the right. (From Reaven. [57] Reprinted with permission of *Diabetologia*.)

Figure 2 displays an analysis of the impact of *primary* muscle insulin resistance on glucose metabolism in primitive and modern man. As seen on the left, muscle insulin resistance conserves glucose for use by the central nervous system, decreasing the amount of muscle protein needed to be converted to glucose. As a result, muscle mass is preserved, thereby increasing the likelihood of a successful search for food. The muscle insulin resistance that permitted primitive man to survive is accentuated by the increased longevity, sedentary lifestyle, and obesity of modern man as depicted on the right. At some point, the combined burden of muscle insulin resistance and lifestyle can no longer be overcome by compensatory

hyperinsulinemia, and Type 2 diabetes occurs.

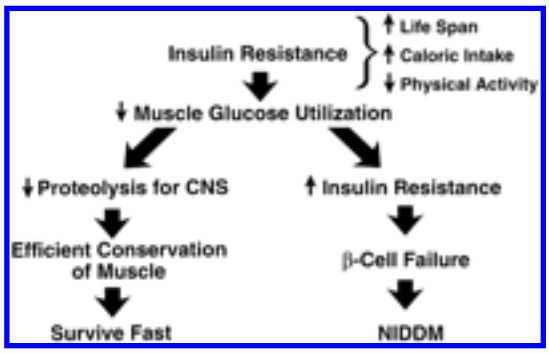

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FIGURE 2. "Not-so-thrifty" genotype: an alternative view, based on the experimental studies by Cahill and colleagues. The survival advantages of muscle insulin resistance to primitive man are illustrated on the left. The sequence on the right outlines how such an "advantage" can lead to Type 2 diabetes in modern man. (From Reaven. [57] Reprinted with permission of *Diabetologia*.)

Does the Neel Genotype Predict the Epidemic of States of Glucose Intolerance?

Available evidence strongly suggests that a quick insulin trigger, leading to more efficient energy storage, is not the phenotype that predicts loss of glucose tolerance. For example, in normal glucose-tolerant individuals, there is evidence [2] that the more insulin *resistant* glucose-tolerant individuals are, and the *lower* their early insulin response to glucose, the higher will be their plasma glucose response to oral glucose. Similarly, cross-sectional studies of non-diabetic, first-degree relatives of patients with Type 2 diabetes indicate that they are insulin resistant, with no evidence of a quick insulin trigger. [43,44] Turning now to prospective studies of true pre-diabetic subjects, the evidence indicates that insulin resistance, not insulin sensitivity, significantly predicts conversion to Type 2 diabetes, accompanied by either a normal or reduced acute insulin response. [8-11] Finally, studies of the progression of patients with impaired glucose tolerance (IGT) to Type 2 diabetes have also identified insulin resistance and a low insulin response as the predictors of this conversion. [45] Based upon the results of the above studies and the absence of contradictory data, the evidence in normal glucose-tolerant individuals, non-diabetic first-degree relatives of patients with Type 2 diabetes, pre-diabetic subjects, and patients with IGT demonstrates that neither a quick insulin trigger nor insulin-sensitive tissues predict progression of Type 2 diabetes.

Is There Evidence that Muscle Insulin Resistance Is under Genetic Regulation?

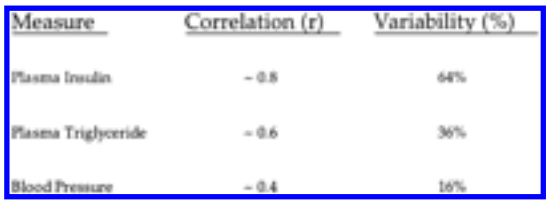
Given the view that muscle insulin resistance could have provided primitive man with a useful survival advantage, and that this phenotype predicts an inability to maintain normal glucose homeostasis in modern man, it seems relevant to ask what evidence is there that insulin-mediated glucose disposal is genetically related. Unfortunately, at this time this evidence is primarily indirect. For example, cross-

sectional studies [46] show that in healthy volunteers of European ancestry and Pima Indians that only 50% of the variance in insulin-mediated glucose disposal from person to person could be accounted for by known acquired variables like obesity, level of physical activity, age, etc. By inference it was suggested that genetic factors accounted for the remaining 50% of the observed variability. More specifically, direct measures of insulin-mediated glucose disposal in family members demonstrated that *in vivo* insulin action was a familial characteristic in non-diabetic Pima Indians. [47] Essentially identical data have also been found in a somewhat similar study in family members of European ancestry. [48] Finally, it is clear that the alarming increase in the incidence of Type 2 diabetes is occurring primarily in non-European ethnic groups, and the same populations have been shown to be more insulin resistant than well-matched populations of European ancestry. [49-51] Evidence that insulin resistance varies as a function of either familiality or ethnicity certainly supports the view that muscle insulin resistance is, at least to some extent, a genetically determined characteristic.

