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Insulin Resistance: The Linchpin Between Obesity and Obesity-Related Metabolic Abnormalities

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Introduction

Based upon measures of body mass index (BMI), it has been estimated[1] that more than 50% of the U.S. population is overweight (BMI>25 kg/m2), with ~20% designated as being obese (BMI>30 kg/m2). The disease-related implications of the "obesity epidemic" have received an enormous amount of publicity in the popular media, but public awareness of the risks of excess weight has not led to an effective approach to dealing with the dilemma. The gravity of the problem is accentuated in light of the report that approximately only 50% of physicians polled provided weight loss counseling[2] and that pharmacological treatment of weight loss has not been used appropriately in overweight/obese individuals.[3]

Glossary of Abbreviations
BMI: Body Mass Index
CRP: C-Reative Protein
CVD: Cardiovascular Disease
HDL-C: High-Density Lipoprotein Cholesterol
IFG: Impaired Fasting Glucose
IST: Insulin Suppression Test
LDL: Low-Density Lipoprotein
SSPG: Steady-State Plasma Glucose
SSPI: Steady-State Plasma Insulin
TG: Triglyceride
2DM: Type 2 Diabetes

Given the importance of excess adiposity as increasing risk of cardiovascular disease (CVD), type 2 diabetes (2DM) and hypertension,[4-6] and the combination of an increase in the prevalence of overweight/obesity and a health care system unprepared to deal with this situation, it is essential that thought be given as to how to address this dilemma. In this context, it must be emphasized that CVD, 2DM and hypertension are characterized by resistance to insulin-mediated glucose disposal,[7,8] and that insulin resistance, as well as the compensatory hyperinsulinemia associated with insulin resistance, have been shown to be independent predictors of all three clinical syndromes.[9-11]

It also has been apparent for many years that overweight/obese individuals tend to be insulin-resistant and become more insulin-sensitive with weight loss.[12] In light of these observations, it seems reasonable to suggest that insulin resistance is an important link between overweight/obesity and the adverse metabolic changes associated with excess adiposity. Based on this fundamental assumption, our research group has performed a series of studies over the past several years in an effort to provide new information that might make the clinical approach to the overweight/obese individual more effective. The results of these efforts provide the framework of this presentation.

Obesity Does Not Equal Insulin Resistance

The number of individuals in need of medical assistance would overwhelm the health care system if all overweight/obese individuals were insulin-resistant and at increased risk for the associated adverse consequences. Fortunately, that is not the case. For example, studies in Pima Indians and individuals of European ancestry demonstrated that physical fitness was as powerful a modulator of insulin resistance as body weight, with each variable accounting for ~25% of the differences in insulin-mediated glucose disposal in non-diabetic individuals.[14] In support of this evidence, a report[14] from the European Group for the Study of Insulin Resistance (based on analysis of specific measures of insulin resistance in 1,146 non-diabetic, normotensive volunteers) showed that only ~25% of the obese volunteers were classified as being insulin resistant. Parenthetically, neither waist circumference nor ratio of waist-to-hip girth was related to insulin sensitivity after adjustments for age, gender and BMI.

Our results[15] in this context support and extend these observations. In all our studies, insulin-mediated glucose disposal was estimated by use of the insulin suppression test (IST). The IST was introduced and validated some years ago,[16,17] and in its current form involves the continuous infusion for 180 minutes of octreotide, insulin and glucose.[18] Under these conditions, endogenous insulin secretion is inhibited, as is the secretion of all other hormones that modulate glucose uptake. Steady-state plasma

insulin (SSPI) and steady-state plasma glucose (SSPG) concentrations are reached 90 to 120 minutes after the start of the infusion, and blood is drawn for measurement of plasma insulin and glucose concentrations every 10 minutes during the last 30 minutes of the continuous infusion.

