Type 2 Diabetes in the Young: The Evolving Epidemic: The International Diabetes Federation Consensus Workshop

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Type 2 Diabetes in the Young: The Evolving Epidemic

The International Diabetes Federation Consensus Workshop

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EXECUTIVE SUMMARY

1. The aims of the consensus meeting were to review the epidemiology, pathophysiology, management, and implications of the rising prevalence of type 2 diabetes in young people and to suggest means by which the continuing rise in incidence and prevalence might be prevented.
2. The overall global prevalence of type 2 diabetes is rising steadily. Previously, type 2 diabetes was predominantly a disease of middle-aged and older people. In recent decades, the age of onset has decreased and type 2 diabetes has been reported in adolescents and children worldwide, particularly in high-prevalence populations. Japan has seen an approximate fourfold rise in the incidence of type 2 diabetes in 6- to 15-year-olds, and between 8 and 45% of newly presenting children and adolescents in the U.S. have type 2 diabetes. The problem is particularly noticeable in indigenous peoples. Population-based data, however, are sparse and indeed absent in most countries.
3. Additional cardiovascular risk factors are often associated with type 2 diabetes in the young, and microangiopathy is as common or commoner in those developing type 2 diabetes at a young age as in those with type 1 diabetes. This has profound societal implications.
4. Diagnostic separation of type 2 from other types of diabetes in young people can be difficult, and sophisticated testing may be necessary.
5. Data on the pathophysiology in the young are sparse, but there is no evidence to suggest differences from adults. The incidence of type 2 in the young is rising in parallel with the incidence of overweight and obesity, suggesting a possible causal relationship, particularly when the obesity is central and in relation to decreased physical activity. Other factors include family history, gestational diabetes in the mother, and low birth weight. All of these are associated with insulin resistance, although decreased insulin secretion is also required.
6. Mass screening for type 2 diabetes in the young has been carried out in certain countries (Taiwan and Japan) but is probably appropriate only for individuals at very high risk. The best screening test for young people is not known.
7. Treatment should be aimed at physical and psychological well-being and avoidance of long-term complications. Lifestyle modification must accompany other forms of therapy. In certain countries, metformin is available for treatment of children, but efficacy remains unproven. Newer oral agents have not been tested systematically in children or adolescents. Insulin remains the most frequently used treatment. Hypertension and dyslipidemia are also common and require active intervention.
8. Prevention must be the main strategy for the future. School-based programs have been shown to be effective in the U.S. and Singapore. Major governmental actions that focus on lifestyle will be required.
9. Recommendations for action are made.

RECOMMENDATIONS

1. Population-based prevalence studies are urgently needed, particularly in "at-risk" populations. These should be followed by outcome studies.
2. Study methods need to be standardized with regard to classification, diagnostic methods, and diagnostic criteria.
3. Data on the natural history of type 2 diabetes in the young, particularly on complications, are required.
4. Further research is required to determine the role of the oral glucose tolerance test (OGTT) in screening asymptomatic young people, as well as the appropriate glucose load and tim-

The International Diabetes Federation Consensus Workshop, "Type 2 Diabetes in the Young: The Evolving Epidemic," took place in Santa Monica, California, on 7–9 February 2003. A complete list of workshop participants and their respective affiliations is listed in the APPENDIX.

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Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; DKA, diabetic ketoacidosis; IDF, International Diabetes Federation; HNF, hepatocyte nuclear factor; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MODY, maturity-onset diabetes of youth; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

ing of blood sampling to be used in the OGTT.
5. The costs and psychosocial impact of screening in young people need to be examined.
6. The safety and efficacy of oral hypoglycemic drugs in children need to be determined.
7. The role of insulin therapy for children with type 2 diabetes needs to be determined in multicenter randomized controlled trials. These should examine the optimum type, timing, intensity, and duration of insulin therapy.
8. Existing registers for type 1 diabetes in children should be expanded to include those with type 2 diabetes.
9. Innovative ways of working with children with diabetes and their families to institute long-standing and sustainable lifestyle change need to be sought.
10. Strategies for the prevention of type 2 diabetes in children need to involve government and societal, as well as individual, change. Programs should focus on the prevention of obesity through increasing physical activity and promoting healthy eating, the promotion of breast feeding, and achieving excellent pregnancy outcomes with regard to avoiding low birth weight and treating gestational diabetes.