TO CLUSTER OR NOT TO CLUSTER?

With general acceptance of the notion that a cluster of abnormalities is associated with insulin resistance, a number of new issues have begun to receive attention. Among them has been the use of statistical methods in the analysis of population data to decide what abnormalities do or do not comprise Syndrome X, or the insulin-resistant syndrome. I believe this approach, which fundamentally ignores physiological relationships between insulin resistance and its many manifestations, is likely to lead to more confusion than insight.

Figure 3 displays estimates of the correlation coefficients between insulin resistance and three of its manifestations typical of what would obtain in populations at large. Not surprisingly, the closest relationship is between insulin resistance and compensatory hyperinsulinemia. However, the relationship is far from perfect, accounting for only two-thirds of the variability in the plasma insulin response to glucose. This should not be surprising, given physiological information that the plasma insulin response to glucose is a complex function of at least three variables: insulin resistance, insulin secretory capacity, and insulin catabolism.



Measure	Correlation (r)	Variability (%)
Plasma Insulin	~ 0.8	64%
Plasma Triglyceride	~ 0.6	36%
Blood Pressure	~ 0.4	16%

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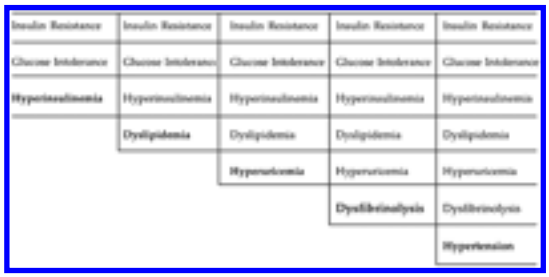
FIGURE 3. Estimates from published data of the relationship between resistance to insulin-mediated glucose disposal and putative related variables.

The more the number of factors controlling a given manifestation of insulin resistance, the lower will be the magnitude of its relationship to insulin resistance; more to the point, the less likely that the manifestation will be discerned by cluster analysis to be related to insulin resistance. Thus, of the three manifestations shown in Figure 3, it is certain that hyperinsulinemia is identified as being associated with insulin resistance. Hypertriglyceridemia is also likely to end up in the same cluster with insulin resistance, whereas hypertension almost certainly will not be recognized as belonging to Syndrome X.

The thrust of this point is enlarged in Figure 4, which uses published data to predict the likelihood of the "clusters" that will be identified as belonging to Syndrome X. Again the abnormality least likely to be included will be essential hypertension.



Insulin Resistance	Insulin Resistance	Insulin Resistance	Insulin Resistance	Insulin Resistance
Glucose Intolerance	Glucose Intolerance	Glucose Intolerance	Glucose Intolerance	Glucose Intolerance
Hyperinsulinemia	Hyperinsulinemia	Hyperinsulinemia	Hyperinsulinemia	Hyperinsulinemia
	Dyslipidemia	Dyslipidemia	Dyslipidemia	Dyslipidemia
		Hyperuricemia	Hyperuricemia	Hyperuricemia
			Dysfibrinolysis	Dysfibrinolysis
				Hypertension

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FIGURE 4. Theoretical likelihood that a postulated manifestation of insulin resistance will "cluster" with insulin resistance, based upon statistical analysis of epidemiologic data. This figure suggests that the most likely cluster will include insulin resistance, plasma glucose concentration, and plasma insulin concentration. The abnormality *least* likely to cluster with insulin resistance will be hypertension.

The fact that essential hypertension may not "cluster" with insulin resistance is not surprising. Insulin resistance is only present in approximately 50% of patients with essential hypertension. [17] Furthermore, the failure of essential hypertension to "cluster" with insulin resistance cannot be interpreted to mean, as

has been the case, that the two are unrelated. The extensive evidence, presented above, that insulin resistance plays an important role in the pathogenesis of essential hypertension will not be reviewed again. However, information pertaining to the relationship between insulin resistance, its manifestations, essential hypertension, and CHD risk is worth discussion.

