WHY IS IT IMPORTANT TO BE INSULIN SENSITIVE?

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Over the past 30 years it has become apparent that resistance to insulin regulation of muscle and adipose tissue, insulin resistance, for short, plays a central role in the rapid increase in the prevalence of several major diseases. Perhaps the most dramatic example of this phenomenon is the recent development of a world-wide epidemic of type 2 diabetes. If it is assumed that type 2 diabetes results from the interaction between genes and environmental influences, it is obvious that the relatively enormous increase in the incidence of type 2 diabetes in the last two decades can only have resulted from the powerful impact of changes in life-style on a population genetically at increased risk to develop type 2 diabetes. What is perhaps most interesting about the epidemic of type 2 diabetes, as distinct from HIV-AIDS, for example, is that we can: 1) explain why the prevalence of diabetes is increasing; 2) prevent its development by interventions that are well-established and easily implemented; and 3) provide effective treatment for the full-blown disease when present.

There is ample evidence that the vast majority of patients with type 2 diabetes are resistant to insulin-mediated glucose disposal (1,2). Furthermore, insulin resistance can be detected in normoglycemic, first degree relatives of patients with type 2 diabetes, and it predicts the development of both impaired glucose tolerance and type 2 diabetes. Although the genetic abnormalities that predispose an individual to develop type 2 diabetes remain obscure, a reasonable argument can be made that insulin resistance is the phenotypic expression of the genes involved (3). For example, ethnic groups most at risk for developing type 2 diabetes have been shown to be more insulin resistant than, for example, people of European ancestry (4). Furthermore, there is evidence that insulin resistance is at least a familial characteristic (5).

Resistance to insulin-mediated glucose disposal varies substantially in apparently healthy volunteers, (6,7) and approximately 50% of this variability can be explained by differences in degree of obesity and maximal aerobic capacity (8). The two life-style variables are approximately equally powerful in their ability to modulate insulin-mediated glucose disposal, and weight loss and increased physical activity can lead to enhanced insulin sensitivity. Thus, it seems highly likely that the current epidemic of type 2 diabetes, particularly in developing countries, is the result of the untoward effects on insulin-mediated glucose disposal of weight gain and decreased physical activity, acting on individuals who are genetically prone to be insulin resistant. Since weight loss and/or increased physical activity will improve insulin sensitivity in insulin resistant individuals, it is not surprising that these interventions can be effective in both the prevention of glucose intolerance, as well as in improving glycemic control.

The fact that life-style interventions are effective in both the prevention and treatment of type 2 diabetes is both encouraging and discouraging. Encouraging, because the interventions are safe and address the fundamental metabolic abnormality. Discouraging, because they are difficult to implement on a large scale. In this context, the availability of the thiazolidinedione (TZD) class of anti-hyperglycemic compounds provide for the first time an effective pharmacologic approach to improving insulin sensitivity (9). The availability of drugs that address the root cause of type 2 diabetes is appealing, and a strong theoretical argument can be made that TZDs will be more...
effective in reducing macrovascular disease than other currently available anti-hyperglycemic agents (10).

The more insulin sensitive an individual, the less likely the chance of developing type 2 diabetes. However, the advantages of remaining insulin sensitive go far beyond decreasing the risk of hyperglycemia. The vast majority of insulin resistant individuals do not develop type 2 diabetes, but the combination of insulin resistance and compensatory hyperinsulinemia greatly increases their risk of developing a number of life-threatening conditions.

The most widely-recognized of these is the cluster of abnormalities, secondary to insulin resistance/compensatory hyperinsulinemia (Syndrome X), that greatly increases CHD risk (1,2). Abnormalities associated with Syndrome X include some degree of glucose intolerance, an atherogenic lipoprotein phenotype consisting of a high TG and low HDL cholesterol concentration, increased postprandial lipemia, smaller and dense LDL particles, and a procoagulant state resulting from higher concentrations of plasminogen activator inhibitor-1 and fibrinogen. Insulin resistance/compensatory hyperinsulinemia predict the development of hypertension; ~50% of patients with high blood pressure are insulin resistant and hyperinsulinemic (11), and it is these individuals who are most at risk of CHD (12,13). A more recent addition to this cluster is polycystic ovary syndrome (PCOS), thought to result from enhanced insulin-stimulated testosterone secretion from the ovary (14).

Unfortunately, the list of serious diseases associated with insulin resistance seems to be growing. For example, there is increasing evidence that patients with HIV/AIDS are at increased risk of type 2 diabetes and CHD, most likely related to insulin resistance and its consequences. Whether this is part of the fundamental disease, or due to the use of protease inhibitors, remains to be determined. On the other hand, there seem to be little question that the prevalence of Syndrome X-like cluster is becoming a common phenomenon in patients with HIV/AIDS (15).

There is also emerging evidence of an association between insulin resistance/hyperinsulinemia and cancer. Obesity is considered to increase risk of several forms of cancer, and results of recent papers may have provided a possible mechanistic basis for this association in that hyperinsulinemia has been identified as predicting an increase in incidence of cancer (16). Since obesity decreases insulin-mediated glucose disposal, and leads to hyperinsulinemia, the possibility that this explains why obesity is a cancer risk factor is certainly plausible. Furthermore, since insulin resistance/hyperinsulinemia can occur in normal weight individuals, the potential importance of insulin resistance as a risk factor for cancer will not be limited to overweight individuals.

In conclusion, it is not difficult to become insulin resistant, whereas remaining insulin sensitive throughout life is an arduous task. On the other hand, it should be obvious how important this goal is, and there are well-defined behavior patterns that can increase the likelihood of achieving it. The availability of pharmacologic agents that can enhance insulin sensitivity provide for the first time an additional approach to overcoming the untoward effects of insulin resistance. Although the theoretical benefits of these new agents are almost infinite, how much of this will be realized depends upon the results of the clinical studies that must be done to establish the utility of these new agents.

REFERENCES