AIM AND OBJECTIVES OF THE WORKSHOP

— The Consensus Workshop on "Type 2 Diabetes in the Young: The Evolving Epidemic" was convened by the International Diabetes Federation (IDF) in response to the many reports of the occurrence of type 2 diabetes in children and adolescents. The objective of this document is to review the current information on type 2 diabetes in youth and to reach a consensus on what actions need to be taken to slow or reverse this trend. The topic has become a clinical, research, and health economic priority, with important implications for the health status of future generations throughout the world.

The workshop sought to:

- Assess current information on type 2 diabetes in the pediatric population in terms of epidemiology and public health implications
- Review the classification and diagnosis of type 2 diabetes in children and adolescents
- Discuss the pathogenesis of type 2 diabetes in youth
- Evaluate screening recommendations
- Assess the burden of complications
- Make recommendations on therapeutic options
- Assess the opportunities for prevention in order to reach a consensus on what actions need to be taken to slow or reverse the epidemic.

INTRODUCTION AND BACKGROUND

— Until recently, type 2 diabetes was typically regarded as a disease of the middle-aged and elderly. While it still is true that this age-group maintains a higher risk than younger adults, evidence is accumulating that onset in those aged under 30 years is increasingly common. Even children and adolescents are now becoming caught up in the diabetes epidemic. Although type 1 diabetes remains the main form of the disease in children worldwide, it is likely that type 2 diabetes will be the predominant form within 10 years in many ethnic groups. Type 2 diabetes has already been reported in children in a number of countries, including Japan, the U.S., India, Australia, and the U.K. (1–5).

This new phenomenon brings a serious new aspect to the global diabetes epidemic and heralds an emerging public health problem of major proportions. Among children in Japan, type 2 diabetes is already more common than type 1 and accounts for 80% of childhood diabetes. The rising prevalence of obesity and type 2 diabetes in children is yet another symptom of the effects of sedentary lifestyles as part of globalization and industrialization affecting all societies (1).

This fall in the age of onset of type 2 diabetes is an important factor influencing the future burden of the disease and was part of the stimulus for the IDF to organize the workshop. Onset of diabetes in childhood or adolescence heralds many years of disease and an increased risk that the full range of both micro- and macrovascular complications will occur when affected individuals are still relatively young. Thus, future generations may be burdened with morbidity and mortality at the height of their productivity, potentially affecting the workforce and health care systems of countries across the world.

EPIDEMIOLOGY

— The global burden of type 2 diabetes is both significant and rising, with most of the increase registered in the last two decades (6). From 2003 to 2025, the worldwide prevalence of diabetes in adults is expected to increase from 5.0 to 6.2%, or 328 million (7). The largest proportional and absolute increase will occur in developing countries, where the prevalence will rise from 4.2 to 5.6%. In India and China, the adult diabetic population is expected to double by 2025 to about 73 million and 46 million, respectively.

While most of the rise in the prevalence of type 2 diabetes has been seen in the middle-aged and elderly, there is now strong evidence of a rise among younger adults. In Australia, 1.7 and 1.4% of persons aged 35–44 and 45–54 years had diabetes in 1981 (8), and these prevalence rates increased to 2.4 and 6.2%, respectively, in 2000 (9). Chinese data show that the prevalence of diabetes among 35- to 44-year-olds rose from 1.7% in 1994 to 3.2% in 2000 (10). These data confirm a trend to an earlier age of onset of diabetes.

There are ever increasing reports of type 2 diabetes in children worldwide, with some as young as 8 years old being affected (11). These are mostly in ethnic groups with a high susceptibility to type 2 diabetes. However, there are now also reports of type 2 diabetes occurring among Europid (white Caucasoid) teenagers (4). In Japan, the prevalence of type 2 diabetes among junior high school children has doubled from 7.3 per 100,000 between 1976 and 1980 to 13.9 per 100,000 in 1991–1995, with type 2 diabetes now outnumbering type 1 diabetes in that country (1). Recent studies from the U.S. indicate that between 8 and 45% of recently diagnosed diabetes in the young is due to type 2 diabetes (12). Despite the large increase, the prevalence is still, fortunately, much lower than in the adult population.

