Type 2 Diabetes in the Young

The evolving epidemic

ZACHARY T. BLOOMGARDEN, MD

The topic of the International Diabetes Federation Consensus conference, held 7–9 February 2003 in Santa Monica, California, was "Type 2 Diabetes in the Young: The Evolving Epidemic" (1). The topic has become a clinical and health economic priority, with important implications for an increasing health care burden throughout the world. Aspects of these conditions have recently been reviewed (1,2).

Epidemiology

We are in the midst of an epidemic of lack of exercise, of obesity, of the insulin resistance syndrome (IRS), and of diabetes in young persons. The diabetogenic process begins in fetal life, with low birth weight and poor nutrition combining with sedentary lifestyle and dietary factors to produce an insulin-resistant phenotype that may accelerate the development of renal pathology and cardiovascular disease (CVD). Worldwide, the number of persons with diabetes has tripled since 1985. In Australia, 1.7 and 1.4% of persons aged 35–44 and 45–54 years, respectively, had diabetes in 1981, and these rates increased to 2.5 and 6.2% in 2000 (3), suggesting a trend to earlier age of onset of diabetes.

Obesity. The prevalence rates of obesity (BMI exceeding the 95th percentile) among U.S. children and adolescents aged 6–11 and 12–19 years, respectively, were 4.2 and 4.6% in 1963–1970, 4.0 and 6.1% in 1971–1974, 6.5 and 5.0% in 1976–1980, 11.3 and 10.5% in 1988–1994, and 15.3 and 15.5% in 1999–2000, an alarming rate of increase. Obesity (weight corrected for height >95th percentile) among U.S. children increased between 1988 and 1999 from 7 to 10% among those aged 2–5 years (Fig. 1) (4,5). In a cross-sectional survey of children 9–12 years old in Hong Kong, 38% of girls, but 57% of boys, were overweight, with overweight children of both sexes showing higher systolic blood pressure, triglyceride, and insulin and lower HDL cholesterol than the normal-weight group (6). In Australia, ~5% of children are currently obese and an additional 16% overweight (BMI 85th to 95th percentile) (7). These prevalences doubled over the past decade after being nearly stable around 10% from 1969 to 1985 (8). There appear to be ethnic differences within countries, with African-American and Hispanic children aged 4–12 years in the U.S. showing an increase to 22% prevalence of overweight between 1986 and 1998, while non-Hispanic whites showed no significant change with a 12% overweight prevalence (9). It is noteworthy that BMI may underestimate the prevalence of obesity in young people. Recent analysis of trends in British youth suggest that waist circumference has increased more rapidly than BMI over the past two decades, with 14 and 17% of boys and girls, respectively, exceeding the 98th percentile in this measure in 1997, while 10 and 8% exceed the 98th percentile for BMI; both measures exceeded the 98th percentile only in 2–3% of adolescents between 1977 and 1987 (10).

These considerations suggest that the phenomenon of increasing type 2 diabetes among children and adolescents may be a result of increasing obesity and, particularly, of increasing central obesity (2). There is a strong relationship between childhood obesity and the development of insulin resistance in early adulthood (11). Fasting insulin levels show correlation with blood pressure (12) and triglyceride and inverse correlation with HDL cholesterol levels (13), important components of the IRS.

Diabetes. In populations with low prevalence of diabetes, children with obesity may be relatively protected against the development of diabetes, with an Italian study of 710 obese children showing just 0.2% with type 2 diabetes and 4.5% with impaired glucose tolerance (IGT) (14). In contrast, a U.S. study of 167 obese adolescents and children showed a 4% prevalence of type 2 diabetes, all occurring among Hispanic and black adolescents, while IGT was seen in 16, 27, and 26% of the obese white, black, and Hispanic adolescents, respectively, suggesting environmental and/or genetic differences contributing to the more common occurrence of glycemic abnormality in the U.S. than in Italy (15). In the U.K., the risk of type 2 diabetes is 13.5 times greater among Asian than white children (16,17). Gender is also important, with girls being 1.7 times more likely than boys to develop type 2 diabetes in analysis of a large set of studies (18). Family history plays a crucial role, with more than two-thirds of children with type 2 diabetes having at least one parent with type 2 diabetes (19). Among children with type 2 diabetes in Japan, onset in 77% is between 12 and 15 years of age, 57% are female, and 26% are of normal weight, with 29% mildly, 26% moderately, and 19% severely obese. Japanese children with type 2 diabetes show familial clustering, with siblings having a 175- to 250-fold increase in diabetes over the frequency in the general population and parents a 48–60% likelihood of having type 2 diabetes (20).

Certain ethnic groups show a particularly high prevalence of glycemic abnormality among young persons, and diabetes prevalence appears to be increasing. Type 2 diabetes was seen in <1% of Pima Indian children aged 10–14 years and 2–3% of those aged 15–19 in 1967–1976 but increased to 2–3 and 4–5%, respectively, in the two age-groups in

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Diabetes Center, Mount Sinai School of Medicine, New York, New York.

Abbreviations: CVD, cardiovascular disease; HNF, hepatic nuclear factor; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; MODY, maturity-onset diabetes of the young; NHANES III, Third National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome.