These four values are averaged and used to determine the SSPI and SSPG concentrations observed during that study. Since the SSPI concentrations at the end of the infusion are similar in all individuals and the glucose infusion rate during the infusion also is identical, the SSPG concentrations provide a direct estimate of the ability of the same amount of insulin to promote glucose disposal in the person being studied — the higher the SSPG concentration, the more insulin-resistant the individual. It should be emphasized that quantification of insulin action with the IST and the hyperinsulinemic glucose clamp technique yield results[17] that are highly correlated ($r>0.9$).

Using this approach, we have shown that, in general, the more obese the individuals, the higher their SSPG concentration, and this relationship is highly statistically significant ($p<0.001$). However, the relationship between BMI and SSPG concentration is far from perfect, and result variations in BMI seem to account for no more than 25% of the variability in SSPG concentration. Furthermore, the more physically fit an individual, the more insulin-sensitive,[19] and as pointed out above,[13] differences in degree of physical fitness are approximately as powerful as differences in adiposity in modulation of insulin-mediated glucose disposal. Since overweight/obese individuals also tend to be sedentary, it is very likely that a decrease in physical fitness contributed to some degree to the insulin resistance attributed to obesity, per se.

Although obesity is sometimes considered to be the "cause" of insulin resistance and, at other times, one of the consequences of the defect in insulin action, the results summarized above make it clear that neither is the case and lead to the following straightforward conclusions: 1) Not all obese individuals are insulin-resistant nor are all insulin-resistant individuals obese; 2) obesity is a modulator of insulin resistance, not a consequence; and 3) the adverse effect of insulin resistance on insulin-mediated glucose disposal is almost certainly overestimated because the concomitant effect of decreased physical fitness in obese subjects is almost never taken into consideration.

Weight Loss Is Not More Difficult in Obese, Insulin-Resistant People

In the past few years, there has been considerable airing of the notion that the compensatory hyperinsulinemia preventing frank hyperglycemia from developing in insulin-resistant individuals also renders it extremely difficult for obese individuals to lose weight. The experimental basis for this view is certainly not clear nor is it obvious why it has received such apparent support. By itself, there is not any scientific explanation for how an increase in plasma-insulin concentration can create energy and thereby prevent weight loss. Indeed, if anything, one might expect that if insulin action was defective then weight loss might be more likely to occur, analogous to the situation in insulin-deficient individuals. It could be postulated that insulin is an appetite stimulant, but this seems to be unlikely given the evidence that insulin, if anything, acts centrally to suppress appetite.[23]

Furthermore, there are population-based prospective studies in different ethnic groups showing that baseline insulin resistance and/or hyperinsulinemia either have no effect or may inhibit weight gain over time.[21-23] Finally, results of recent studies addressing this question have demonstrated that the ability to lose weight in response to calorie-restricted diets is unaffected by differences in insulin resistance and/or hyperinsulinemia: Insulin-resistant/hyperinsulinemic obese individuals lose weight as effectively (or ineffectively) as equally overweight individuals who are insulin-sensitive.

In one such study,[24] we were able to demonstrate that the amount of weight loss in response to a calorie-restricted diet that occurred over a two-month period was essentially identical (11% of initial body weight) in equally obese individuals identified with IST at baseline as being either insulin resistant or insulin sensitive. Although baseline degree of insulin resistance (the SSPG concentration as measured by the IST, as described above) varied by more than sixfold in this group of obese individuals, the amount of weight lost was independent of the baseline degree of insulin resistance, and this was true whether the weight loss was considered in absolute terms or as a percentage of initial body weight.

A possible criticism of these data is that the period of observation was relatively short and the General Clinical Research Center at Stanford Medical Center provided meals for the study participants. Thus, it has been argued that the results may have been different if the subjects had been studied for longer periods of time and if they simply were following dietary recommendations under free-living conditions. However, this seems highly unlikely in view of our recent analysis of data in which 1,700 obese individuals were instructed on calorie-restricted diets and their change in weight monitored over a 12-month period.[25]

From this larger group, 247 individuals were classified at baseline as being insulin resistant on the basis of a high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) concentration (n=136) or insulin

sensitive with a low TG and a high HDL-C concentration (n=111). In addition to a calorie-restricted diet, the participants also were randomized to treatment with either placebo or orlistat. The mean percent weight loss in the four experimental groups ranged from 7% to 10% of initial weight over the 12-month study, with significantly more weight loss in those treated with orlistat (p=0.01). However, the amount of weight loss did not vary as a function of whether an individual was classified at baseline as being insulin resistant or insulin sensitive (p=0.95).