Inadequate data at present

The available information on type 2 diabetes incidence and prevalence in childhood and adolescence is sparse compared with that for adults. Most surveys are clinic based or case series, with a paucity of population-based surveys, particularly outside North America (13) and Japan (1). Information on the natural history and etiology of type 2 diabetes in the pediatric age range is also sparse. There is

also a lack of uniformity in case definition (resulting in misclassification so that some children are being misdiagnosed and treated as type 1 diabetes), data collection, and follow-up (14).

The studies in the literature may be divided into population- and clinic-based studies.

Population-based studies

The largest study reported is from Japan (1), with ~7 million youth studied between 1976 and 1997. The initial screening step of the study was a urine glucose test, with blood testing reserved only for those with glycosuria; thus, the figures are probably an underestimate. Over the 20-year period, type 2 diabetes incidence increased 10-fold in children aged 6–12 years: 0.2 per 100,000 per year from 1976 to 1980 vs. 2.0 per 100,000 per year from 1991 to 1995. Similarly, over the same time period, type 2 diabetes incidence doubled among 13- to 15-year-olds: 7.3 vs. 13.9 per 100,000 per year.

A screening program in which fasting blood glucose was measured in those with persistent glycosuria carried out in 3 million students (aged 6–18 years) in Taiwan (15) found the prevalence of undiagnosed diabetes to be 9.0 and 15.3 per 100,000 boys and girls, respectively. The prevalence of undiagnosed diabetes was 62% higher in girls than boys, after adjustment for other factors, and the cases were most commonly identified between the ages of 12 and 14 years. A 3-year follow-up of these cases showed that 54% had type 2 diabetes, 10% had type 1 diabetes, 9% had secondary diabetes, 20% were nondiabetic, and 8% had no definite diagnosis. The cases identified as having type 2 diabetes had a higher mean BMI, cholesterol, and blood pressure than those with a normal fasting glucose, suggesting that even at this young age, cardiovascular risk was starting to rise.

In Pima Indians aged 15–19 years, the prevalence of type 2 diabetes markedly increased from 2.4% in males and 2.7% in females in 1967–1976 to 3.8% in males and 5.3% in females in 1987–1996 (14). In the U.S., among Navajo Indians, diabetes or impaired glucose tolerance (IGT) was found in 3 and 13%, respectively, of girls and boys aged 12–19 years (16). In Canada, among the Cree-Ojibway aboriginals, diabetes and impaired fasting glucose (IFG) were found in 1 and 3% of children aged 4–19 years (17), and IGT was found in 10% of those aged 10–19 years (18). A 4% prevalence of diabetes among adolescent girls in native populations in Canada has been reported from several surveys (19). A cohort of indigenous Australian children aged 7–18 years was surveyed in 1989 and again in 1994. Over the 5 years, the prevalence of type 2 diabetes almost doubled to 1.3%, while that for IGT increased almost sevenfold to 8.1% (20). At the follow-up, 18% of the population was overweight or obese, and one-third had elevated cholesterol levels.

National U.S. data from 1988 to 1994 (21) show that of ~3,000 persons aged 12–19 years, the prevalence of IFG was 1.8% and the prevalence of elevated HbA_{1c} (>6%) was 0.4%, while diabetes of all types (9 of the 13 diagnosed with diabetes were on insulin) was diagnosed in 0.4%, suggesting some glycemic abnormality in ~600,000 adolescents in the U.S.

Clinic studies

Clinic and register-based studies make up the largest group of studies. They reveal type 2 diabetes occurring in children as young as 8 years old (11). In addition, they have demonstrated a female preponderance (22–24), a strong family history of diabetes (22,25,26), and associations with obesity (11,22,25–27), acanthosis nigricans (11,26,27), and polycystic ovary syndrome (PCOS) (28).

A number of clinic-based studies have estimated incidence rates. In Cincinnati, Ohio, the annual incidence of type 2 diabetes in 10- to 19-year-olds increased from 0.7 per 100,000 in 1982 to 7.2 per 100,000 in 1994 (26). Among African-American and Latino children (aged 0–17 years) in Chicago, Illinois, the incidence of type 2 diabetes rose by 9% per year from 1985, reaching 3.8 per 100,000 per year (29) by 1994. This study showed higher rates in girls and in African Americans.

The prevalence of diagnosed diabetes among American Indians aged 15–19 years, as reported right across the Indian Health Service, increased from 0.32 to 0.54% from 1990 to 1998 (30). Although the prevalence of type 2 diabetes was higher among females, the relative increase over this time period was greater among males (0.23 to 0.41% for males vs. 0.42 to 0.68% for females). Over the same time period, the prevalence among those younger than 15 years was unchanged at 0.12%.