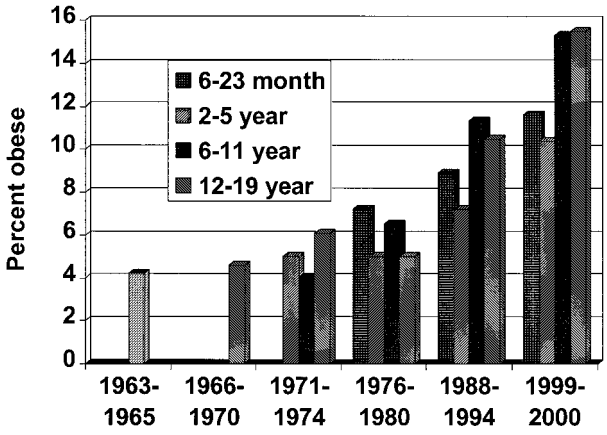

Figure 1—*Trends in childhood obesity (≥95th percentile weight-for-length age 6–23 months, BMI age 2–19 years) from birth through 19 years by age-group (from data in 5).*

1987–1996 (Fig. 2) (21). In a rural South-Asian population in Bangladesh in 1995, IGT was reported in 5.7% of persons aged 15–29 (22). Among an indigenous population in Australia, IGT was found in 8.1% of persons aged 7–18 years (23). In the U.S., among Navajo Indians, diabetes or IGT was found in 3 and 13%, respectively, of girls and boys aged 12–19 (24). In Canada, among the Cree-Ojibway aboriginals, diabetes and impaired fasting glucose (IFG) were found in 1 and 3% of children aged 4–19 (25), respectively, and IGT in 10% of those aged 10–19 (26). A 4% prevalence of diabetes among adolescent girls in native populations in Canada has been reported from several surveys (27). The prevalence of diagnosed diabetes among American Indians aged 15–19 in the southwestern U.S. increased from 3.2 to 4.5 per 1,000 from 1990 to1997 (28).

Clinic-based studies have also been used to assess changes in frequency of type 2 diabetes in young persons. Incidence rates of type 2 diabetes among young persons increased ~10-fold from 1982 to 1994 in Cincinnati, Ohio (29). From 1994 to 1998, the proportion of diabetic children diagnosed with type 2 diabetes in Florida increased from 9.4 to 20% (30). Among newly diagnosed children and adolescents in Bangkok, type 2 diabetes increased from 5% during 1986–1995 to 17.9% during 1996–1999 (31). In the United Arab Emirates, among those <18 years, 12.5% of persons with diabetes have type 2 (32). A 10-country study in Asia has shown ~10% of young people with diabetes attending major pediatric centers having type 2 diabetes, with considerable regional variation (33). Currently, approximately one-third of children and adolescent presenting with diabetes in Ohio, in Arkansas, and, among Hispanics, in California have type 2 diabetes (18).

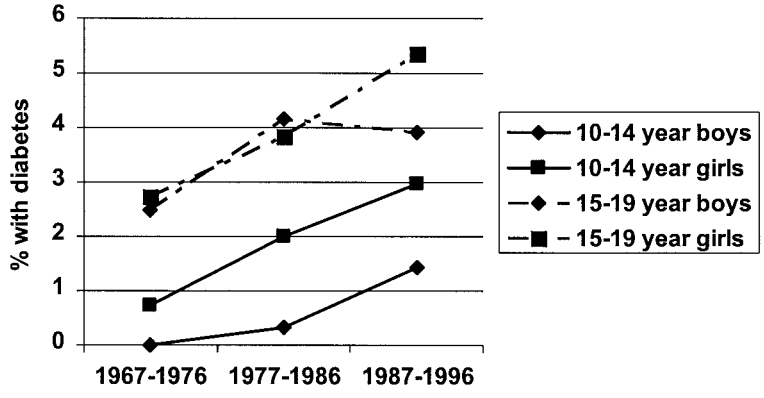

Figure 2—*Sex-specific prevalence of diabetes in Pima children age 10–14 and 15–19 years, in three time periods from 1967 to 1996.* $P < 0.0001$ *for temporal trend for both age-groups (from data in 21).*

Estimates of diabetes and IFG in the U.S. population from 1988 to 1994 are available from the Third National Health and Nutrition Examination Survey (NHANES III). Of almost 3,000 persons aged 12–19 tested in this representative national sample, the prevalence of IFG was 17.6 per 1,000, the prevalence of HbA_{1c} >6% was 3.9 per 1,000, while diabetes of all types (9 of the 13 diagnosed with diabetes were on insulin) was diagnosed in 4.1 per 1,000, suggesting that ~600,000 adolescents in the U.S. have some degree of glycemic abnormality, although the estimates are imprecise because of the relatively low prevalence (34). Using the "capture-recapture" method to estimate the prevalence of type 2 diabetes among school children in Osaka suggests a prevalence of almost 30 per 100,000 (35). The trend to increasing obesity closely parallels that of increasing diabetes among children in Japan, where ~1, 2, 3, and 4% of children were obese and incident type 2 diabetes occurred among 2, 3, 5, and 8 per 100,000 children in Tokyo in 1975, 1980, 1990, and 1995, respectively, in an annual urine screening for diabetes in school children aged 6 and 15 years (36). A similar increase in diabetes over time was seen in the city of Yokohama, further suggesting this to be a valid set of observations (35). A urine-based screening program of some 3 million students in Taiwan has shown similar annual type 2 diabetes incidence rates of 4 and 7 per 100,000 boys and girls (37). In these studies, not only obesity but also elevated blood pressure and cholesterol, both high and low birth weight, and positive family history of diabetes were associated with type 2 diabetes found at screening.

There may be underestimation of the magnitude of type 2 diabetes in youth because of underdiagnosis with no or few symptoms, misclassification as type 1 diabetes for those persons with more severe hyperglycemia, and case reporting mainly by pediatric endocrinologists leading to few data for those in the 15- to 19-year age-group. The likelihood of underdiagnosis for lack of symptoms can be appreciated from the Japanese studies, where the mean HbA_{1c} of those found at screening was 7.9%, with 46% having levels <6.5%, while those presenting with symptoms had mean HbA_{1c} at diagnosis of 10% (38). A screening methodology

not relying on glycosuria would presumably find cases at even lower levels of glycemia.