The advent of more effective antihypertensive drugs has greatly decreased morbidity and mortality in patients with high blood pressure. However, the clinical benefit of lowering blood pressure has been much more dramatic in decreasing risk of stroke as compared to heart attack. [52] Because heart attack is the major cause of morbidity and mortality in patients with hypertension, this apparent paradox has received a great deal of attention. Not surprisingly, many different explanations have been proposed to account for this unwelcome finding. For example, it has been argued that stroke is more directly related to blood pressure than is heart attack, and that the apparent difference in outcome is a function of the relatively short duration of the intervention trials. Another suggestion has been that the problem lies with the fact that thiazide diuretics and/or beta receptor antagonists, the drugs used in the controlled clinical trials, have untoward effects on carbohydrate and lipid metabolism that tended to mitigate their beneficial effects on blood pressure. Although this may be true to some extent, there is a much simpler explanation of the apparent paradox between lowering blood pressure and CHD. Specifically, patients with high blood pressure, as a group, tend to be insulin resistant, glucose intolerant, hyperinsulinemic and dyslipidemic, changes recognized as increasing the risk of CHD in normotensive individuals. [13-16,53] More direct evidence that the metabolic changes associated with hypertension may be the link between high blood pressure and CHD can be derived from the results of a recent study of untreated hypertensive patients, without clinical evidence of CHD, who either had or did not have ischemic heart disease by Minnesota Code criteria. [54] Glucose tolerance test results from this study demonstrated that hypertensive patients with electrocardiographic evidence of ischemic heart disease were somewhat glucose intolerant, insulin resistant, and hyperinsulinemic as compared to either healthy volunteers and patients with high blood pressure and normal electrocardiograms. Patients with high blood pressure and an abnormal electrocardiogram were also dyslipidemic as compared to normotensive individuals or hypertensive patients with normal electrocardiograms.

More recently, we have presented preliminary data [55] providing a mechanism to account for the apparent increase in the prevalence of CHD in patients with hypertension who are also insulin resistant. Specifically, we have shown that the adherence of isolated mononuclear cells to cultured endothelium is enhanced in patients with hypertension. Furthermore, the more insulin resistant an individual, the greater was the avidity of their isolated mononuclear cells for endothelium. Because the adherence of circulation mononuclear cells to endothelium represents an early step in atherogenesis, [56] the relevance of these results to the pathogenesis of CHD in patients with hypertension is self-evident.

In summary, depending on the population studied, insulin resistance and/or hyperinsulinemia may or may not "cluster" with blood pressure in population-based studies. On the other hand, it is quite clear that (1) insulin resistance and/or hyperinsulinemia predicts the development of hypertension in normotensive

individuals; (2) blood pressure and insulin-mediated glucose disposal are significantly correlated; (3) the prevalence of insulin resistance and its manifestations is significantly increased in patients with essential hypertension; and (4) surrogate and clinical markers of CHD are greatly increased in patients with hypertension who are also insulin resistant. Based upon these conditions, it is clear that insulin resistance and its manifestations play a significant role in the pathogenesis and clinical course of patients with essential hypertension. In this light, epidemiological conclusions that insulin resistance and hypertension do not "cluster" do not seem very relevant.

CONCLUSION

The ability of insulin to stimulate glucose uptake varies widely from person to person. In an effort to maintain normal plasma glucose concentrations, the pancreatic ß-cell will attempt to secrete whatever amount of insulin is required to accomplish this goal. If this compensatory effort is not successful, insulin-resistant individuals develop Type 2 diabetes. Normal, or near-normal, glucose tolerance is maintained as long as insulin-resistant individuals are able to sustain a state of chronic hyperinsulinemia. Unfortunately, this represents a dubious victory, and the combination of insulin resistance and hyperinsulinemia places an individual at risk to develop some degree of glucose intolerance, hypertension, and multiple other abnormalities that increase risk of coronary heart disease. The prevalence of clinical syndromes related to insulin resistance is increasing at epidemic proportions, and an attractive hypothesis to account for this phenomenon is that muscle insulin resistance is the phenotypic expression of a genotype that helped primitive human beings survive. Unfortunately, longer life span, increased obesity, and a sedentary lifestyle have transformed what was formerly a useful genotype into the major cause of what is often referred to as diseases of Western civilization. Finally, caution is urged in the interpretation of statistical analyses applied to population-based epidemiologic data to determine which abnormalities are, or are not, related to insulin resistance.