The fact that those obese individuals who also are insulin-resistant can lose weight as effectively in response to calorie-restricted diets as equally obese, insulin-sensitive individuals does not negate that successful weight-loss programs are extremely difficult to effect. Indeed, it might be more appropriate to state that the ineffectiveness of efforts to bring about weight loss is unrelated to baseline differences in insulin-mediated glucose disposal. On the other hand, the evidence summarized in this section does show that intensive attempts to help obese individuals lose weight should not be avoided because of a belief that they are all insulin-resistant and cannot lose weight for "metabolic" reasons.

Obesity, Insulin Resistance and Risk Factors

Since obese individuals tend to be insulin-resistant, glucose intolerant, hyperinsulinemic and dyslipidemic,[12-15,24-28] it is not surprising that they are more likely to develop 2DM, hypertension and CVD. However, the fact that not all obese individuals are insulin-resistant has important implications concerning the clinical impact of the current epidemic of obesity. In the first place, it seems likely that the adverse metabolic consequences associated with being insulin resistant will be confined to a significant extent to those obese individuals who are also insulin-resistant. We have addressed this question by quantifying insulin-mediated glucose disposal in healthy volunteers with similar degrees of obesity and using the results of these measurements to define these individuals as being either insulin sensitive or insulin resistant.

With this approach we have been able to compare a variety of experimental variables in two groups of equally obese individuals, stratified into insulin-resistant and insulin-sensitive subgroups.[24-28] The results of these comparisons have shown that daylong plasma glucose and insulin concentrations are significantly higher in the insulin-resistant group as compared to the insulin-sensitive group. In addition, the insulin-resistant group had higher plasma TG and lower HDL-C concentrations than the insulin-sensitive group. Finally, elevated plasma concentrations of C-reactive protein (CRP) were confined to the obese individuals who were also insulin resistant.

How to Identify the Overweight/Obese Individuals Who Will Benefit the Most from Weight Loss

The fact that only a proportion of overweight/obese individuals are insulin-resistant and demonstrate the usual metabolic abnormalities associated with this defect in insulin action, and that not all overweight/obese individuals are insulin-resistant, suggests that strategies to overcome the health-related impact of overweight/obesity become more focused. A decision to initiate treatment efforts by stratifying overweight/obese individuals on the basis of their degree of insulin resistance and emphasize disease risk reduction, rather than simple weight loss, requires the ability to recognize the appropriate subpopulation of obese individuals in a clinically useful manner.

The importance of identifying insulin-resistant individuals to be the focus of weight-loss programs is supported by the results of two prospective studies in apparently healthy, non-diabetic volunteers showing that the upper tertile in terms of insulin-mediated glucose disposal, i.e., the most insulin-resistant individuals, were at significantly increased risk to develop type 2 diabetes, CVD or hypertension.[9,11] If insulin is used as a surrogate measure of insulin resistance, another prospective study[10] demonstrated that all three syndromes developed to a significantly greater degree in the 25% of the population with the highest insulin levels.

Directly quantifying insulin-mediated glucose disposal is not clinically practical, and plasma insulin measurements are not standardized. However, once focus is shifted to the downstream consequences of insulin resistance/hyperinsulinemia, the task becomes simpler. A BMI>25 kg/m2 is currently used to define being overweight, with BMI>30 kg/m2 meriting the designation as obese. Based on these definitions, it would be prudent to evaluate any person with a BMI>25 kg/m2 for manifestations of insulin resistance. Since individuals with a BMI>27 kg/m2 are considered to be at such great risk that the FDA approved prescription anti-obesity drugs, these individuals certainly require CVD risk-factor evaluation. The presence of a family history of 2DM, hypertension or CVD makes it even more imperative to identify risk factors.