Estimates from the Japan and Taiwan screening programs suggest a cost of ~$10,000 (U.S.) per case found, so that unless it is possible to demonstrate benefit, it may not be appropriate to recommend that this be applied to all populations and it may be necessary to rely on "targeted screening" case-finding approaches. Indeed, cost-effectiveness analysis in adults suggests this to be an optimal approach for ascertainment of diabetes (39), although these analyses have not been carried out for children. Thus, screening for hyperglycemia among young persons with hypertension, dyslipidemia, insulin resistance and obesity may offer the most effective approach to diagnosis of type 2 diabetes in this age-group.

The greatest costs of screening will be those from treatment of persons who are discovered to have illness, so cost-effectiveness studies of diabetes screening among young persons must include analysis of the overall diagnostic and therapeutic process. Screening for type 2 diabetes in children appears, however, to meet a number of criteria, suggesting this to be an appropriate target. The disease is common, is serious in terms of morbidity and mortality, exhibits prolonged latency without symptoms, and can be assessed by blood glucose measurement with acceptable sensitivity and specificity. Furthermore, a number of interventions can prevent or delay disease onset, and it may be more effective to treat diabetes early in order to delay or prevent the complications. The consensus position of the American Diabetes Association and the American Academy of Pediatrics recommends testing at age >10 years or onset of puberty for children with BMI above the 85th percentile, with a first- or second-degree relative having diabetes, in an at-risk race/ethnic group, particularly with signs of insulin resistance such as acanthosis nigricans, hypertension, polycystic ovarian syndrome (PCOS), or dyslipidemia (19). The NHANES III data suggest that the American Diabetes Association risk criteria would lead to testing of 10% of youths, for a total of ~2.5 million adolescents between 12 and 19 years of age, of whom 5% might be expected to have IFG or undiagnosed diabetes, while 1.8% of those not tested under such recommendations would be expected to have IFG (40).

The measurement of fasting plasma glucose is preferred, with other potential tests being the 2-h oral glucose tolerance test (OGTT), a 2-h postprandial or random postprandial blood glucose, or HbA_{1c}. This is similar in concept to recommendations for screening of adults <45 years of age with major risk factors for type 2 diabetes (41). The fasting glucose measurement without an OGTT may, however, fail to identify all persons at risk. Furthermore, as children have lower mean glucose levels, the criteria used for diagnosis of diabetes, IGT, and IFG in adults may not be sufficiently low for full appreciation of hyperglycemia in younger persons. The glucose load needed for the OGTT may also need to be more fully assessed. The notion of "pre-diabetes" has become more important with these considerations. The term may be considered to mean IGT and/or IFG (42) or, alternatively, to represent a state before the existence of abnormality in glycemia in persons who subsequently develop diabetes. In either form, the concept may serve the purpose of "inform[ing] both the general public and health professionals about a modifiable state which, if reversed, could reduce the likelihood of type 2 diabetes" (43). It is, however, possible that identifying a young person as being "pre-diabetic" could cause psychosocial harm, particularly if effective intervention is not available, so that caution is needed before generally employing such approaches.

Pathogenesis of type 2 diabetes in the young

Genetics. A number of monogenic disorders causing diabetes in children have been described. These include β-cell defects such as maturity-onset diabetes of the young (MODY), types 1–6, transient neonatal diabetes, permanent neonatal diabetes, the syndrome of maternally inherited diabetes and deafness, the Wolfram syndrome, and the renal cysts and diabetes syndrome. There are also syndromes of insulin resistance, including type A insulin resistance, leprechaunism, familial partial lipodysptrophy, and total lipodystropy, and obesity syndromes, such as Prader Willi, Alstroms, and Bardet-Beidel. Diagnosis is important, as MODY-3 patients with hepatic nuclear factor (HNF)-1α mutations are sensitive to sulfonylureas (44) and actually tend to exhibit increased insulin secretory response to sulfonylureas and increased insulin sensitivity compared with persons with type 2 diabetes (45). They may therefore exhibit hypoglycemia on sulfonylurea initiation and a marked rise in HbA_{1c} if this treatment is discontinued. MODY patients with glucokinase mutations generally require no pharmacological treatment because the glycemic abnormality is mild.

Type 2 diabetes is probably caused by the same continuum of genetic abnormalities in children as in adults. A number of major predisposing genes have been found on chromosomes 1q, 12q, 20q, and 17q, with the only major gene identified being the calpain 10 gene in Mexican Americans (46). Minor genes that have been defined by the "candidate" approach include the Pro12Ala polymorphisms in peroxisome proliferator–activated receptor γ (47) and the Kir 6.2 E23K variant (48). The HNF-1α G319S private mutation predisposes to type 2 diabetes in Cree-Ojibway aboriginals in Canada (49). Carriers of 2 and 1 copies of the gene present ~12 and 6 years earlier, respectively, than those without the variant (50). Among children in this group with type 2 diabetes, there is a high prevalence of HNF-1α G319S (51). As diagnostic molecular testing is now available (for example, from www.diabetesgenes.org), it may be reasonable to employ this test in appropriate populations.

