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# INSULIN RESISTANCE AND COMPENSATORY HYPERINSULINEMIA: THE LINCHPIN BETWEEN OBESITY AND CARDIOVASCULAR DISEASE

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## *Introduction*

It has been estimated [1] that more than 50% of the U.S. population is overweight (body mass index (BMI)>25.0 kg/m$^2$), with ~20% designated as being obese (BMI>30 kg/m$^2$). Given the importance [2] of excess adiposity in increasing risk of cardiovascular disease (CVD) and the increase in the prevalence of overweight/obesity, it is essential that considerable thought be given as to how to address this dilemma. Patients with CVD tend to be insulin resistant [3, 4], and insulin resistance (and the compensatory hyperinsulinemia associated with insulin resistance) are independent predictors of CVD [5-8]. Overweight/obese individuals tend to be insulin resistant and become more insulin sensitive with weight loss [9]. Thus, it can be postulated that a major contributor to the association between obesity and CVD is insulin resistance and that the risk of CVD will decrease when overweight/obese individuals lose weight. As straightforward as this formulation seems to be, the situation is not quite that simple and it ignores some important issues that must be addressed.

## *Obesity Does Not Equal Insulin Resistance*

Not all overweight/obese individuals are insulin resistant and at increased risk for the associated adverse consequences. For example, studies in Pima Indians and individuals of European ancestry demonstrated that physical fitness was as powerful a modulator of insulin action as body weight, with each variable accounting for ~25% of the differences in insulin-mediated glucose disposal in nondiabetic individuals [10]. Furthermore, the report [11] from the European Group for the Study of Insulin Resistance (based on the analysis of specific measures of insulin resistance in 1146 nondiabetic, normotensive volunteers) showed that only ~25% of the obese individuals were classified as being insulin resistant.

On the other hand, the fact that not all overweight/obese individuals are insulin resistant should not obscure the relationship between excess adiposity and insulin sensitivity: in general, the more obese an individual, the more likely they are to be insulin resistant. However, this relationship is far from perfect, and, as seen in Figure 1, it appears that differences in BMI in apparently healthy, nondiabetic volunteers account for ~25% of the variability in insulin-mediated glucose uptake as assessed by the insulin suppression test [12]. Furthermore, this estimate does not take into consideration the fact that overweight individuals are often sedentary. Consequently, and similar to most studies examining the relationship between obesity and insulin action, the adverse impact of obesity on insulin resistance seen in Figure 1 is, if anything, exaggerated.

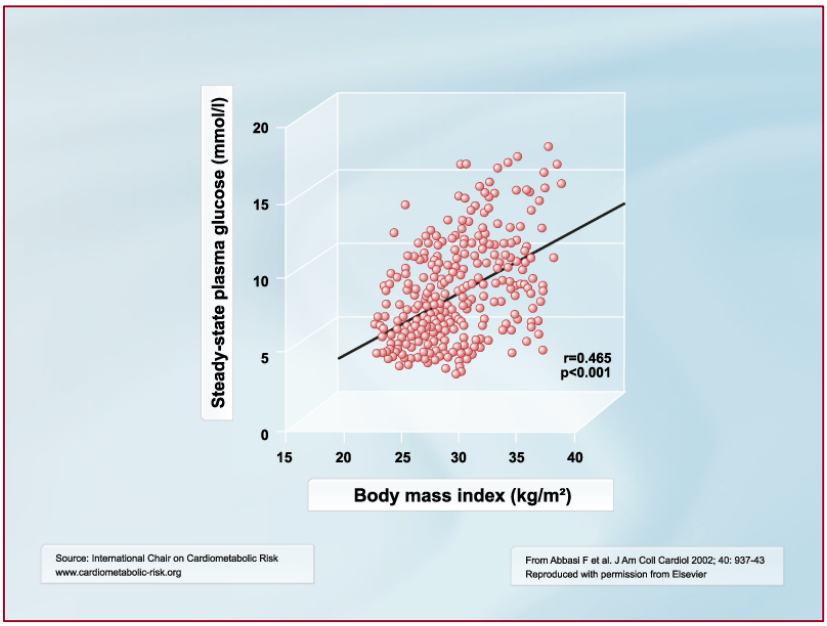


*Figure 1: Relationship between body mass index and measurement of insulin sensitivity in apparently healthy men and women. Insulin sensitivity was quantified by determining the steady-state plasma glucose concentration during the insulin suppression test. The higher the steady-state plasma glucose concentration, the more insulin resistant the individual.*