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ARTICLES

Variations in insulin-stimulated glucose uptake in healthy individuals with normal glucose tolerance

C Hollenbeck and GM Reaven

Measurements were made of both glucose disposal (M) during hyperinsulinemic clamp studies and plasma glucose and insulin responses to an oral glucose challenge in 100 individuals with normal glucose tolerance. The subjects were divided into 4 quartiles on the basis of M values, ranging from a low mean (+/- SEM) value of 140 +/- 3 mg/m2 X min (quartile 1) to a high of 349 mg/m2 X min (quartile 4). The plasma insulin response to oral glucose inversely correlated with the M value (r = -0.60; P less than 0.001), being highest in those with the lowest M (quartile 1) and lowest in those with the highest M (quartile 4). On the other hand, the plasma glucose responses of the 4 quartiles were virtually identical. These results document that insulin-stimulated glucose uptake varies widely in subjects with normal glucose tolerance, and that these differences are independent of any change in the plasma glucose response to oral glucose. Furthermore, the results indicate that insulin resistance in normal individuals is associated with hyperinsulinemia.

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ARTICLES

Insulin resistance and insulin secretion are determinants of oral glucose tolerance in normal individuals

GM Reaven, RJ Brand, YD Chen, AK Mathur and I Goldfine
Department of Medicine, Stanford University School of Medicine, Palo Alto, California.

Plasma glucose values after oral glucose challenge vary widely in nondiabetic subjects. We have now evaluated the role of insulin resistance in determining the plasma glucose response to oral glucose in 74 volunteer subjects with normal glucose tolerance. In these subjects, we determined the plasma glucose and insulin responses over a 3-h period to a 75-g oral glucose challenge, and the steady-state plasma glucose concentration during a continuous infusion of somatostatin, glucose, and insulin (a quantitative measure of insulin resistance). The plasma glucose response was defined as the incremental increase in plasma glucose concentration above the fasting value for 3 h after the oral glucose challenge. Multiple regression analysis was used to define the relationship between the dependent variable (plasma glucose response) and various predictors of this response. These analyses indicated that both the steady-state plasma glucose and the incremental insulin response during the first 30 min after the glucose load were significant predictors of the plasma glucose response. In those individuals in whom insulin action was impaired and the 30-min plasma insulin response was decreased, plasma glucose values reached higher levels. When standardized regression coefficients were determined, the incremental glucose response was directly correlated with steady-state plasma glucose ($r = 0.700$, $P < 0.001$) and inversely with the insulin response during the first 30 min ($r = 0.268$, $P = 0.023$). Furthermore, the correlation between steady-state plasma glucose and glucose response was significantly greater ($P < 0.005$) than that between the glucose response and 30-min insulin concentration.(ABSTRACT TRUNCATED AT 250 WORDS)

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☐ **1:** Physiol Rev 1995 Jul;75(3):473-86

Pathophysiology of insulin resistance in human disease.

Reaven GM.

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The ability of insulin to stimulate glucose uptake varies widely from person to person, and these differences, as well as how the individual attempts to compensate for them, are of fundamental importance in the development and clinical course of what are often designated as diseases of Western civilization. Evidence is presented that non-insulin-dependent diabetes mellitus (NIDDM) results from a failure on the part of pancreatic beta-cells to compensate adequately for the defect in insulin action in insulin-resistant individuals. In addition, a coherent formulation of the physiological changes that lead from the defect in cellular insulin action to the loss in glucose homeostasis is presented. However, the ability to maintain the degree of compensatory hyperinsulinemia necessary to prevent loss of glucose tolerance in insulin-resistant individuals does not represent an unqualified homeostatic victory. In contrast, evidence is presented supporting the view that the combination of insulin resistance and compensatory hyperinsulinemia predisposes to the development of a cluster of abnormalities, including some degree of glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, high blood pressure, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plaminogen activator inhibitor 1. The cluster of changes associated with insulin resistance has been said to comprise syndrome X, and all of the manifestations of syndrome X have been shown to increase risk of coronary heart disease. Thus it is concluded that insulin resistance and its associated

abnormalities are of utmost importance in the pathogenesis of NIDDM, hypertension, and coronary heart disease.