Although there is no single test to identify those overweight individuals most likely to be at increased risk for 2DM, CVD and hypertension, considerable clinical insight can be gained from the following relatively simple and straightforward measurements.

Dyslipidemia

Insulin-resistant individuals have a characteristic atherogenic lipoprotein profile, including a high-plasma TG and a low HDL-C concentration,[7,8,29] a decrease in

the diameter of the low-density lipoprotein (LDL) particles,[30] and an increase in postprandial lipemia.[31,32] LDL particle diameter and postprandial lipemia are not routinely determined, but plasma TG concentration is usually <150 mg/dL in insulin-sensitive individuals.[7,8] When this level is exceeded, LDL particles will become smaller and denser,[33] and the postprandial accumulation of remnant lipoproteins accentuated.[31,32]

A low HDL-C concentration is the fourth lipoprotein abnormality in insulin-resistant/hyperinsulinemic individuals, and a value <40 mg/dL is associated with both the insulin-resistant syndrome[7,8] and increased coronary heart disease risk.[34] Thus, overweight individuals with a TG concentration >150 mg/dL and a HDL-C concentration <40 mg/dL are almost certainly insulin-resistant and highly likely to also have smaller and denser LDL particles and elevated postprandial concentrations of remnant lipoproteins. They also will have the greatest decrease in CVD risk with weight loss.

Although both a high TG and a low HDL-C concentration have been identified as CVD risk factors,[34,35] their plasma concentration ratio may be even more useful in this regard. Thus, the observation[36] that the TG/HDL-C concentration ratio was as powerful a predictor of CVD as the more conventional ratios of LDL-C/HDL-C, or cholesterol/HDL-C, is supported by evidence[37] that the risk of ischemic heart disease was much greater when the "conventional" risk factors, i.e., high LDL-C concentration, hypertension, smoking and physical inactivity, were associated with a high TG/HDL-C concentration ratio.

It also was shown that the effects of these four conventional risk factors were significantly attenuated in individuals with a low TG/HDL-C ratio. Given this information, we have examined our database of approximately 500 apparently healthy volunteers to see how effective the TG/HDL-C concentration ratio might be in identifying those overweight/obese individuals who also are insulin-resistant. Based upon these data, it appears that a TG/HDL-C ratio > 3 (units in mg/dL) is useful in identifying overweight/obese individuals who are insulin resistant to the degree that predicts adverse outcomes.[38]

Hypertension

Insulin resistance and compensatory hyperinsulinemia are probably present in no more than 50% of patients with essential hypertension.[39] Thus, the presence or absence of hypertension is not as closely associated with insulin resistance as is a high TG and low HDL-C concentration. However, it is those patients with essential hypertension who have the characteristic atherogenic lipoprotein profile associated with insulin resistance and compensatory hyperinsulinemia who are most at risk of CVD.[39,40] The presence of a high TG (>150 mg/dL) and a low HDL-C (<40 mg/dL) concentration in an overweight individual with hypertension identifies a person at greatly increased CVD risk and one requiring intensive intervention to address all the CVD risk factors.

Glucose Intolerance

The majority of insulin-resistant individuals are able to maintain the degree of compensatory hyperinsulinemia needed to prevent gross decompensation of glucose homeostasis. In subjects with a normal fasting plasma glucose concentration (<100 mg/dL), a plasma-glucose concentration 120 minutes after a 75 g oral glucose load >200 mg/dL is diagnostic of type 2 diabetes. A value between 140 to 200 mg/dL constitutes impaired glucose tolerance.[42] In both instances, it is highly likely that the glucose intolerance will be associated with insulin resistance, hyperinsulinemia and the characteristic atherogenic lipoprotein profile of the insulin resistance syndrome.