In summary: 1) not all obese individuals are insulin resistant, nor are all insulin resistant individuals obese; 2) obesity is a modulator of insulin resistance, it is not a consequence; and 3) the adverse effect of insulin resistance on insulin-mediated glucose disposal is almost certainly exaggerated 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/Hyperinsulinemic Persons*

There seems to be a general perception that the compensatory hyperinsulinemia that prevents frank hyperglycemia from developing in insulin resistant individuals makes it extremely difficult for obese individuals to lose weight. As appealing as this notion seems to be, it is not consistent with available information. For example, there are population-based prospective studies in different ethnic groups showing that baseline insulin resistance and/or hyperinsulinemia either have no effect on weight gain over time or actually predict that this is less likely to occur [13-15]. Furthermore, results of two recent studies have shown 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 [16, 17]. An example of this is seen in Figure 2, which demonstrates the lack of any relationship between the amount of weight lost over a 2-month period of calorie restriction and the daylong plasma insulin concentrations to a test meal prior to starting the diet.

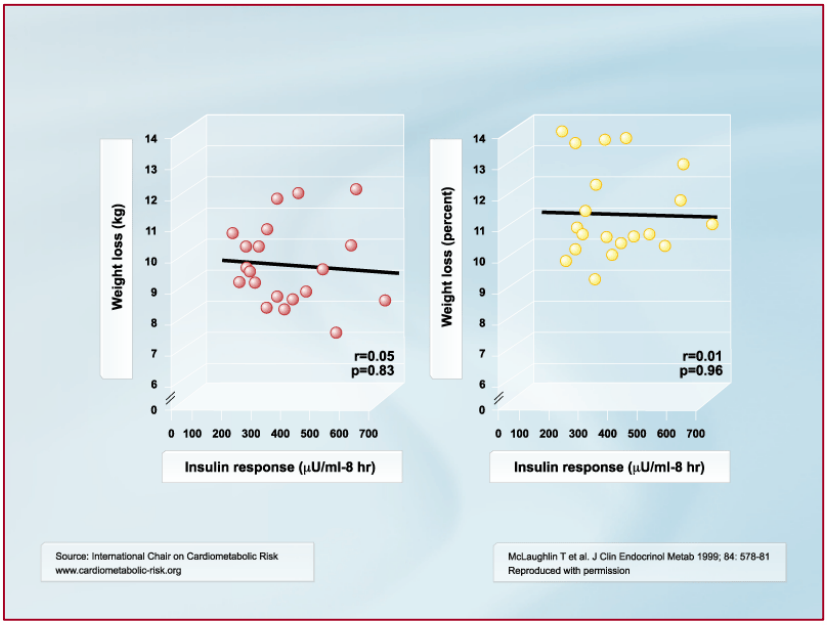


*Figure 2: Relationship between daylong integrated insulin response (8 AM-4 PM) to a standard meal before the dietary intervention, and the amount of weight loss in absolute terms (left panel) and as a percentage of body weight (right panel) after 2 months of a calorie-restricted diet in 20 apparently healthy, overweight individuals.*

