The Big Picture on Obesity and Insulin Resistance*

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In this issue of the Journal, Abbasi et al. (1) use data from previous studies in 314 individuals to quantify the relationship between body mass index (BMI) and insulin resistance and the relationship between these two factors and other coronary heart disease (CHD) risk factors. The modified insulin suppression test, previously validated by this group, was used to define whole body insulin resistance. The main findings were that only about a quarter of the variability in insulin resistance was explicable by BMI. Second, at any BMI those individuals classified as insulin-resistant had higher insulin levels and were more glucose intolerant than insulin-sensitive individuals. Third, of the risk factors examined, low high-density lipoprotein (HDL)-cholesterol and hypertriglyceridemia were most strongly associated with insulin resistance.

Some aspects of methodology of this study, or series of studies, mean that the surprisingly low estimate of 22% variability in insulin resistance being explained by obesity may be conservative. First, individuals with diabetes, CHD, and hypertension were excluded. Because these conditions are related to both BMI and insulin resistance, exclusion of such individuals is likely to push the observed correlation between BMI and insulin resistance downward. So too will measurement error, which is likely here because only single measurements of BMI and insulin resistance have been taken. Third, BMI is not a perfect measure of adiposity. However, although 22% may be an underestimate, the main conclusion still holds; substantially less of the variance in insulin resistance or sensitivity than previously believed is likely to be attributable to obesity. Importantly, these data support the previous result from the European Group for the study of Insulin Resistance (EGIR) study, which used the gold standard hyperinsulinemic euglycemic clamp method for defining insulin resistance. In that study too, only about a quarter of the variability in insulin resistance could be explained by BMI (2).

Beyond total body fat mass, a tendency towards central deposition of body fat as measured by increased waist-hip ratio is thought to be a feature of, or a determinant of, insulin resistance (3,4). Central fat deposition may reflect visceral obesity. However, the importance of visceral obesity remains controversial (5), and an independent association between waist-hip ratio and insulin resistance was not observed in the EGIR study. Given the controversy, it is unfortunate that Abbasi’s large study was not able to provide any information on this issue.

So why are some individuals apparently resistant to the effect of obesity on insulin sensitivity, and why are others insulin-resistant despite apparently being thin? The answer may yet lie with fat. A considerable body of evidence now points towards intramyocellular lipid (IMCL) content, as measured by nuclear magnetic resonance spectroscopy, as being a critical determinant of insulin resistance (6,7). The correlation between IMCL and insulin resistance as measured by the hyperinsulinemic euglycemic clamp is much higher than the correlation of BMI with insulin resistance (6). While BMI is positively correlated with IMCL, some people have high IMCL despite having a fairly low BMI and vice versa. In several studies those subjects who were insulin-resistant despite being thin had high IMCL. Such individuals might be considered to be “metabolically obese.” An extreme example of the importance of IMCL is seen in congenital lipodystrophy where, because of a lack of adipose tissue, postprandially free fatty acids are directed to other tissues including myocytes with consequent accumulation of IMCL and insulin resistance (8). Beyond obesity the determinants of IMCL in the general population are as yet unclear.

Abbasi et al. (1) conclude that it is self-evident that efforts to reduce diabetes and CHD in overweight and obese people should target those who are insulin-resistant. They show that among insulin-resistant but not insulin-sensitive individuals, those with higher BMI are less glucose-tolerant and have higher insulin. The not unexpected implication of these data is that prevention of diabetes through weight reduction is more likely in overweight people who are already on their way to becoming diabetic than those who are not. But what does this actually mean for clinical practice? Screening for insulin resistance in a clinical setting is not feasible at present—there is no consensus on a clinically applicable test for, or definition of, insulin resistance. Even assuming that insulin-resistant individuals could be identified easily, what interventions are cost-effective for preventing diabetes? The Diabetes Prevention Program in the U.S. and the Diabetes Prevention Study in Finland have recently demonstrated that lifestyle modification programs and metformin can delay the onset of diabetes in glucose-intolerant individuals (9,10) but that achieving increased physical activity and maintaining weight reduction requires intensive and expensive interaction with patients. We do not yet know how feasible, effective, or affordable the nonpharmacologic interventions are outside of the trial setting. Because the implementation of programs for preventing diabetes in glucose-intolerant patients is in

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its infancy, extending these interventions to those insulin-resistant overweight or obese subjects who are not yet glucose-intolerant would seem to be some way off.

In the study by Abbasi et al. (1), those with higher BMI had a worse risk factor profile, the slope of the relation being similar among insulin-resistant and sensitive individuals for systolic blood pressure (SBP), total and low-density lipoprotein cholesterol and triglyceride, and being steeper among insulin-sensitive subjects for HDL cholesterol. The usual caveats about inference from cross-sectional data notwithstanding, these data suggest that weight reduction would be expected to achieve a similar reduction in SBP, total cholesterol, and triglyceride, and perhaps a greater increase in HDL cholesterol, in insulin-sensitive as resistant individuals. So the data do not support the idea that only insulin-resistant overweight subjects should be targeted for weight reduction for prevention of CHD on the grounds of efficacy. In Europe, Australasia, and increasingly in the U.S., there is recognition that clinical intervention for primary prevention of CHD should be based on absolute CHD risk rather than on the level of any one risk factor (11). Such an approach acknowledges that the number needed to treat to prevent an event is a function of absolute, not relative, risk. Therefore, deciding which overweight patients are most in need of risk factor intervention will involve consideration of their entire risk factor profile, not just insulin-resistance status. Indeed, there is the practical difficulty that the risk equations, such as the Framingham risk equation (12), that are being advocated for risk estimation in clinical practice do not make provision for data on insulin-sensitivity status or even for plasma insulin levels. To argue that they should would require that insulin resistance be shown to predict CHD independently of risk factors with which it is associated. This remains controversial (13), and no data on this has been provided by this article.

The article by Abbasi et al. (1) makes an important point that lean people can be insulin-resistant and that not all insulin resistance is attributable to obesity. Some obese individuals may be immune to the adverse metabolic or cardiovascular effects of obesity. However, targeting those overweight individuals who are insulin-resistant for risk factor intervention in clinical practice has both theoretical and practical limitations. Meanwhile, in the Western world and in emerging economies, obesity is now so common across the entire age spectrum that type 2 diabetes is appearing in children, and not just in children from high-risk ethnic groups (14). Reversing this increasing imbalance between energy intake and energy expenditure requires action at a population level. We know relatively little about what policies are most cost-effective at shifting the population towards greater energy balance, and this is where research efforts need to be directed in the future.

**REFERENCES**