Incidence of Diabetes in Children and Youth—Tracking a Moving Target

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DIABETES MELLITUS TAKES A HUGE TOLL ON INDIvidual patients in terms of health care complications, such as blindness, kidney failure, cardiovascular disease, and amputations, and also exacts a huge burden on society, in terms of consumption of health care resources. Diabetes occurring early in life has even more devastating effects on the ability of young patients to live full lives and results in substantially increased health care costs related to treating a lifelong, complex disease. Diabetes is the most prevalent chronic disease of childhood after asthma[1]; therefore, monitoring trends in childhood diabetes is a public health imperative.

The need for standardized data on diabetes began to be addressed in the 1980s, with the establishment of the World Health Organization–sponsored Diabetes Mondiale (DiaMond) study, a consortium of approximately 150 population-based registries that used the same methods for case definition, ascertainment, and validation.[2,3] This study initially included 6 registries in the United States (Birmingham, Ala; Philadelphia, Pa; Allegheny County, Pa; Chicago, Ill; US Virgin Islands; and Puerto Rico). Soon thereafter, a collaboration among more than 40 centers across Europe was established, again using standardized methods.[4] During the past 20 years, these projects have contributed valuable surveillance data on diabetes, as well as key information on geographic differences, environmental contaminants, infectious exposures, and other potential risk factors.[5]

Although there has been an unprecedented increase in childhood obesity during the past 2 decades, a careful examination of the epidemiological data on diabetes in youth presents a more complicated picture. Longstanding incidence studies in the United States and elsewhere[2-9] show increasing rates of type 1 diabetes mellitus (DM) since 1980, concurrent with the increase in childhood obesity. The DiaMond consortium demonstrated an average annual increase in diabetes incidence of 5.6% per year in the United States during the 1990s.[2,3] Major increases in diabetes have occurred in all areas of the globe, averaging 2.8% per year between 1990 and 1999 in children aged 0 to 14 years.[2,3] The convergence of these trends suggests that obesity may be driving the autoimmune beta-cell failure underlying type 1 DM, a notion that is gaining credence.[10,11] Specifically, excess adiposity appears to play a role in stimulating and prolonging autoimmune insulitis.[12]

An alternative and quite logical explanation might attribute the documented increase in childhood type 1 DM to unrecognized type 2 DM presenting in obese, young individuals. Certainly, physician diagnostic practices are in flux. Before 1997, virtually all diabetes in young individuals was thought to be autoimmune type 1 DM. Now there is widespread recognition that insulin-resistant type 2 DM can occur in childhood.[13,14] However, type 2 DM is still rare among young individuals, as demonstrated in the accompanying article in this issue of *JAMA* by the SEARCH for Diabetes in Youth Study Group,[15] and by other studies.[8,9] In absolute terms, the number of young individuals with type 2 DM is low, estimated at 39 000 among those younger than 20 years in the United States compared with approximately 19 million adults (≥20 years).[16]

Despite this relatively low prevalence, obesity in youth carries a variety of other perils. Obesity is directly linked to insulin resistance and increased likelihood of early adult cardiovascular disease, type 2 DM, and gestational diabetes. Women with gestational diabetes experience a 50% risk for developing type 2 DM within 5 years,[17] and exposure to diabetes in utero is a promoter of childhood obesity in their offspring,[18] setting up a vicious cycle. The earlier in life insulin resistance appears, the earlier its pathologic sequelae. Consequently, increasing rates of childhood obesity may be driving "epidemics" of both type 1 and type 2 DM.

A key issue for epidemiological research, genetics, and clinical practice is to distinguish type 1 DM from type 2 DM as accurately as possible. This is often not straightforward: most patients with "true" type 1 DM continue to secrete some insulin for several years after diagnosis,[19] and patients clinically determined to have type 2 DM frequently display islet autoantibodies, particularly to glutamic acid decarboxylase. Furthermore, evidence is accumulating that type 2 DM in young individuals is qualitatively different from that in older adults, often resulting from an interplay of insulin resistance and autoimmunity.[20] In a study from Chicago,[8] chil-

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dren classified at onset (mean [SD], 13.1 [3.2] years; range, 0-17 years) as having type 2 DM on the basis of medical records displayed severe onset signs and symptoms, including a high prevalence of diabetic ketoacidosis. When these children were examined approximately 8 years after their initial diagnosis, more than half of the young patients with type 2 DM demonstrated islet autoantibodies, no residual beta-cell function, or both.[21] The study by Umpaichitra et al[22] described a group of young non-Hispanic black patients with intermediate type 2 DM features, and the study by Reinehr et al[23] reported that follow-up of a large cohort of young patients in Germany demonstrated islet autoimmunity in more than 30% of young people who were clinically diagnosed with type 2 DM.

The SEARCH for Diabetes in Youth study[15] in this issue of *JAMA* offers a snapshot of diabetes risk for US children and teenagers in 2002-2003. The incidence rates were developed as part of the SEARCH study, a recent Centers for Disease Control and Prevention effort to collect data across the United States that has features in common with the ongoing DiaMond protocols, but is not fully integrated with the existing long-term databases. The SEARCH collaboration encompasses 10 geographically distinct sites: 4 population-based registries (Cincinnati, Ohio; the states of Colorado, South Carolina, and Washington), 4 American Indian reservation-based health plans in Arizona and New Mexico, and 2 large health maintenance organizations (Kaiser-Permanente in California and Hawaii). Physician reports, hospitals, and patient self-referrals contributed cases, and the completeness of ascertainment was validated in the 4 population-based registries. All cases of diabetes in youth younger than 20 years were registered, except for gestational diabetes, and the phenotype (type 1 DM, type 2 DM, mixed, secondary diabetes, type unknown) was determined from physician diagnoses or patient self-reports.