Fasting plasma glucose concentration is a less sensitive guide to the presence or absence of insulin resistance, and a "normal" fasting plasma glucose concentration (<100 mg/dL) does not mean that an individual is insulin-sensitive. A fasting plasma glucose concentration >126 mg/dL is diagnostic of type 2 diabetes[42] and almost certainly defines an individual as being insulin-resistant. Subjects with a fasting plasma glucose concentration between 100 to 126 mg/dL are classified as having impaired fasting glucose (IFG) and are also likely to be insulin-resistant/hyperinsulinemic.

What Are the Metabolic Benefits of Weight Loss in Obese Individuals

Evidence published approximately 30 years ago demonstrated that weight loss in obese individuals was associated with enhanced insulin sensitivity, a decrease in the plasma insulin response to an oral glucose challenge and lower plasma TG concentrations.[12] In these initial studies, there was no attempt to see if the metabolic benefits of weight loss varied as a function of baseline insulin resistance. However, there is now considerable evidence that this is the case, and we have shown that there is essentially no change in insulin-mediated glucose disposal, fasting lipid and lipoprotein concentrations, daylong plasma glucose and insulin concentrations with weight loss in insulin-sensitive individuals.[24-28]

In contrast, in these same studies, we demonstrated that a similar degree of weight loss in equally obese individuals, who were also insulin resistant, was associated with considerable improvement in a variety of metabolic abnormalities. For example, both insulin resistance and daylong plasma insulin concentrations decreased significantly with weight loss of approximately 10% of initial

body weight in a group of obese, insulin-resistant people.[28] However, the loss of weight did not entirely overcome their defect in insulin action, and they were still insulin-resistant and hyperinsulinemic as compared to a group of equally obese, insulin-sensitive individuals who had lost a similar amount of weight. Daylong plasma glucose concentrations, which were slightly higher at baseline in the obese, insulin-resistant group, also fell significantly with the loss of weight and in this case were no longer different than the values in the weight-matched group of insulin-sensitive individuals. Obviously, the improvement in insulin-mediated glucose disposal associated with weight loss now enabled the insulin-resistant group to normalize their glucose tolerance.

The fact that insulin and compensatory hyperinsulinemia are highly correlated with increased hepatic TG secretion and higher plasma TG concentration was demonstrated approximately 35 years ago,[43,44] and it was subsequently shown that plasma TG concentrations fall in parallel to the enhanced insulin sensitivity and lower plasma insulin levels that occur with weight loss in obese individuals.[12] It is now clear that overweight/obese individuals are not necessarily insulin-resistant nor hypertriglyceridemic, and significant decreases in plasma TG concentrations with weight loss are limited to those subjects who share these metabolic abnormalities.[25,27] Perhaps the most dramatic example of this phenomenon can be seen from the findings of the 12-week study referred to above, in which improvement in lipid metabolism associated with weight loss was limited to those individuals classified at baseline as being insulin resistant.[27]

Evidence that blood pressure will fall in association with weight loss was initially published in 1978.[45] More recently, it was suggested that the improvement in blood pressure following weight loss in obese adolescents was related to the associated changes in insulin sensitivity.[46] A similar conclusion was reached in a study in adults with hypertension, in which there was a highly significant relationship between the improvement in insulin sensitivity and the fall in blood pressure.[47]

Conclusion

Being overweight significantly increases morbidity and mortality from a variety of diseases. Relatively simple measures can identify the subset of overweight/obese individuals who are insulin resistant/hyperinsulinemic, and the benefit of weight loss in these individuals has been established. Although not solving all the health-related problems associated with obesity, a useful beginning might be to recognize the fact that not all obese individuals are at equal risk and that it is clinically useful to identify those at highest risk. If this is done, intense efforts at weight control can be brought to bear on those who need it the most. Given the difficulty in achieving weight loss, efforts should be focused on those who have the most to gain.

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