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Reaven G, Miller R.

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Shen SW, Reaven GM, Farquhar JW.

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☐ **1:** J Clin Invest 1975 Mar;55(3):454-61

Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia.

Ginsberg H, Kimmerling G, Olefsky JM, Reaven GM.

We have used a continuous intravenous infusion of glucose (6 mg/kg/min), insulin (80 mU/min), epinephrine (6 mug/min), and propranolol (0.08 mg/min) to directly assess insulin resistance in 14 untreated adult onset diabetics with a mean (plus or minus SE) fasting plasma glucose level of 217 plus or minus 17 mg/100 ml. During the infusion endogenous insulin secretion is inhibited and steady-state plasma glucose and insulin levels are achieved after 90 min. Since similar steady-state levels of plasma insulin are achieved in all subjects, the plasma glucose concentration observed during the steady-state period is a measure of an individual's insulin resistance. Under these conditions, the mean (plus or minus SE) steady-state plasma glucose level of the 14 diabetic patients was 350 plus or minus 16 mg/100 ml, while that of 12 normal subjects was 121 plus or minus 4 mg/100 ml. Additional studies were performed in which control subjects and patients with diabetes had their fasting plasma glucose levels acutely raised or lowered to comparable levels before receiving the basic infusion mixture of glucose, insulin, epinephrine, and propranolol. The results of these studies indicated that differences in initial plasma glucose levels could not account for the different glucose responses of the two groups to the basic infusion. Finally, the mean (plus or minus SE) steady-state plasma glucose level of 104 plus or minus 17 mg/100 ml observed during the same basic infusion in five patients with fasting hyperglycemia (mean plus or minus SE, 142 plus or minus 12 mg/100 ml) secondary to chronic pancreatitis suggested that neither chronic hyperglycemia nor hypoinsulinemia per se necessarily lead to insulin resistance. These results demonstrate that marked insulin resistance exists in adult onset diabetics with fasting hyperglycemia. Since

previous studies have documented the presence of insulin resistance in patients with chemical diabetes, the possibility exists that insulin resistance may be characteristic of adult onset diabetes mellitus.

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ARTICLES

Plasma insulin response among Nauruans. Prediction of deterioration in glucose tolerance over 6 yr

RA Sicree, PZ Zimmet, HO King and JS Coventry

A longitudinal study of 266 randomly selected nondiabetic Nauruans [215 with normal tolerance and 51 with impaired glucose tolerance (IGT)] over 6 yr showed that deterioration in glucose tolerance status had occurred in 61 subjects. Of the subjects with initially normal tolerance, 34 (16%) progressed to IGT and 14 (6.5%) progressed to diabetes. Thirteen of the subjects with IGT (25%) progressed to diabetes. Subjects were examined in 1975 through 1976, and follow-up examinations were performed in 1982. After age, a high 2-h plasma insulin response to a glucose load was the factor most predictive of progression from normal tolerance to both diabetes (P less than .001) and IGT (P less than .01). Both a high 2-h glucose level and greater obesity independently predicted progression from IGT, and a diminished 2-h insulin response just failed to significantly improve the model (P less than .06). The negative parameter of the insulin response associated with deterioration from IGT differed significantly (P less than .01) from the positive-parameter estimate of the response associated with progression to diabetes from normal tolerance (P less than .01), implying a qualitative difference between these nondiabetic subgroups. The use of a glucose-insulin interaction term to predict progression to diabetes for all nondiabetic subjects confirmed this difference; this term's addition improved the model (P less than .01), and progression to diabetes was associated with a high insulin response for 2-h glucose less than 7.8 mM but a low response for 2-h glucose greater than 7.8 mM.

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Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents.