Familial factors and intrauterine growth retardation. The thrifty genotype and thrifty phenotype hypotheses have been combined into the concept of adverse effect of undernutrition. With the latter hypothesis, effects of intrauterine undernutrition and subsequent overnutrition lead to insulin resistance, while the thrifty genotype hypothesizes a survival advantage accrued from many generations of episodic malnutrition increasing the expression of this state. A U-shaped relationship has been shown, with diabetes prevalence being highest among persons with either low or high birth weight (52). Those persons with highest prepubertal body weight and those with lowest birth weight are particularly at risk of insulin resistance and diabetes (Fig. 3) (53,54). Other factors include family history, with there being a marked increase in diabetes frequency with one parent and an even greater frequency with two par-

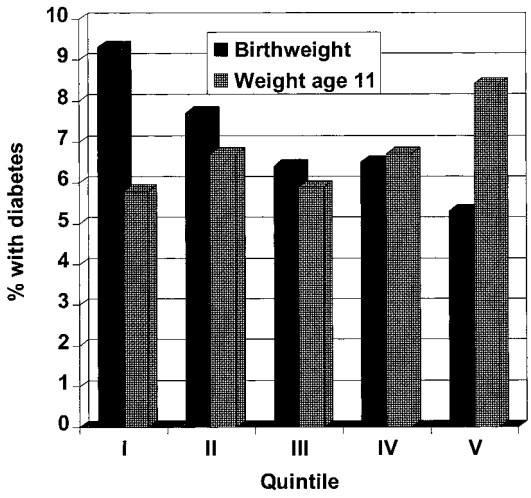

Figure 3—*Cumulative incidence of diabetes based on quintile of birth weight (*P *value for trend <0.005) and weight at age 11 (*P *value for trend <0.001) (from data in 54).*

ents having diabetes among Pima Indians age 5–19 (55). Exposure in utero to a mother with gestational diabetes is particularly associated with increased risk of diabetes (21) and appears to decrease insulin secretory capacity rather than decreasing insulin action (56).

Physical activity and insulin sensitivity. Children differ from adults in metabolic response to exercise, showing a lesser increase in the intramuscular inorganic phosphate-to-phosphocreatine ratio and a lesser decrease in pH (57). Obesity and dietary factors may alter the expected metabolic response to exercise. This can be seen with high-fat feeding, which reduces the growth hormone response to exercise (58). Growth hormone and epinephrine responses to exercise are blunted in obese subjects (69). Both intra- and extramyocellular triglyceride stores are greater in obese than in lean children (60). In children, there appears to be a body composition threshold around the 75th percentile of weight for height, above which abnormalities are seen in fitness, as measured by the maximal oxygen consumption, with reductions in insulin sensitivity also seen (61). Physical activity increases insulin sensitivity in children (62), and this is also seen among obese children undergoing regular exercise who show a fall in fasting insulin that is reversed by a return to a sedentary lifestyle (63).

Australian aborigines were a population exhibiting high levels of physical fitness in their traditional hunter-gatherer lifestyle, with low BMI, blood pressure, and cholesterol, although with elevated fasting insulin and triglyceride levels suggesting insulin resistance. With westernization, this population changed to one with high levels of unemployment, welfare dependency, poor education, overcrowded living conditions, poor health with heavy infectious disease burden, particularly among children (perhaps causing an inflammatory load), and increased lifestyle-related chronic disease among adults (64). The change in health and socioeconomic status is associated with central obesity, early-onset type 2 diabetes, and premature CVD with IRS features of dyslipidemia, hypertension, hyperinsulinemia, and microalbuminuria.

Low birth weight and diabetes in pregnancy have emerged as important risk factors in this group. The age profile of this group is similar to that of an underdeveloped country, with the majority in the younger age-groups and life expectancy 20 years less than that of the nondisadvantaged Australian population. The diabetes prevalence is 7% at age 25–34, 20% at age 35–44, and 28% at age 45–54, as compared with respective levels of nil, 3%, and 6% in the nondisadvantaged population, although the prevalence of obesity is similar in both groups (65). During the period from 1987 to 1995, the aboriginal population had a marked increase in BMI, with the incidence of diabetes among persons with BMI <25 kg/m^2 ~10 per 1,000 person-years, and more than a tripling of this rate among persons with BMI of ≥25 kg/m^2 (66). The Aboriginal Birth Cohort has traced 686 singleton births of Australian Aboriginal mothers between 1987 and 1990, 70% from remote rural locations, with follow-up beginning in 1998 of 482 children age 8–14 years showing decreased linear growth rates in the rural group, but with higher blood pressure, cholesterol, and insulin levels in the urban group and almost a fourfold increase in prevalence of BMI >25 kg/m^2, suggesting early development of features of the IRS (67). Similar evidence of high prevalence of overweight and obesity in urban Aboriginal children has been reported in other studies (68).

Studies in Japan suggest that weight gain is caused by a reduction in energy expenditure among young people, with participation by young people in Japan in exercise and sports showing a consistent decrease in all age-groups (69). Twenty-seven and 43% of high school boys and girls, respectively, in the U.S. participate in an insufficient amount of physical activity (70). Habitual leisure-time physical activity in girls decreases by approximately two-thirds among Caucasian girls and to an even greater extent among African-American girls in the U.S. as age in-

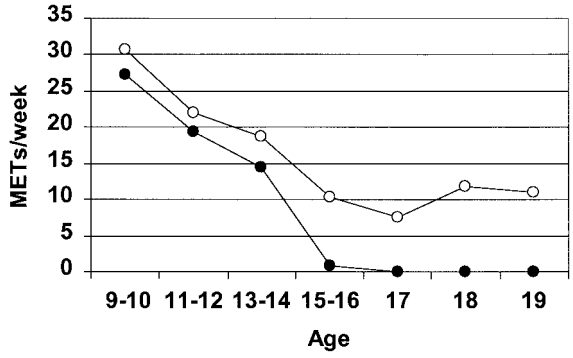

Figure 4—*Median habitual activity (in metabolic equivalent times [METs] per week). ●, black girls; □, white girls (from data in 72).*

creases from 9 to 18 years (Fig. 4) (71). This is particularly related to television viewing (72), which shows an interaction with decreased physical activity in relation to obesity (73). There is high correlation between television viewing and consumption of high-energy foods, further exacerbating this effect (74). Part of the cause may be the frequency of food advertisement on television programs directed at children. On average, children's programming includes 12 food advertisements hourly, more than twice that in adult viewing, with the average child in the U.S. seeing >20,000 advertisements per year (75). Parental influences are also important, with the NHANES III survey showing nearly one-third of mothers of overweight children to believe that the children are at "about the right weight" (76).

