Impaired Glucose Tolerance

A Target for Intervention?

Designation of the category of impaired glucose tolerance by the National Diabetes Data Group (NDDG) and by the World Health Organization (WHO) has served to highlight the dearth of knowledge about the significance of glucose tolerance levels that fall short of being diagnostic of diabetes, but that are above normal if these are defined as glucose levels above the mean plus two standard deviations in healthy young adults with no family history of diabetes. As pointed out in the accompanying editorial, in some populations glucose concentrations, fasting or following an oral glucose load, are bimodally distributed, and when the logarithms of the glucose concentrations are used, the frequency distributions conform well to a model of overlapping gaussian distributions in which those with diabetes constitute the hyperglycemic component of distribution. What, then, does the lower component represent?

One view might be that the lower component, whose upper boundaries extend well beyond those defined as normal in young healthy adults, is a reflection that glucose tolerance tends to diminish with increasing age, obesity, or physical inactivity and that in the general population the distribution is skewed and both the mean and the variance of glucose levels are greater. If so, glucose tolerance levels above the range seen in young healthy adults which now fall into the range labeled “impaired glucose tolerance” might still be considered to be of no particular significance. However, several observations appear to make this viewpoint untenable.

As Stern and his colleagues points out, impaired glucose tolerance is associated with an increased risk for the development of diabetes, as well as an increased risk for the development of cardiovascular disease. Whether the latter can be “explained” on the basis of other risk factors and the glucose intolerance is merely an innocent bystander, or whether impaired glucose tolerance has a more direct, pathogenetic role has been a matter of considerable debate and controversy. However, the fact that diabetics have more coronary heart disease than nondiabetics, even after other risk factors such as age, smoking, cholesterol levels, and hypertension have been accounted for in the statistical sense, certainly leaves some questions about the pathogenetic significance of impaired glucose tolerance in atherosclerosis.

Many studies have shown that diabetes is much more likely to develop in persons with impaired glucose tolerance. This risk increases markedly as a function of the degree of the glucose intolerance, even when other risk factors, such as obesity or a family history of noninsulin-dependent diabetes, are taken into account. In general, the degree of glucose intolerance and family history of diabetes have been found to be the strongest predictors of the development of diabetes. The degree of obesity also has often, but not always, remained as a significant predictive factor, and in some studies other factors, such as very low density lipoprotein (VLDL) or increased serum cholesterol levels and high blood pressure, have been shown to be independent determinants.

Impaired glucose tolerance is accompanied by hyperinsulinemia. Typically, after an oral glucose load such persons have an exaggerated and attenuated insulin response, which is indicative of impaired insulin action. Indeed, in subjects without diabetes the fasting or postload glucose and insulin levels are generally proportional to the degree of insulin resistance. Up to a certain point the pancreas attempts to compensate by increasing insulin output. Thus, persons with impaired
glucose tolerance have high circulating insulin levels and impaired insulin-mediated glucose disposal. Obesity tends to aggravate the situation and is associated with even greater insulin resistance and higher insulin levels for a given degree of impairment of glucose tolerance. Only when the pancreas fails to increase insulin output appropriately and/or insulin action becomes diminished to the extent that further increase in insulin secretion is ineffective, does the rate of disposal of glucose fall below the input, and then diabetes appears.

There is remarkably little information about the time course of these events. The Bedford and Whitehall Studies in England showed that among persons with impaired glucose tolerance, 11% developed diabetes within 5 years, and in the subsequent 5 years 12% more developed the disease.\textsuperscript{19} Decompensation rates to diabetes among those with impaired glucose tolerance did not depend upon the age of the subject. On the other hand, among the Bedford group, 53% of those with impaired tolerance at the outset showed improved glucose tolerance after 5 years, and the remainder had persistent impairment. Thus, among those with impaired glucose tolerance at the beginning, the risk of developing diabetes was high; the high risk persisted for many years, but the high rate of remission indicated that, while impaired glucose tolerance may be heterogeneous, it is often reversible.

Studies among the Pima Indians appear to be the only ones where the course of decompensation to diabetes has been examined prospectively.\textsuperscript{16} Among subjects who developed diabetes and who had serial observations at 2-year intervals from 4 years before to 2 years after the development of the disease, the mean 2-hour postload plasma glucose levels increased from about 130 mg/dl at 2 and 4 years before diagnosis to an average of 300 mg/dl at diagnosis.\textsuperscript{20} Thus, most subjects showed a "quantum" change in glucose tolerance at the time the diabetes appeared, as predicted from the bimodal glucose tolerance distributions in the population.\textsuperscript{3}

The data suggest, therefore, that in many subjects impaired glucose tolerance may persist for several years. Although spontaneous improvement may often occur, the presence of persistent impaired glucose tolerance may perhaps indicate a greater likelihood of an unfavorable outcome.\textsuperscript{15} If this is the case, the possibility of intervention at this stage to prevent decompensation to diabetes or other unfavorable outcomes, such as the development of cardiovascular disease, must be considered.

Impaired glucose tolerance is associated with a constellation of abnormalities. Hyperinsulinemia, increased VLDL or serum cholesterol levels, hypertension, and obesity are each associated, and may contribute to the development of both diabetes and atherosclerosis. The extent to which each of these abnormalities is an independent contributor to cardiovascular disease is difficult to discern, but it has even been suggested that the increased risk of coronary heart disease among diabetics may be due to the fact that diabetes develops in persons who already possess characteristics that increase the risk of coronary heart disease as well as the risk of diabetes.\textsuperscript{18}

There have been surprisingly few attempts to determine the effect of intervention on impaired glucose tolerance, although a number of possibilities exist—drug treatment, dietary intervention, weight loss, exercise, or multiple interventions.\textsuperscript{21} Three studies using oral hypoglycemic agents have been reported. In two,\textsuperscript{11,15} although numbers were small, there was no discernable effect of diet and tolbutamide or phenformin on the subsequent incidence of diabetes. In a third study, the Malmohus study from Sweden,\textsuperscript{22} a significant difference in the rate of development of diabetes was found between subjects randomized to treatment and a "no therapy" group. While there was no overall difference in those randomized to tolbutamide, placebo, or diet only, it was notable that of 23 subjects who continued to take tolbutamide throughout the trial, none developed diabetes. These subjects represented only half of those randomized to this group, and whether this represents a true therapeutic effect, or whether those who elected to continue tolbutamide were a self-selected group who for other reasons had a lower risk of development of disease, is unknown. On the other hand, the size of the samples in the earlier trials is so small that their results are compatible with an effect as great as a 50% reduction in the incidence of diabetes. There is, therefore, an urgent need to replicate the study.
Other randomized controlled trials of therapeutic modalities, even such commonly recommended therapies as weight reduction or the effects of dietary changes on the incidence of diabetes or on the incidence of cardiovascular disease among those with impaired glucose tolerance, have not been reported. Yet, if the WHO criteria for impaired glucose tolerance are used, the second National Health and Nutrition Examination Survey has indicated that there are 17 million persons aged 20 to 74 years in the United States with the condition. If intervention could successfully alter the natural history of this condition, this would be a major public health achievement which could lead to reduction in the incidence of diabetes and perhaps also of coronary heart disease.

References


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