### *Obesity, Insulin Resistance, and CVD Risk Factors*

Since obese individuals tend to be insulin resistant, glucose intolerant, hyperinsulinemic, and dyslipidemic [9, 12, 16-19], it is not surprising that they are more likely to develop 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. Insulin-mediated glucose disposal can be quantified in apparently healthy, equally obese volunteers, and this data can be used to classify these individuals as being either insulin sensitive (IS) or insulin resistant (IR). This is an operational definition based on evidence from prospective studies that the most insulin resistant third of an apparently healthy population is at increased risk to develop CVD, whereas the most insulin sensitive third is not [5, 6]. When CVD risk factors are compared in IR and IS subgroups of moderately obese individuals stratified in this manner [12, 19, 20], daylong plasma glucose, insulin, and free fatty acid concentrations are significantly higher in IR as compared to IS obese individuals. In addition, the IR group has higher plasma triglyceride (TG) and lower high-density lipoprotein cholesterol HDL cholesterol concentrations. Furthermore, elevated C-reactive protein concentrations appear to occur primarily in moderately obese individuals who are also insulin resistant. Perhaps the most dramatic example of the metabolic variability in equally obese individuals comes from a study of 211 individuals, in which the prevalence of impaired glucose tolerance (IGT) was 1% in the most insulin sensitive third, as compared to 46% in the most insulin resistant third of the population [20]. These relationships are summarized in Figure 3.

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

If only a proportion of overweight/obese individuals are insulin resistant, it seems reasonable to suggest that intensive intervention strategies to overcome the untoward health-related impact of overweight/obesity should focus on those individuals who will benefit the most. In order to stratify overweight/obese individuals on the basis of their degree of insulin resistance and emphasize disease risk reduction, rather than simple weight loss, the appropriate subpopulation of obese individuals must be recognized in a clinically useful manner.

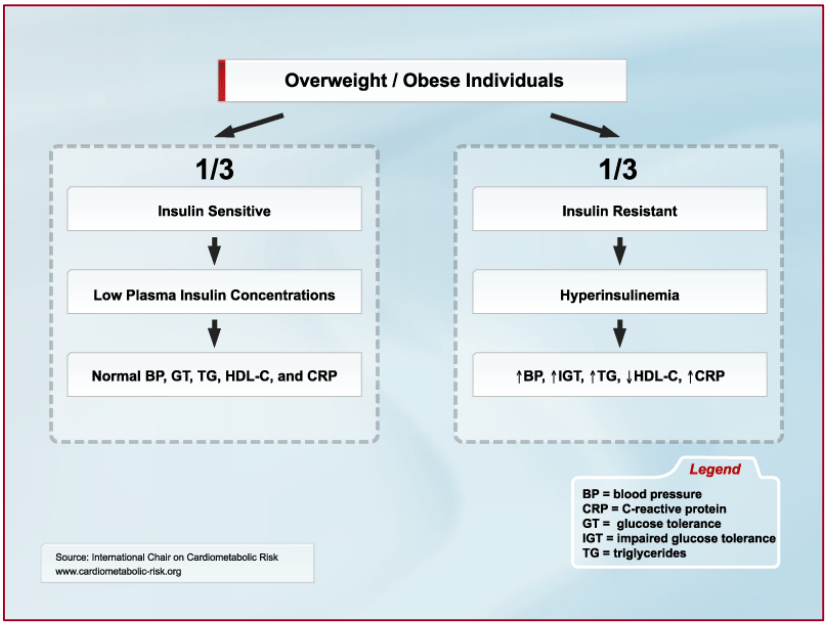


*Figure 3: Schematic representation of the differences in cardiovascular disease risk factors seen between the most insulin sensitive and most insulin resistant thirds of a population of apparently healthy, overweight/moderately obese individuals.*

The importance of identifying insulin resistant individuals for weight loss programs is supported by the results of prospective studies in apparently healthy, nondiabetic volunteers showing that the upper third in terms of insulin-mediated glucose disposal (i.e., the most insulin resistant individuals) were at significantly increased risk to develop CVD [5, 6]. Fasting plasma insulin concentration is often used as a surrogate measure of insulin resistance, but its clinical use is compromised by the lack of nationwide standardization of the measurement, and direct quantification of insulin-mediated glucose disposal is not clinically practical. However, if focus is shifted to the down-stream consequences of insulin resistance/hyperinsulinemia, the task becomes simpler. Normal weight is currently defined as a BMI<25.0 kg/m$^2$, and it would be prudent to evaluate any person with a BMI$\geq$25.0 kg/m$^2$ for the manifestations of insulin resistance. The simultaneous presence of a family history of type 2 diabetes, hypertension, or CVD makes it even more imperative to identify CVD risk factors in that individual.