Insulin resistance in young persons. The development of type 2 diabetes involves a loss of the balance between insulin sensitivity and secretion, as has been reported in adults, where the normal inverse relationship between the two factors leads to a constant glucose disposition index in a given person, with decline in this parameter being associated with the development of IGT and type 2 diabetes (77). Insulin resistance in the young has been reported in a variety of ethnic groups and is strongly associated with obesity (78). Furthermore, obese children exhibit glucose intolerance, which is strongly associated with evidence of both insulin resistance and impaired insulin secretion (14).

There are important ethnic differences in the degree of insulin resistance (79). In a study comparing 22 black and 22 white nonobese prepubertal children, the former group was found to have a significant decrease in insulin sensitivity with hyperinsulinemia, showing, however, lower glucose disposition indexes, suggesting an increase in ultimate diabetes risk. Circulating levels of the insulin-sensitizing adipocyte secretory product adiponectin were ~60% higher in white children. Important dietary differences were found, with the black children consuming 10% fewer calories from carbohydrates and showing a 36% increase in the dietary fat–to–carbohydrate ratio, which had strong negative correlation with insulin sensitivity. Whether this is causally related to metabolic abnormalities remains to be determined (80). One important determinant of obesity may be the relative propensity to retain fat in adipose tissue, with evidence that rates of lipolysis are lower in black than in white boys and girls (81).

Comparing obese and normal-weight black and white adolescents, insulin sensitivity is decreased with obesity regardless of ethnicity, showing inverse correlation with body fat (82). A number of studies have shown that black children have higher total fat and cholesterol intake, prefer greater sweetness in liquids, are physically less active, and spend more time watching television. Black girls have higher total energy intake than whites, do not perceive themselves as heavy, and actually express a desire to be on the fat side (83–89). Clearly, then, there must be a complex interplay of cultural/environmental and genetic factors explaining the metabolic differences observed between the two ethnic groups.

Of particular importance as a determinant of insulin resistance is central obesity (90). In a cross-sectional study of 14 adolescents with IGT matched with 14 control subjects of similar age, BMI, body fat, and leptin, the children with IGT were insulin resistant, with increased intramyocellular fat measured by ^{1}H nuclear magnetic resonance spectroscopy showing strong correlation with insulin sensitivity and with 2-h postload plasma glucose. Those with IGT had higher visceral and lower subcutaneous abdominal fat and decreased first-phase insulin secretion and glucose disposition index (91). Comparing black and white children with obesity and similar insulin sensitivity levels, blacks have lower hepatic glucose output, lower total and LDL cholesterol, and lower triglyceride levels, with considerably lower visceral fat levels. Blacks who do have visceral obesity, however, have a fall in the glucose disposition index (92), suggesting greater diabetogenic risk of obesity among blacks, but greater atherogenic risk among whites. Important additional risk of diabetes is seen among black children with a positive family history of diabetes, who show an ~20% lowering of insulin sensitivity in the first decade of life (93).

A major cause of insulin resistance is puberty (94). Insulin sensitivity decreases by ~30% during puberty with compensatory increase in insulin secretion (95,96). Insulin action decreases similarly during puberty in black and white children (97). The further metabolic derangement of PCOS is associated with decreased glucose disposition (98), with ~30% of adolescent girls with PCOS having IGT and 4% type 2 diabetes (99). Adolescents with PCOS who develop IGT have similar degrees of obesity and elevations in circulating testosterone to those with normal glucose tolerance but show blunting of first-phase insulin secretion in response to intravenous glucose with a consequent decrease in the glucose disposition index (100).

Complications

Microvascular disease. Among Pima Indians with type 2 diabetes diagnosed during childhood, microalbuminuria was seen in 22% at diagnosis and in 58% at follow-up, macroalbuminuria in 0 and 16%, and hypercholesterolemia in 18 and 30%, suggesting the tendency to progression of both micro- and macrovascular disease (101). In another study of 178 Pima Indians with onset of type 2 diabetes before age 20, a urinary protein-to-creatinine ratio >0.5 g/g was seen in 20% after 25 years, implying a similar relationship between duration of diabetes and nephropathy to that seen in persons with adult onset of diabetes, while there was relative protection against retinopathy, which had developed in 15% (Fig. 5) (102). Retinopathy progression rates are similar in Japanese young persons with type 1 and type 2 diabetes, but nephropathy occurs approximately two times more commonly among young persons with type 2 than among those with type 1 diabetes (104). After a 20-year diabetes duration, 50 of 1,065 Japanese persons with onset of type 2 diabetes before age 30, whose mean age at diagnosis was 20, required dialysis and 128 had developed proliferative retinopathy before age 35, of whom 23% were on dialysis. An additional important finding is that both primary and acquired renal disease not caused by diabetes appear to be common in populations with a high prevalence of type 2 diabetes in young persons (105,106). Children developing end-stage renal disease have a 1,000-fold increase in CVD mortality in young adulthood that is associated with hypertension and dyslipidemia, suggesting a particular challenge (107). In a study of Manitoba Cree young adults, mortality was 9%, 6% required dialysis, 38% of the women who had become pregnant had

