Insulin Resistance is the Link between Obesity and Cardiovascular Disease
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Insulin-mediated glucose disposal varies more than six-fold in apparently healthy individuals, and the third of the population that is most insulin resistant is at greatly increased risk to develop a number of adverse outcomes, including cardiovascular disease (CVD). Approximately 25 % of the variability in insulin action is related to being overweight, and the importance of the adverse effects of excess adiposity is apparent in view of the ongoing worldwide epidemic of obesity.

Given the enormity of the problem, it is important to differentiate between the CVD risk related to obesity, *per se*, as differentiated from the fact that the prevalence of insulin resistance and compensatory hyperinsulinemia are increased in overweight/obese individuals. Although the majority of individuals in the general population considered to be insulin resistant are overweight/obese, not all overweight/obese persons are insulin resistant. Furthermore, significant improvement following weight loss in the metabolic abnormalities associated with insulin resistance is confined to the subset of overweight/obese individuals that demonstrate this defect in insulin action.

The fact that equally obese individuals can vary dramatically in their degree of insulin sensitivity, and that only the subset of overweight/obese persons that are also insulin resistant obtain significant metabolic benefit from weight loss, focuses on two unanswered questions. In the first place, the cellular/molecular explanation for the diversity in insulin action in equally obese persons has not been defined, and preliminary evidence will be presented suggesting that a basic defect in those obese individuals that are also insulin resistant is impairment in the ability of adipose tissue cells to fully differentiate. As a consequence, there is a decrease in total fat storage capacity, leading to the ectopic deposition of excess fat.

Secondly, in view of the large number of overweight subjects likely to be insulin resistant, and thereby at increased CVD risk, and the difficulty in achieving weight loss in asymptomatic individuals, it would be useful to identify the subset of the overweight population that would benefit the most from weight loss. In an effort to accomplish this task, we have evaluated use of the plasma concentration ratio of triglyceride/high-density lipoprotein cholesterol (TG/HDL-C); selected because: 1) a high TG and a low HDL-C are characteristic of insulin resistance; 2) both changes increase CVD risk; 3) the TG/HDL-C ratio is as useful a predictor of CVD risk as the total cholesterol/HDL-C ratio; and 4) the TG/HDL-C ratio is as good a surrogate measure of insulin resistance as the fasting insulin concentration. A recent analysis of approximately 300 overweight/obese men and women suggests that

a TG/HDL-C ratio >3.0 provides an approach with a reasonable degree of sensitivity and specificity in the effort to identify those overweight/obese individuals that are not only insulin resistant and hyperinsulinemic, but also have an atherogenic lipoprotein profile. As such, it seems to provide a simple, and clinically relevant, means to find those overweight/obese individuals at greatest risk to develop CVD, and thereby the patients that deserve the most intensive efforts to bring about and sustain weight loss.

In conclusion: 1) resistance to insulin-mediated glucose disposal, and its consequences, greatly increase CVD risk; 2) the prevalence of insulin resistance is significantly greater in overweight/obese individuals, and the increased CVD risk associated with excess adiposity is primarily seen in the subset of overweight/obese individuals who are also insulin resistant; 3) a basic defect contributing to insulin resistance in some obese individuals may be an impairment in adipose tissue cell differentiation, favoring entopic fat deposition; 4) given the difficulty in achieving weight loss, it seems reasonable to identify overweight/obese individuals that are also insulin resistant, the group that will benefit the most from weight loss, and target this population for the most intensive therapeutic efforts; and 5) the TG/HDL-C ratio may provide the means to focus attention on overweight/obese individuals who will gain the most from losing weight.