Age and Glucose Intolerance

Effect of fitness and fatness

The fact that glucose intolerance increases with age has been apparent for over 30 years, leading to the suggestion at one time that the diagnostic criteria for diabetes be amended to account for this inevitable consequence of the aging process (1). However, these earlier findings did not differentiate the effects on the plasma glucose response to an oral glucose challenge of age per se from those due to the impact of a number of age-related variables (2). In this context, the article by Imbeault et al. in this issue of *Diabetes Care* (3) provides additional information concerning the effect of body fat on glucose tolerance, as apparently healthy volunteers grow older. However, the potential effect of differences in fitness, an age-related variable of comparable magnitude, was apparently not considered in their study.

Maneatis et al. (4) quantified the impact of differences in age-related variables on the plasma glucose response to a mixed meal in healthy volunteers between the ages of 47 and 90 living in a retirement community. When adjusted for differences in body weight and physical activity, they found no significant correlation between age and plasma glucose response in men, and differences in age could account for no more than 6% of the variability in glucose response in women. Similarly, when adjusted for differences in weight, physical activity, and use of diabetogenic drugs, age only accounted for 6% of the variance in plasma glucose response to an oral glucose challenge in men and 1% in women in a study of 732 Italian factory workers aged 22–73 years (5). Perhaps the most definitive information in this regard is the results of the Baltimore Longitudinal Study of Aging (6), performed in 743 healthy individuals, comparing glucose tolerance in three age groups: 17–39, 40–59, and 60–92 years. When differences in overall and regional obesity as well as fitness (assessed by both history and maximal aerobic capacity) were taken into account, Shimokata et al. (6) could find no effect of age on plasma glucose responses to oral glucose in the 17–39 and 40–59 age groups. Furthermore, partial correlation coefficients, adjusted for differences in adiposity and fitness level, indicated that <10% of the variability of the plasma glucose concentration 120 min after oral glucose in this population ranging from 17 to 92 years of age was attributable to age per se. Thus, there is substantial evidence that the decline in glucose tolerance is most prominent after the age of 60; this is primarily due to the fact that people tend to get fatter and less fit as they get older, and the effect of age, itself, is modest in magnitude.

Although the study by Imbeault et al. (3) focused on visceral obesity as the age-related variable most responsible for the decline in glucose tolerance, the impact of a sedentary lifestyle should not be overlooked. For example, it has been shown that ~50% of the variability in insulin-mediated glucose disposal in healthy Pima Indians and subjects of European ancestry was related to differences in fitness and fatness, with each contributing 25% of the variance (7). Evidence that glucose tolerance was significantly worse in older Taiwanese office workers than in laborers of the same age provides indirect support for the lack of fitness playing an important role in the glucose intolerance associated with aging. Indeed there was no loss of glucose tolerance with age in the laborers (8). The results of Seals et al. (9), showing that glucose tolerance was similar in older and younger athletes, provide more direct evidence of the impact of fitness

The conclusion by Shimokata et al. (6) that loss of glucose tolerance occurs primarily after the age of 60 is consistent with the findings from several studies showing that insulin-mediated glucose disposal is also decreased in these individuals (10–12). However, Rosenthal et al. (12) pointed out that this change was far from uniform and that the variance in insulin-mediated glucose disposal was twice as great in older compared with younger individuals. Subsequent studies (13) indicate that insulin-mediated glucose disposal was significantly correlated with maximal aerobic capacity, independent of BMI or percentage body fat, and that the variance in insulin-mediated glucose disposal in men between 60 and 75 years of age was primarily related to differences in level of reported physical activity and measurement of maximal aerobic capacity.

Although the glucose intolerance and decrease in insulin action associated with aging may be largely attributed to age-related increases in adiposity and decreases in physical activity, this does not seem to be the case regarding the effect of age on glucose-stimulated insulin secretion. It has been clearly shown in rodents that insulin secretion per β-cell declines progressively with age, irrespective of gender, level of physical activity, or degree of obesity (14). However, rodents are able to compensate for this inexorable loss of insulin secretory function by a compensatory increase in β-cell mass. The effect of age on insulin secretory function in humans has not been as well defined. On the one hand, the plasma insulin of an oral glucose challenge in older individuals is usually greater than or equal to that in matched younger subjects, and the glucose intolerance reported to occur with aging is not associated with an absolute decrease in plasma insulin concentrations (4,5,8,12). However, it appears that older humans do not have the ability to increase insulin secretion to the degree necessary to prevent some degree of glucose intolerance from developing. Evidence that basal insulin secretion rates decreased with age, independent of differences in fasting plasma glucose concentration, insulin sensitivity, or abdominal circumference is in support of this view (15). In addition, results of studies measuring the β-cell response to a graded glucose infusion indicated that older individuals had a shift to the right of the glucose-stimulated insulin secretion rate dose-response curve, i.e., the insulin

secretory response was decreased at any given increment in plasma glucose concentration (16). In this sense, the abnormality in β-cell function associated with aging resembles that of subjects with maturity-onset diabetes of the young who have a mutation in the glucokinase gene (17).

Faced with a population that is getting fatter and less fit with age, the article by Imbeault et al. should serve as a wake-up call. Loss of glucose tolerance with age is primarily related to weight gain and sedentary lifestyle, and level of physical activity is as powerful a factor as adiposity in this regard. In light of the more subtle loss of insulin secretory function with age, a phenomenon that seems more directly related to age per se, the best way to stem the rapidly growing epidemic of type 2 diabetes is by concerted efforts beginning at a young age to prevent fatness and encourage fitness.

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