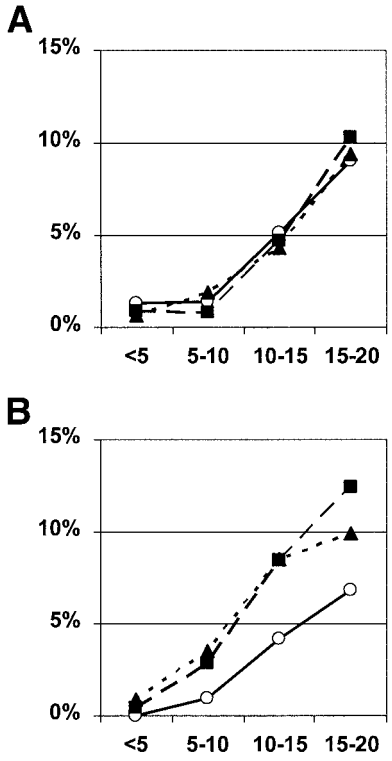

Figure 5—*Prevalences of diabetic nephropathy* (A) *and retinopathy* (B) *among Pima Indians versus diabetes duration among persons developing diabetes before age 20* (○)*, 20–39* (■)*, and ≥40* (▲) *years.*

pregnancy loss, 35% were lost to clinical follow-up, and 67% had poor glycemic control (108).

Macrovascular disease. Fibrous plaque lesions are present in the aorta and coronary arteries of children and young adults and associated with obesity, dyslipidemia, and cigarette use (109). Risk factors for CVD predate the onset of type 2 diabetes in adults, but there are no prospective studies on CVD risk factors and long-term outcomes in childhood and adolescent type 2 diabetes. The dyslipidemia of type 2 diabetes is not fully corrected by strict glycemic control, suggesting the need for assimilation of new concepts for pediatric treatment. Certainly, correction of risk factors, including those involved in dyslipidemia, such as triglyceride, VLDL, LDL, small dense LDL, apolipoprotein B, HDL, and apolipoprotein A-1 should be an important treatment emphasis (110). Treatment of hypertension is important, (111,112), as is cigarette discontinuation (113) and treatment of microalbuminuria and other renal disease manifestations (114). Obesity is itself important to address (115). Attention to control of glycemia is reasonable (116), although little evidence shows that intensive glycemic control delays or prevents macrovascular disease. An important clinical factor is the presence of family history of complications. Finally, treatment of hypercoagulability and decreased fibrinolysis is important (117), although the relatively small risk of Reye's syndrome, which is rare after puberty, has dissuaded pediatricians from using aspirin.

The National Cholesterol Education Program lipid guidelines for children include LDL <110, HDL >45, and triglyceride <125 mg/dl as "desirable," whereas levels >130, <35, and >125 mg/dl, respectively, are termed "undesirable" (118). The American Diabetes Association has recently proposed that desirable levels of LDL for children without and with diabetes be considered <130 and <100 mg/dl, respectively (119). Pharmacological treatment is generally instituted with caution in young persons, starting with dietary lipid management with staged diet, and niacin and cholestyramine are the best-studied agents in children, although safety studies for statins are now appearing (120,121). Microalbuminuria measurement at diagnosis and yearly thereafter, as well as ACE inhibitor treatment for children with microalbuminuria or hypertension, appear appropriate, with recognition of the potential teratogenicity of these agents. Blood pressure goals among children need to be adjusted for age, height, and sex, and there is currently no evidence as to whether the 95th or 90th percentile should be chosen as the appropriate target (122).

Other complications associated with type 2 diabetes in young persons. Nonalcoholic fatty liver disease is associated with obesity and insulin resistance. Among young persons with diabetes in the Manitoba Cree, there was a 16% prevalence of alanine aminotransferase elevation to three times the upper level of normal (123). Of the Cree group, 38% smoked cigarettes, and some authors have suggested urine cotinine screening because of the high frequency of "covert" cigarette use (124).

Treatment

Goals of treatment include the achievement of glycemic control (at HbA_{1c} <7%), striving for a level as near to normal as possible in order to eliminate symptoms of hyperglycemia and reduce microvascular complications (125). Furthermore, maintenance of reasonable body weight, improvement of CVD risk factors, and improvement of physical and emotional well-being are additional reasonable goals. Strategies for glucose self-monitoring need to be delineated, particularly addressing evidence that such approaches are cost-effective and necessary for young persons with type 2 diabetes. Such a treatment approach may be aided by participation in a structured diabetes education program. For young persons, the important role of the family in diabetes management cannot be underestimated, and it is crucial to include direct family supervision in optimizing glycemia (126). One needs to take into account familial and/or psychosocial dysfunction, ethnic influences, and barriers to compliance, recognizing that the long lifespan of children requires the development of safe and effective therapeutic approaches.

A proposed therapeutic algorithm for asymptomatic children with type 2 diabetes therapy is to start with lifestyle intervention approaches to diet and exercise; then to add monotherapy, particularly emphasizing the use of metformin; then to use combinations of two oral medications, although recognizing that neither sulfonylureas nor thiazolidinediones have been fully studied in the pediatric age-group; and then to add insulin. For symptomatic children, with blood glucose >300 mg/dl or when ketoacidosis is present, a reasonable approach is to start with insulin with subsequent efforts to taper this and substitute metformin (127). If diabetes is diagnosed early in a young person, lifestyle intervention may suffice, although this only appears to be applicable to ~10% of patients at the time of presentation. Such approaches require intensive and expensive counseling efforts, and it remains to be seen whether they can be employed in clinical practice.