Some studies that analyzed referrals to diabetes clinics have reported the percentage of diabetes cases labeled as type 2. From 1994 to 1998, the proportion of new cases of pediatric diabetes in Florida that were labeled as having type 2 increased from 9.4 to 20% (31). In Cincinnati in 1994, type 2 diabetes accounted for 16% of all new cases of diabetes in children aged up to 19 years and accounted for 33% of new cases among the 10- to 19-year-old age-group (26). In Mexican-American youth aged 0–17 years, a California clinic reported that 31% of the diabetic children had type 2 diabetes (32). Among newly diagnosed diabetic children and adolescents in Bangkok, type 2 diabetes increased from 5% of all cases during 1986–1995 to 17.9% during 1996–1999 (27). In contrast, among European populations, which have lower overall prevalences of type 2 diabetes, two very large studies have reported that only 0.5% of children and adolescents with diabetes have been classified as having type 2 diabetes (33,34).

Complications—morbidity and mortality

As with adults, it can be expected that youth with type 2 diabetes will also develop diabetes-related micro- and macrovascular complications, and there is already evidence available of microvascular complications. In a study from Canada, subjects who developed type 2 diabetes as children were resurveyed as young adults aged between 18 and 33 years. Of the 51 subjects, 9% had died, 6% were on dialysis, 1 had a toe amputation, and 1 was blind (35). Another follow-up study from Japan compared those with type 1 and type 2 diabetes diagnosed at <30 years of age for development of nephropathy (36). After 30 years of diabetes, 44% of those with type 2 and 20.2% of those with type 1 had nephropathy. Krakoff et al. (37) looked at incidence of retinopathy and nephropathy among Pima Indians diagnosed with type 2 diabetes at <20 years of age (youth), 20–39 years of age (young adults), and 40–59 years of age (older). Nephropathy was equally common in all age-groups and was not related to age of diabetes onset (at <5 years' duration of type 2 diabetes, nephropathy incidence per 1,000

Table 1—*Features to differentiate type 1 and 2 diabetes in young people*

	Type 1 diabetes	Type 2 diabetes
Onset	Acute—symptomatic	Slow—often asymptomatic
Clinical picture	● Weight loss ● Polyuria ● Polydipsia	● Obese ● Strong family history type 2 diabetes ● Ethnicity—high-prevalence populations ● Acanthosis nigricans ● PCOS
Ketosis	Almost always present	Usually absent
Insulin	● C-peptide negative	● C-peptide positive
Antibodies	● ICA positive ● Anti-GAD positive ● ICA 512 positive	● ICA negative ● Anti-GAD negative ● ICA 512 negative
Therapy	Insulin invariably	Oral hypoglycemic agents
Associated autoimmune diseases	Yes	No

person-years was 13/1,000 youth, 8/1,000 young adults, and 7/1,000 older). However, unlike those with adult-onset diabetes, in whom retinopathy was apparent at even this short duration, retinopathy did not appear among youth-onset cases until at least 5 years' duration. Retinopathy was less common in youth-onset than in adult-onset groups at all durations of diabetes.

Although it is not known if the complication rate is similar for other ethnic groups, these studies have important implications in that they highlight the risk of complications occurring at a young age and soon after diagnosis. This will place a significant burden on health budgets as well as on society as a whole, especially as these people would be entering their peak working and earning capacity at the time when complications begin to occur. Early detection and intervention are therefore essential to reduce the risk of future complications.

CLASSIFICATION AND DIAGNOSIS

— The appearance of type 2 diabetes in children and adolescents has exacerbated the existing issues in the classification of diabetes. There is now a problem in clinically distinguishing the etiology of diabetes in children and adolescents, often necessitating laboratory studies to differentiate type 1 from type 2 diabetes (Table 1). This requires tests that are not always available in the primary care environment or in many developing countries.

