Over the past half century, the nomenclature for the major forms of diabetes changed from juvenile- and adult-onset to insulin-dependent or ketosis-prone and non–insulin-dependent or ketosis-resistant and, most recently, in an attempt to shift from treatment to what is now known of pathogenesis as the basis, type 1 and type 2 diabetes.

Challenges to the concept of two main and distinct forms of diabetes go back to epidemiologic studies in the 1960s and 1970s. Yemenite immigrants to Israel had very few instances of diabetes but, after 25 years in the land of milk and honey, experienced a 40-fold increase in frequency of diabetes. The proportion of insulin dependency was similar to that in Israelis of European origin, suggesting common environmental influences (most likely nutritional) on the expression of both major forms of diabetes (1). In a comparison of diabetes expression in >1,500 siblings of middle-aged newly diagnosed patients (both insulin dependent and non–insulin dependent) and siblings of childhood-onset insulin-dependent patients who had reached the same age bracket, Gottlieb (2) described a tendency, but not a requirement, for similar disease expression in families. Of siblings of childhood-onset patients, 12% had developed diabetes, evenly divided between what we would now consider type 1 and type 2 diabetes; siblings of adult-onset insulin-dependent patients had similar frequency and proportions. Siblings of type 2 diabetic patients had an 11% diabetes frequency; one-fourth of them were insulin dependent. More recently, a study of 3,500 incident cases of type 1 diabetes in Sweden found a family history for type 1 diabetes to be increased in relatives of patients with type 1 diabetes than in patients with type 2 diabetes. Among 764 Swedish patients aged 15–34 years with newly diagnosed diabetes, 76% were classified as type 1, 14% as type 2, and the rest unclassified. Forty-seven percent of type 2 diabetic patients and 59% of unclassified patients were positive for one or more diabetes-specific autoantibodies, with the antibody-positive type 2 or unclassified diabetic patients being significantly lighter and with lower C-peptide concentrations than the antibody-negative patients (5). Two studies in children with type 2 diabetes have paralleled some, but not all, of the findings in adults with type 2 diabetes. Among 48 children, 8% were positive for the ICA512 fragment, 30% were GADA positive, and 35% insulin autoantibody positive. Unlike adults, there was no correlation between antibody positivity and degree of obesity (6). In a group of 37 black children and adolescents, 10.8% were positive for GADA, insulinoma-associated protein 2, or both, with no difference in treatment requirements (oral agent versus insulin) related to the presence or absence of antibodies (7).

There is also evidence of genetic overlap between type 1 and type 2 diabetes through HLA class II risk haplotypes. In 695 Finnish families with more than one member having type 2 diabetes, 14% also had members with type 1 diabetes. There was marked overlap of risk haplotypes independent of the presence of GADA (8). These findings were interpreted to suggest genetic interaction between these forms of diabetes, mediated by the HLA locus. In a somewhat different approach, Hungarian investigators found no difference in measures of obesity, lipids, or frequency of hypertension between 54 patients with LADA and 57 with adult-onset type 1 diabetes, whereas significant differences were found with those having type 2 diabetes; HLA high-risk haplotype frequencies did not differ between the LADA and adult-onset type 1 diabetic groups, but were not studied in the type 2 diabetic group. These investigators concluded that LADA was simply a slowly progressive form of type 1 diabetes (9).

It is against this background of uncertainty about the relationship between diagnostic classification based on clinical phenotype and that based on diabetes-related autoantibody studies, 2 epidemiologic and genetic data failing to support a clear distinction between the two major forms of diabetes, and 3) concomitant increases in incidence rates and decreasing mean age of onset of type 1 and type 2 diabetes paralleling obesity rates, that Wilkin advanced the intriguing accelerator hypothesis (10). This unifying concept proposes that hyperglycemia resulting from ponderosity-mediated insulin resistance induces β-cell apoptosis, setting up the conditions for β-cell autoimmunity in genetically susceptible individuals. This hypothesis was supported by analysis of 300 contemporary British children born at term who were found to have insulin resistance at age 5 years unrelated to birth weight but to current weight and weight catch-up (11). The report from this investigative group (12), in the current issue of Diabetes Care, examines the relationship of fatness and age at diagnosis of type 1 diabetes in 94 children.
aged 1–16 years. BMI SD score (SDS) at diagnosis, weight SDS change since birth, and BMI SDS 12 months after diagnosis were all inversely related to age at diagnosis, consistent with the notion that greater weight is associated with earlier onset of type 1 diabetes (12). Although consistent with the accelerator hypothesis, this study provides no information about weight influence on the overall, rather than age-specific, incidence of type 1 diabetes in childhood or on biochemical characteristics or autoimmunity.

Libman et al. (13), in another report in this issue, describe addressing the question of weight related to the onset of type 1 diabetes by matching black and white patients diagnosed from 1979 to 1989 to those diagnosed from 1990 to 1998. There were no biochemical differences between the races, but 89% of white and only 68% of black patients had at least one diabetes-specific autoantibody. The sole difference between the two eras was a tripling in the percentage with obesity, from ~12 to ~36%, which is similar to the greater-than-twofold increase in overweight in this population over this period of time. The increase was greatest among those with antibodies, from 5.1 to 24.4%; in those without antibodies, the increase was from 46 to 75%. These investigators have noted a threefold increase in diabetes incidence from the early 1980s to 1994 in their referral population. No calculations are made or speculation provided about how much of this increase might be attributable to increasing weight in the population at risk; however, if 64% of contemporary incident cases and 88% of those from the earlier era were not overweight, this difference is inadequate to explain the threefold increase in type 1 diabetes incidence.

In a third study in this issue (14), the Pittsburgh group describes the clinical, biochemical, and autoimmune characteristics at diagnosis and follow-up in 130 black and 130 matched (for age at diagnosis, sex, and year of diagnosis) white patients <19 years of age at diagnosis of presumed type 1 diabetes, excluding those with a primary or subsequent diagnosis of type 2 diabetes. The percent of black youths who were obese was four times that of whites (43 vs. 11%). Blacks also had significantly lower frequencies of all antibodies, as has long been recognized (15), and in this group obesity rates in the absence of antibodies were far greater (83 vs. 24% for those with at least one antibody), presentation with ketosis far less common, and serum cholesterol levels significantly higher. These differences did not occur in the white population, but the small proportion without antibodies may have been inadequate to demonstrate such differences.

These three reports indicate an influence of ponderosity on time of onset of type 1 diabetes and increasing rates of obesity in newly diagnosed type 1 diabetic patients that is ethnically disproportionate, includes features of insulin resistance, and is related to the presence or absence of diabetes-specific autoimmunity markers. These studies depend on BMI to define obesity; however, this measure is a crude proxy for percentage fat mass and its distribution and for the critical variable of cardiovascular fitness that is the determinant of insulin sensitivity (16).

The concept remains fundamentally valid that autoimmune β-cell destruction accounts for typical type 1 diabetes and that typical type 2 diabetes results from absolute or relative adiposity-related insulin resistance in individuals with limited β-cell compensatory ability. However, these two archtypical disorders appear to be increasingly overlapping and simultaneously rising in frequency, as the result of population changes in body fat and fitness. The accelerator hypothesis provides a useful speculative link among the three forces of insulin resistance, β-cell loss, and β-cell autoimmunity. How these forces interact will involve a wide range of environmental and hereditary factors, with great variability between and within populations. While these complex issues are being sorted out, it is important for the physician to treat individual patients based on their clinical, phenotypic, and biochemical characteristics, rather than their presumptive classification.

References

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