Pharmacological treatment. Pharmacological treatment may include insulin, metformin, insulin secretagogues, thiazolidinediones, and α-glucosidase inhibitors. Insulin is familiar to pediatricians and pediatric diabetologists and is effective in treating acute metabolic decompensation, particularly when it is uncertain whether the patient has type 1 of type 2 diabetes. It may in addition convey a message of more serious illness, perhaps improving compliance (128). In

clinical practice in the U.S., approximately one-half of young patients with type 2 diabetes receive insulin and one-half oral agents, most commonly metformin (127).

Metformin is approved in the U.S. for pediatric use. It is typically used as the initial pharmacological treatment in the absence of severe hyperglycemia, lowering HbA_{1c} by 1.1% and fasting blood glucose 64 mg/dl in such patients (129). It will be important to obtain outcome studies. Analysis of efficacy of metformin in a group of Cree in Canada showed little effect of metformin on HbA_{1c} or body weight after 1 year among adolescents with type 2 diabetes, although gastrointestinal side effects were more common with treatment (130). Poor adherence to oral therapy among relatively asymptomatic young persons with type 2 diabetes may be a major barrier to improvement in outcome.

Sulfonylureas are well studied in adults and are effective, safe, and inexpensive, although they may cause weight gain and hypoglycemia and have no effect on lipids. Newer sulfonylureas and nonsulfonylurea insulin secretagogues and combination approaches with metformin may allow greater flexibility and improvement in outcome. The thiazolidinediones are being used in studies for pediatric use, and although associated with weight gain, their reduction in visceral fat suggests overall benefit if long-term safety concerns can be addressed. The safety profile with regards to edema and congestive heart failure may be more favorable in pediatrics, although this needs to be determined. α-Glucosidase inhibitors are used infrequently but are safe and have been shown to have a role in prevention (131), although their gastrointestinal side effects may decrease acceptance among young persons.

Prevention

It may be possible to combat the trend to increasing obesity with programs aimed at increasing activity levels in children. In Singapore from 1992 to 2000, the "Trim and Fit" program led to a fall in obesity prevalence from 16 to 14% of primary and secondary school students (132). An exercise intervention in Japan decreased the prevalence of overweight from 40 to 37% among boys and to 32% among girls between ages 10 and 13, with no change in a control group (133).

In an analysis of 173 Mexican-American children age 9 years from a low-income neighborhood, ingestion of total and saturated fat was greater than recommended national dietary guidelines and reported daily fruit and vegetable intake was half of what was recommended. Their physical fitness level, measured with modified Harvard exercise protocol, was low, they watched television on average of 3.5 h daily, and they had high body fat. Sixty percent had a first- or second-degree relative with diabetes (134). The Bienestar school-based diabetes prevention program, based on the concept that increasing knowledge is not sufficient to change health behavior, aimed to create a network of social support in the classroom, home, school cafeteria, and among friends and classmates. School cafeteria staff and parents may themselves need education to decrease saturated fats and increase fruits and vegetables and to participate in the development of healthy food and exercise habits among children. Of 93 sessions in the program, one-third were for children and the rest for school personnel and parents. Using such an approach, in a population of 1,420 students, fasting capillary glucose at baseline was 110–125 mg/dl in 35 and >125 mg/dl in 7, with a decrease in fasting blood glucose from 127 to 97 mg/dl among children in the intervention program compared with a fall from 117 to 99 mg/dl children not participating in the program. Of the remaining children whose initial blood glucose was <110 mg/dl, 10 of 651 in the intervention group, but 19 of 618 in the control group, had glucose ≥110 mg/dl after the 1-year program. Physical fitness increased in the intervention group but decreased in the control group. The intervention group showed higher calorie intake, which was compatible with the increased physical activity. BMI increased in both groups, but the intervention group had a 1.3% and the control group a 0.65% decrease in body fat (135).

Risk reduction and prevention strategies for obesity, as for all illnesses, are difficult and time consuming because of the multicausal etiology of the condition, heterogeneous time perspectives, low compliance, competition for prevention of other illnesses, calls for additional evidence, economic priorities, and information overload of the persons who are targeted for this and other interventions (136). One difficulty is the perception by physicians and overweight persons that large weight loss is required. Analysis of a strategy of weight gain prevention in Holland, assuming that the expected 3.5% mean increase would be prevented for 10 years, suggested that a decrease in osteoarthritis by 5–6% and consequent decrease in work loss by 2–3% could be anticipated (137). Furthermore, persons who develop obesity must have greater annual weight gain than persons who remain nonobese, so simply sustaining a stable weight represents an important achievement, and the recommended 5–10% maintained weight loss for persons with or at risk of diabetes would be highly effective, although neither physicians nor patients are satisfied with such outcomes. For overweight and obese children, appropriate goals may include weight maintenance or even retardation of weight gain.

There are a number of barriers to effective weight loss in obese persons with diabetes (138). Physical activity is particularly a problem in older persons with diabetes, who often have contraindications to exercise and may not be able to perform even mild exercise to aid in their attempts at weight loss (139). The decrease in fitness among young persons with obesity and pre-diabetes may similarly potentiate their weight gain. A particular problem in adults, which may be important in children as well, is weight gain before and during holidays, amounting annually to an average of 0.6 kg and hardly offset by the average 0.1-kg weight loss following the holiday (140). There is a weak but significant negative correlation between obesity and decreased sense of smell, so that the obese person may overeat because of failure to achieve olfactory satisfaction (141).