The presence of diabetic ketoacidosis (DKA) is a classic manifestation of type 1 diabetes. However, DKA may occur at presentation in subjects who are eventually found to have type 2 diabetes (38); that is, they have elevated C-peptide and an absence of antibodies to islet cells (ICA) or glutamic acid decarboxylase (anti-GAD), and after the initial period of severe metabolic disturbance, they do not require insulin (13). Initial reports were among African-American adults, and an autosomal dominant inheritance was suggested (38,39). Subsequent studies have confirmed that type 2 diabetes often presents with ketosis or DKA and occurs in ~40% of African-American children (40,41) with type 2 diabetes, 4% of children with Canadian aboriginal backgrounds (42), and 30% of children with Mexican-American backgrounds (32). A strong family history of type 2 diabetes is common, but an autosomal dominant inheritance has not been confirmed. It has variously been called Flatbush diabetes, atypical diabetes (ADM), and phasic insulin dependence.

At the root of the classification problem is the incomplete understanding of the pathogenesis of the two major types of diabetes, as knowledge of causation is the optimal basis for classification. The association of autoimmune serologic reactions and particular HLA alleles in type 1 diabetes strongly implicates autoimmunity in the pathogenesis, and these tests can be used to help with classification. However, classification is complicated because autoimmunity (at least as determined by current antibody assays) does not contribute to type 1 diabetes as substantially in non-Europid as in Europid populations (43,44).

Further differential diagnoses are maturity-onset diabetes of youth (MODY), which is attributable to mutations of the glucokinase genes and hepatocyte nuclear factor (HNF)-1α and -4α genes (45), and diabetes due to mutations of mitochondrial DNA (46).

The increasing recognition of difficulties with diagnosis and the potentially major influence of diagnosis on therapy (particularly the decision to institute lifelong insulin treatment) suggest the need to consider laboratory investigations, even in apparently typical cases. Therefore, in ideal circumstances it is recommended that apparently typical cases of type 1 diabetes are confirmed with a measurement of autoantibodies, and typical cases of type 2 diabetes are confirmed with an assessment of insulin resistance (e.g., fasting C-peptide). It is recognized that in many settings worldwide such an approach is not affordable and that precise cutoffs for some of the diagnostic tests (especially for insulin resistance) have not been established. When diagnostic tests do not confirm the clinical diagnostic label, further investigations are indicated. In such cases, particularly when there is a parental history of diabetes, genetic testing will often be required. Diagnostic molecular testing is now available (for details, visit www.diabetesgenes.org) and when used appropriately provides valuable clinical information on diagnosis, prognosis, and treatment since most patients with MODY respond best to sulfonylureas (47). It is relevant to note that among non-Hispanic Europid populations, the prevalence of monogenic diabetes in children is similar to or higher than that of type 2 diabetes and is not excluded by the presence of obesity (48).

PATHOGENESIS

— There is sparse information on the pathophysiology of type 2 diabetes in the young; therefore, extrapolation from adults is necessary. Type 2 diabetes is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature (49). Both are usually present at the time that type 2 diabetes clinically manifests. Persons with type 2 diabetes usually have plasma insulin concentrations that appear normal or elevated but insulin secretion, particularly first phase, is defective and insufficient to compensate for the insulin resistance (49). The specific reasons for the develop-

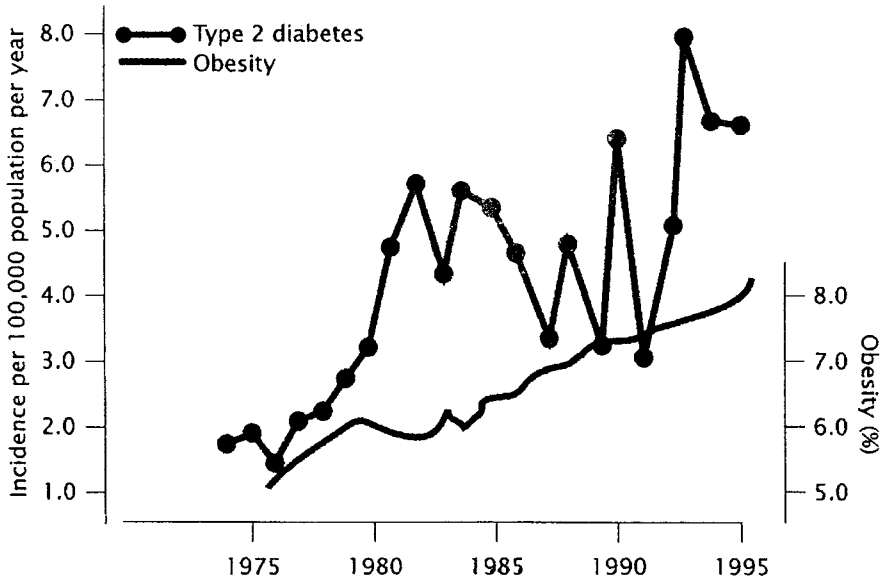

Figure 1—*Annual incidence of type 2 diabetes and prevalence of obesity among Japanese school children. Adapted from Kitagawa et al. (1), with permission.*

ment of these abnormalities are not yet known, but it is of heterogeneous etiology with behavioral and environmental risk factors unmasking the effects of genetic susceptibility (50).