The risk of diabetes before age 20 years was determined to be 24.3 per 100 000 per year overall, with higher risk (>25 per 100 000 per year) for non-Hispanic white, non-Hispanic black, and American Indian youth compared with Hispanics and Asian ethnicities, whose risk was less than 20 per 100 000 per year. Although the majority of cases (78%) were classified as type 1 DM, rates of apparent type 2 DM increased with age and were more frequent among non-Hispanic black, Asian, and American Indian individuals. Diagnosis of type 2 DM was not confined to minority youth, as 15% of non-Hispanic white youth aged 10 to 19 years were classified as having type 2 DM. Furthermore, a significant fraction of American Indian and Asian youth aged 10 to 19 years were diagnosed with type 1 DM (14% and 30%, respectively).

The SEARCH research group was able to determine beta-cell function and glutamic acid decarboxylase antibody status on approximately 40% of their registered study participants within approximately 1 year of diagnosis, in an attempt to validate their reported phenotypes. However, testing for IA-2 (a tyrosine phosphatase–associated molecule) antibodies, considered the best indicator of type 1 DM at onset, was not performed, and testing for residual beta-cell function is not very useful so soon after diagnosis.[19] Among patients diagnosed at ages 10 to 19 years who were examined, only 22% of the patients with type 1 DM (and 1 of the 151 patients with type 2 DM) had no endogenous insulin production. Fully 66% of type 1 DM and 22% of type 2 DM patients had evidence of positive glutamic acid decarboxylase antibody, and one third of the patients with type 2 DM were using insulin. Although these observations must be viewed with caution, they suggest that a substantial fraction of young patients with diabetes appears to have a mixed etiology, in agreement with other studies.[20-23]

The SEARCH project[15] adds some detail to the understanding of the changing nature of diabetes risk in the United States. The authors have ascertained cases in a range of settings, under the stringent privacy regulations that have constrained much population-based research in the United States recently.[24] In particular, their group is well positioned to examine geographic differences in diabetes risk among the diverse locations represented in the SEARCH study. As this and other research goes forward, it may be possible to develop a better understanding of the interplay of autoimmunity with youth-onset diabetes. There is an urgent need to go beyond studies such as this one by implementing a coordinated approach for childhood diabetes surveillance (ie, mandated case-reporting). Only then can society respond effectively to the serious and increasing challenge of diabetes in youth.

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Childhood Cancer Survivors, Late Effects, and a New Model for Understanding Survivorship

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In 1950, AT A TIME WHEN CANCER REMISSION WAS MEASURED in days, Farber stated that "The use of chemotherapeutic agents now available . . . should do much to reduce the number of instances of 'incurable cancer' in infants and children."[1] Today, in 2007, approximately 80% of children with cancer are cured.[2]

However, it gradually was realized that this cure had a cost; ie, the curative therapy could damage a child's developing organ systems. Some problems, such as cognitive deficits following cranial radiotherapy, were apparent soon after completion of therapy. However, many sequelae were not recognized until survivors were a decade or more beyond their cancer. In 1974, Meadows and D'Angio described different methods and approaches to "detect the late effects of cancer therapy"[3]; thus began the expansion of the concept of cure to include long-term outcomes.

In this issue of *JAMA*, Geenen and colleagues[4] provide a noteworthy and important contribution to understanding the long-term consequences of cancer therapy experienced by survivors of childhood cancer. Even though much research had been conducted in this area, resulting in many reports on the quality of life of long-term survivors or the prevalence of specific late effects, prior to 2006 there were no studies with adequate sample sizes that provided a composite estimate of the morbidity associated with therapy for childhood cancer. Last year, the report from the Childhood Cancer Survivor Study (CCSS) on chronic health conditions included more than 10 000 adult survivors of childhood cancer.[5] These 2 studies complement each other, filling the gaps of respective study design limitations and providing a robust estimate of morbidity in this population of survivors, many of whom are now entering their young and mid-adult years.

The study by Geenen and colleagues,[4] from the late-effects clinic (Polikliniek Late Effecten Kindertumorien) of the Emma Children's Hospital/Academic Medical Center (EKZ/AMC), Amsterdam, the Netherlands, has several strengths. For example, it is truly remarkable that among childhood cancer survivors treated from 1966-1996, only 1.5% were lost to follow-up. For perspective, in a report on long-term outcomes of survivors of acute lymphoblastic leukemia, Pui et al[6] from St Jude Children's Research Hospital reported that 5.1% of survivors were lost to follow-up and another 16% did not respond to a short mailed questionnaire.[6] One primary limitation in survivorship research is the potential bias of estimates introduced by such loss to follow-up or to nonparticipation. With 98.5% capture of data, this is not an issue for the EKZ/AMC study. Another major limitation in survivorship research is the frequent dependence on self-reported outcomes. Not only were the survivors in the EKZ/AMC study successfully contacted, but 94.3% were evaluated by a physician, including 79% of the cohort who were evaluated at a single institution using standard-

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