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OBJECTIVE: To determine whether insulin resistance or insulin deficiency is primary in the pathogenesis of type II diabetes. DESIGN: Cohort analytic study of persons with normal glucose tolerance but with a high risk for developing type II diabetes (average follow-up time, 13 years). SETTING: Outpatients had an intravenous glucose tolerance test and were contacted periodically to ascertain diagnoses of diabetes. PARTICIPANTS: One hundred and fifty-five normal offspring, ranging in age from 16 to 60 years, of two parents with type II diabetes and 186 normal control subjects in the same age range who had no family history of diabetes. MEASUREMENTS AND MAIN RESULTS: Two phenotypic characteristics distinguished the offspring of diabetic parents from control subjects. They had slower glucose removal rates (Kg) (P less than 0.01) and higher insulin levels (fasting and during the second phase of insulin response to intravenous glucose; P less than 0.0001) than did control subjects, even after adjustment for differences in obesity. Sixteen percent of the offspring developed type II diabetes. Mean Kg at baseline was 1.7%/min among offspring who subsequently developed diabetes, 2.2%/min among offspring who remained nondiabetic, and 2.3%/min among control subjects. Corresponding means for first-phase insulin were 498, 354, and 373 pM, respectively, whereas second-phase insulin means were 329, 117, and 87 pM, respectively. In multivariate

analysis, low Kg and high serum insulin levels independently increased the risk for developing diabetes among the offspring of diabetic parents. CONCLUSIONS: One to two decades before type II diabetes is diagnosed, reduced glucose clearance is already present. This reduced clearance is accompanied by compensatory hyperinsulinemia, not hypoinsulinemia, suggesting that the primary defect is in peripheral tissue response to insulin and glucose, not in the pancreatic beta cell.

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ARTICLES

Incidence of type II diabetes in Mexican Americans predicted by fasting insulin and glucose levels, obesity, and body-fat distribution

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Few data exist on predictors of non-insulin-dependent (type II) diabetes mellitus. We examined body mass index (BMI), ratio of subscapular-to-triceps skin fold (centrality index), and fasting glucose and insulin concentrations as predictors of decompensation to type II diabetes in Mexican Americans, a population at high risk for this disorder. Twenty-eight of 474 initially nondiabetic Mexican Americans developed type II diabetes after 8 yr of follow-up. Converters to diabetes were older and had higher BMIs, centrality indices, and fasting glucose and insulin concentrations than nonconverters. Subjects in the highest quartile of the insulin distribution had 6.6 times the risk of developing type II diabetes as subjects in the remaining three quartiles combined (95% confidence interval [CI] = 3.14-13.7). In multivariate analysis, fasting glucose (odds ratio [OR] = 5.80, 95% CI = 2.57-13.1) and insulin (OR = 3.12, 95% CI = 1.36-7.14) remained significantly related to conversion to diabetes. However, BMI and centrality index, which were significantly related to conversion in the univariate analysis, were no longer significant in the multivariate analysis once glucose and insulin concentrations were taken into consideration, suggesting that the effect of these variables may be mediated by insulin resistance. Nearly half of the incident cases developed in a subset of the population who were simultaneously in the highest quartile of both fasting insulin and glucose concentrations (population-attributable risk 44.2%). Our results support the insulin resistance/pancreatic exhaustion theory of type II diabetes.

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ORIGINAL ARTICLE

◀ Previous Volume 329:1988-1992 December 30, 1993 Number 27 Next ▶

Insulin Resistance and Insulin Secretory Dysfunction as Precursors of Non-Insulin-Dependent Diabetes Mellitus: Prospective Studies of Pima Indians

Stephen Lillioja, David M. Mott, Maximilian Spraul, Robert Ferraro, James E. Foley, Eric Ravussin, William C. Knowler, Peter H. Bennett, and Clifton Bogardus

ABSTRACT

Background The relative roles of obesity, insulin resistance, insulin secretory dysfunction, and excess hepatic glucose production in the development of non-insulin-dependent diabetes mellitus (NIDDM) are controversial. We conducted a prospective study to determine which of these factors predicted the development of the disease in a group of Pima Indians.

Methods A body-composition assessment, oral and intravenous glucose-tolerance tests, and a hyperinsulinemic-euglycemic clamp study were performed in 200 nondiabetic Pima Indians (87 women and 113 men; mean [±SD] age, 26 ±6 years). The subjects were followed yearly thereafter for an average of 5.3 years.

Results Diabetes developed in 38 subjects during follow-up. Obesity, insulin resistance (independent of obesity), and low acute plasma insulin response to intravenous glucose (with the degree of obesity and insulin resistance taken into account) were predictors of NIDDM. The six-year cumulative incidence of NIDDM was 39 percent in persons with values below the median for both insulin action and acute insulin response, 27 percent in those with values below the median for insulin action but above that for acute insulin response, 13 percent in those with values above the median for insulin action and below that for acute insulin response, and 0

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in those with values originally above the median for both characteristics.

