

Increasing Incidence of Type 2 Diabetes in the Third Millennium

Is abdominal fat the central issue?

Central abdominal adiposity, even when estimated crudely by anthropometric measures, predicts the development of type 2 diabetes (1,2), cardiovascular morbidity, and cardiovascular mortality (3,4) and is now recognized as part of the metabolic syndrome that includes insulin resistance, dyslipidemia, and hypertension. Boyko et al. (5) in this issue reports that, in second and third generation Japanese, intra-abdominal fat is the only fat depot which predicts the development of type 2 diabetes. As they show in this prospective study, the presence of increased central fat precedes the onset of diabetes. Central adiposity is strongly related to insulin resistance (as measured by a hyperinsulinemic clamp) (6,7), which is considered the precursor of type 2 diabetes. The abdominal fat depot may induce deterioration in insulin sensitivity through its characteristic high rate of lipolysis (8) and its rapid turnover of fatty acids (9). Whether intra-abdominal or subcutaneous abdominal fat (or both) is responsible for the metabolic sequelae is under debate (10) and remains unresolved, despite the use of computed tomography and magnetic resonance imaging (6,11). The source of this debate may be the common use of single slice scanning, because there is known to be substantial intra-individual variation in fat distribution throughout the abdominal region (12).

Insulin resistance is present in a substantial proportion of the normal population and is even found in healthy-weight young women, in whom it is accompanied by early features of the metabolic syndrome, which is partly explained by greater subcutaneous and visceral abdominal fat mass (13). Subsequent weight gain in healthy-weight individuals is associated with an increased risk of the metabolic and hemodynamic abnormalities of the metabolic syndrome (14), an alarming threat in the face of the current epidemic of obesity. The recent National Health and Nutrition Examination Survey found a prevalence of overweight and obesity (BMI >25 kg/m²) of 50–60% in adults; non-Hispanic black

women and Mexican-American women have a prevalence of obesity alone (BMI >30 kg/m²) as high as 37 and 33%, respectively (15). Westernization and rapid economic development increase the prevalence of obesity. In Mauritian women, for example, the prevalence of obesity increased by 20% in only 5 years (16). In Asia, the prevalence of obesity is increasing rapidly (17), particularly in children (18).

The epidemic of obesity and diabetes (19) that characterized the end of the second millennium could be attributed to an exquisite genetic susceptibility to central obesity and insulin resistance and, in some populations, an environment which permits fuller expression of this susceptibility. The therapy and prevention of type 2 diabetes should be improved by understanding the determinants of central obesity.

Genetic factors are strong determinants of central adiposity (20,21). Genetic factors also influence insulin resistance (22) and other features of the metabolic syndrome (23) and may account for the close relationships among metabolic syndrome components (23,24). The hypothesis of an underlying polygenic basis to the metabolic syndrome, insulin resistance, and type 2 diabetes is supported by substantial inter-racial variation in the manifestations of the metabolic syndrome (25,26). So far, physical activity has been identified as a prime environmental factor that influences central fat (27) and also prevents type 2 diabetes, particularly in the susceptible (28). Thus far, two studies using direct measures of central fat have found no significant influence of diet (29,30).

The article by Boyko et al. (5) shows that the amount of intra-abdominal fat predicted the incidence of type 2 diabetes in second generation Japanese (nisei) subjects after 6–10 years of follow up regardless of age, sex, family history, impaired glucose tolerance, nonabdominal adiposity, and estimates of insulin resistance and insulin secretion (5). Subcutaneous abdominal fat measured by single slice computed tomography was not predictive. In third genera-

tion Japanese (sansei) subjects, only intra-abdominal fat was predictive of subsequent diabetes, with odds ratios twice those in the nisei, after adjustment for covariates. One explanation lies in the greater BMI of the sansei, which is in keeping with the trends to Westernization as previously discussed. Even though there is only a small number of sansei with diabetes, this explanation suggests central adiposity may be more important in the development of type 2 diabetes in the sansei than in the older nisei.

One other important feature distinguishes diabetes in the nisei and sansei: sansei with type 2 diabetes had hyperinsulinemia and a preserved 30-min insulin response to a 75-g oral glucose load. In contrast, nisei had no hyperinsulinemia and a depressed insulin incremental response, suggesting an insulin-secretory deficit played a greater role in the older nisei. The accurate measurement of insulin secretion in population studies is extremely difficult. When optimally evaluated, some form of defective insulin secretion is almost invariably found at all stages in the development of impaired glucose tolerance and type 2 diabetes (31). It is likely that a predisposition to β -cell failure is the determinant of the onset of hyperglycemia in the face of sustained insulin resistance from central obesity.

The epidemic of type 2 diabetes is attributable to genetically susceptible populations within an increasingly sedentary and Westernized community. The coexistent epidemic of obesity contributes by means of increased central obesity and insulin resistance and forces expression of a pre-existing limitation in insulin-secretory reserve, which is, possibly, genetically determined (32). In the past century, our efforts have been aimed at modifying environmental factors that influence the risk factors of type 2 diabetes. In this new century, understanding how the polygenic susceptibility of different populations interact with the environment can better target therapy and prevention of type 2 diabetes and the related disorders of the metabolic syndrome.

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