Another set of barriers to weight loss is in beliefs and behaviors of the health care provider. Physicians feel that "fat patients" do not comply with advice, and the skills to assist with weight loss decreased among physicians between 1992 and 1997 with diminishing notice of weight problems (142). Physicians identify few persons potentially with sleep apnea, consistently failing to ask questions to identify the syndrome (143). Whether similar characteristics apply to providers of treatment for young persons is again not known.

Predictors of long-term success in weight reduction are early weight loss,

which encourages ongoing participation, male sex, lower age, greater education, more social support, weight history, and behavioral and cognitive strategies; treatment characteristics associated with success include approaches that empower self-confidence and feelings of control, with a good weight-maintenance/follow-up approach. The National Weight Control Registry reports show that 90% of successful dieters show similar approaches to weight maintenance: following a low-fat, high-carbohydrate diet, frequently self-monitoring their weight, eating breakfast, and being physically active (144). Diet may itself be associated with adverse consequences, with a study of 810 teenagers in the U.S. showing that for boys, advice from mothers to diet was associated with more worry about weight gain,and much greater likelihood of binge eating (145).

Pediatric obesity is a novel concern, for which prevention is optimal but not likely with current approaches. Predictors of weight gain are therefore needed so that intervention at early stages of this costly condition can be initiated. For obese diabetic adolescents, diet, exercise, behavior, and drug treatment are options, although very few drug or surgery studies have been carried out in obese children, suggesting that we may be undertreating obese children. Attitudes, prejudice, and stigmatization by the medical profession may be important obstacles. Weight loss is effective among adolescents in increasing insulin sensitivity and reducing blood pressure (146).

Another set of approaches to lifestyle measures at risk reduction can be gained from the perspective of studies of groups with a particularly high risk of diabetes. Potential interventions include glycemic control of diabetic pregnancy and reduction of risk of low birth weight by prevention of smoking and genital infection. Encouraging breast-feeding may minimize excessive energy intake and perhaps improve insulin sensitivity in the child because of the higher polyunsaturated fat content of breast milk than cow milk. Pima Indian studies show a lower prevalence of type 2 diabetes with breast-feeding during infancy (147). In studies of Native Canadians, exclusive breast-feeding results in a fourfold decrease in diabetes during adolescence (148). Supportive environments for regular physical activity and healthy food supply may lead to a decrease in diabetes development. School lunch (and breakfast) programs can be highly effective in providing healthier diet in these settings.

In a trial of 192 children in two California schools, television and videotape viewing and video game use was reduced from 12 to 8 h/week in the intervention group versus no change in the control group. Those in the intervention group had a 0.45-kg/m^2 lesser increase in BMI and a 2.3-cm lesser increase in waist circumference that the control group during the 6-month study (149). The "Kids 'N Fitness" program promotes health and wellness in classrooms across the U.S. (150), with similar programs having been shown to decrease weight gain among at-risk young persons from 1.2 to 0.2 kg/month (151).

Metformin was shown to be of equal efficacy to intensive lifestyle intervention in decreasing conversion from IGT to diabetes among younger obese adults in the Diabetes Prevention Program (152). In a study of 29 obese hyperinsulinemic adolescents with a positive family history of type 2 diabetes randomized to metformin versus placebo, however, although BMI and fasting insulin improved modestly with treatment, no change could be demonstrated in insulin sensitivity, HbA_{1c}, lipids, or glucose disposal; therefore, it is uncertain whether this medication will have a role in the prevention of type 2 diabetes among young persons (153).

Summary

Type 2 diabetes is becoming an increasingly prevalent disorder among young persons who are driven, as is the case in adults, by lifestyle factors leading to increased body weight. Genetic and familial factors, fetal environmental factors, particularly maternal gestational diabetes and intrauterine growth retardation, and lack of physical activity during childhood and adolescence lead to increasing levels of insulin resistance that appear to be crucial in the pathogenesis of type 2 diabetes in the young. The disorder is associated with microvascular disease, with a suggestion of greater risk of nephropathy than of retinopathy, and may also lead to early macrovascular disease. Treatment includes lifestyle modification and the pharmacotherapeutic approaches utilized in adults with type 2 diabetes, with studies to date supporting the roles of insulin and metformin, suggesting the importance of studying insulin secretagogues and thiazolidinediones as approaches in the treatment of type 2 diabetes in the young. The development of effective approaches to disease prevention will be of great importance.

Acknowledgments— Financial support for the International Diabetes Federation Consensus conference was provided by Johnson & Johnson.

The conference organizing group members are George Alberti (London), Francine Kaufman (Los Angeles), Martin Silink (Westmead, Australia), and Paul Zimmet (Caulfield, Australia). Presentations were made by Silva A. Arslanian (Pittsburgh, PA; insulin resistance), Peter Bennett (Phoenix, AZ; pathogenesis), Sonia Caprio (New Haven, CT; insulin resistance and approaches to risk reduction), Lee-Ming Chuang (Taipei, Taiwan; screening), Dan Cooper (Irvine, CA; exercise), Heather Dean (Manitoba, Canada; microvascular disease), Andrew Hattersley (Exeter, U.K.; genetics), Francine Kaufman (screening and treatment), Kaichi Kida (Ehime, Japan; epidemiology) Kerin O'Dea (Casuarina, Australia; Australian aborigines), Michael Marmot (London; socioeconomic considerations), Chittaragnan Yajnik (Rasta Peth, India; fetal and neonatal origins of insulin resistance), Stephan Rössner (Stockholm, Sweden; obesity), Martin Silink (CVD risk management), Roberto Treviño (San Antonio, TX; prevention), Frank Vinicor (Atlanta, GA; epidemiology), and Paul Zimmet (epidemiology).

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