Conclusions Insulin resistance is a major risk factor for the development of NIDDM. A low acute insulin response to glucose is an additional but weaker risk factor.

Source Information

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Insulin resistance in essential hypertension

E Ferrannini, G Buzzigoli, R Bonadonna, MA Giorico, M Oleggini, L Graziadei, R Pedrinelli, L Brandi, and S Bevilacqua

Abstract

High blood pressure is prevalent in obesity and in diabetes, both conditions with insulin resistance. To test whether hypertension is associated with insulin resistance independently of obesity and glucose intolerance, we measured insulin sensitivity (using the euglycemic insulin-clamp technique), glucose turnover (using [3H]glucose isotope dilution), and whole-body glucose oxidation (using indirect calorimetry) in 13 young subjects (38 +/- 2 years [+/- SEM]) with untreated essential hypertension (165 +/- 6/112 +/- 3 mm Hg), normal body weight, and normal glucose tolerance. In the postabsorptive state, all measures of glucose metabolism were normal. During steady-state euglycemic hyperinsulinemia (about 60 microU per milliliter), hepatic glucose production and lipolysis were effectively suppressed, and glucose oxidation and potassium disposal were normally stimulated. However, total insulin-induced glucose uptake was markedly impaired (3.80 +/- 0.32 vs. 6.31 +/- 0.42 mg per minute per kilogram of body weight in 11 age- and weight-matched controls, P less than 0.001). Thus, reduced nonoxidative glucose disposal (glycogen synthesis and glycolysis) accounted for virtually all the defect in overall glucose uptake (1.19 +/- 0.24 vs. 3.34 +/- 0.44 mg per minute per kilogram, P less than 0.001). Total glucose uptake was inversely related to systolic or mean blood pressure (r = 0.76 for both, P less than 0.001). These results provide preliminary evidence that essential hypertension is an insulin-resistant state. We conclude that this insulin resistance involves glucose but not lipid or potassium metabolism, is located in peripheral tissues but not the liver, is limited to nonoxidative pathways of intracellular glucose disposal, and is directly correlated with the severity of hypertension.

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ARTICLES

Resistance to insulin-stimulated-glucose uptake in patients with hypertension

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Plasma glucose and insulin responses to a glucose challenge and insulin- stimulated glucose uptake were measured in 24 age-, weight-, and sex- matched Chinese men (8 with normal blood pressure, 8 with untreated hypertension, and 8 patients with hypertension treated with thiazide and beta-adrenergic antagonist drugs). Plasma glucose and insulin responses were determined by measuring plasma glucose and insulin concentrations before and at 30-min intervals for 2 h after a 75-g oral glucose dose. Insulin-stimulated glucose uptake was estimated by measuring the steady state plasma glucose (SSPG) and insulin (SSPI) concentrations achieved during the last 60 min of a 180-min continuous infusion of somatostatin, insulin, and glucose (insulin suppression test). Under these conditions endogenous insulin secretion was suppressed, and similar SSPI concentrations were achieved in all men; thus, the differences in the resultant SSPG concentrations allowed direct comparison of insulin's ability to stimulate disposal of an identical glucose load in different individuals. The results indicated that the men with hypertension, whether treated or untreated, had significantly elevated plasma glucose (P less than 0.001) and insulin (P less than 0.001) responses to the oral glucose dose compared to the normal men. Mean (+/- SE) SSPG concentrations were also higher (P less than 0.001) in the men with either untreated hypertension [219 +/- 9 mg/dL (12.2 +/- 0.5 mmol/L)] or treated hypertension [211 +/- 18 mg/dL (11.7 +/- 1.0 mmol/L)] than in the normal men [134 +/- 13 mg/dL (7.4 +/- 0.7 mmol/L)]. Since the mean SSPI concentrations were similar in the 3 groups [approximately 70 microU/mL (502 pmol/L)], insulin was less effective in promoting glucose disposal in both groups with hypertension. These results document the fact that

patients with hypertension, whether treated or untreated, are insulin resistant, hyperglycemic, and hyperinsulinemic compared to a well-matched control group.

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