Although there is no single test with which to identify those overweight individuals most likely to be at increased risk for CVD, considerable clinical insight can be gained by focusing on the dyslipidemia characteristic of insulin resistance: a high plasma TG and a low HDL cholesterol concen-

tration [3, 4, 21]. Overweight individuals with a TG concentration >1.69 mmol/l (150 mg/dl) and a HDL cholesterol concentration <1.03 mmol/l (40 mg/dl) are very likely to be insulin resistant. In addition, they are also likely to have a decrease in the diameter of their low-density lipoprotein (LDL) particles [22] and an increase in the postprandial accumulation of TG-rich remnant lipoproteins [23, 24]. LDL particle diameter and postprandial lipemia are not routinely determined, but when the plasma TG concentration is >1.69 mmol/l (150 mg/dl), LDL particles are likely to become small and dense [25], and the postprandial accumulation of remnant lipoproteins accentuated [23, 24]. It is this subset of overweight/obese individuals who are at greatest risk of CVD and will have the greatest decrease in risk with weight loss.

Although both a high TG and a low HDL cholesterol concentration have been identified as CVD risk factors [26, 27], their plasma concentration ratio may be even more useful in this regard. Thus, the observation [28] that the TG/HDL cholesterol concentration ratio is as powerful a predictor of CVD as the more conventional ratios of LDL cholesterol/HDL cholesterol or cholesterol/HDL cholesterol is supported by evidence [29] that the risk of ischemic heart disease is much greater when the "conventional" risk factors (i.e., high LDL cholesterol concentration, hypertension, smoking, and physical inactivity) were associated with a high TG/HDL cholesterol concentration ratio. It has also been shown that the untoward effects of these four conventional risk factors were significantly attenuated in individuals with a low TG/HDL-C ratio. Based upon these observations and a review of our database, we have proposed that a TG/HDL-C concentration (mg/dl) ratio >3.0 can be useful in identifying overweight/moderately obese individuals who are insulin resistant, to a degree that predicts increased risk of CVD [30]. This ratio is far from perfect and is not as sensitive as would be desirable, but it is reasonably specific. Thus, an overweight/moderately obese person meeting this criterion displays the atherogenic lipoprotein phenotype characteristic of insulin resistant individuals, is highly likely to be insulin resistant, and would almost certainly benefit greatly from weight loss and increased physical activity.

## *What are the Benefits of Weight Loss in Insulin Resistant, Overweight Individuals?*

There is essentially no change in insulin sensitivity, fasting lipid and lipoprotein concentrations, daylong plasma glucose, insulin, or free fatty acid concentrations with weight loss in IS individuals [18, 19]. In contrast, a similar degree of weight loss in equally obese, IR individuals will be associated with considerable metabolic improvements. Evidence that blood pressure falls in association with weight loss was initially published in 1978 [31], and it has also been shown that the improvement in blood pressure following weight loss in obese adolescents was related to the associated changes in insulin sensitivity [32]. 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 [31].

## *Conclusion*

There is substantial evidence that insulin resistant/hyperinsulinemic individuals are at increased risk to develop CVD. Relatively simple measures can identify the subset of overweight/obese in-

dividuals who are most likely to be insulin resistant/hyperinsulinemic, and the benefit of weight loss in these individuals has been established. Although it does not solve all of the health-related problems associated with obesity, a useful starting point might be to recognize 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, focus should be placed on those who have the most to gain: the insulin resistant subset of overweight individuals.

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