The key factors involved in the development of type 2 diabetes are as follows:

Genetic

Due to complex inheritance patterns and interaction with the environment, identifying the genes involved in the common forms of type 2 diabetes has proved difficult. Only a small percentage of cases can be explained by the single gene defects such as those known to cause MODY. The genetic component of type 2 diabetes in children and adolescents has yet to be explored, but it is reasonable to assume that it is similar to that in adults, and indeed a strong family history of type 2 diabetes is often seen among adolescents with the disease (see "Other factors" below). A number of major predisposing genes have been found on chromosomes 1q, 12q, 20q, and 17q (51). Minor genes that have been defined by a candidate approach include the Pro12Ala polymorphisms in peroxisome proliferator–activated receptor (PPAR)-γ (52) and the Kir 6.2 E23K variant (53). In Ojibwa-Cree indigenous Canadians, a private mutation (G319S HNF1α) present in 20% of the population predisposes to diabetes (phenotypically like type 2 diabetes), with a relative risk of 2 when a single copy is inherited and a relative risk of 4 when two copies are inherited (54). This may yet prove to be another form of MODY. Sellers et al. showed an inverse relationship between number of copies of the mutation and markers of insulin resistance, suggesting that the gene is related to secretory defects (55). The data on the genetic component in adult type 2 diabetes are extensively reviewed elsewhere (51).

Obesity

On a global basis, the rise in type 2 diabetes rates mirrors the growth in urbanization and economic development (6,56). Obesity appears to be the key link, and this is exemplified by the situation in Japan, where a parallel rise in type 2 diabetes incidence in children and levels of obesity occurred from 1975 to 1995 (1) (Fig. 1). Overweight and obesity are becoming major problems in adolescents around the world (Table 2).

The prevalence of overweight (defined as at or above the 95th percentile of the sex-specific BMI for age growth charts) among children in the U.S. increased from 7% in 1988 to 10% in 1999 among those aged 2–5 years and from 5% in 1976 to 11% in 1988 and to 15% in 1999 among those aged 6–19 years (57). The rise in the prevalence has been much more pronounced among African-American and Hispanic children than among non-Hispanic whites (120% rise vs. 50% rise in 12 years) (58). Behavioral differences have been observed, which may explain some of these differences. While African-American and Europid youth may consume the same amount of calories, African-American children tend to get a greater percentage of their calories from fat, in addition to increased intake of sweetened drinks (59). Moreover, African-American adolescents do not perceive themselves to be heavy and actually express a desire to be heavier (60).

Secular increases in the prevalence of obesity in children have also been recorded in China (62), Hong Kong (63), the U.K. (64), and Australia (65). In Australia (using age- and sex-specific BMI cutoffs designed to be the equivalent percentiles to a BMI of 25 and 30 kg/m^2 in 18-year-olds), ~5% of children are currently obese and an additional 16% are overweight (66). These prevalences doubled over the past decade after being nearly stable at around 10% from 1969 to 1985 (65). In India, a recent study found that the age-adjusted prevalence of being overweight (using the same cutoffs as the Australian study) among 13- to 18-year-olds was 18% in boys and 16% in girls (67). Prevalence rates increased with age, decreasing physical activity, and higher

Table 2—*Prevalence of overweight and obesity in six countries at age 18 years (61)*

	Overweight and obesity (BMI ≥25 kg/m^2)		Obesity (BMI ≥30 kg/m^2)	
	Males	Females	Males	Females
Brazil	4.7	15.2	0.1	2.0
Great Britain	9.6	11.7	0.9	1.2
Hong Kong	11.7	9.8	3.1	1.8
Netherlands	5.5	6.5	0.3	0.3
Singapore	10.5	7.0	1.7	1.0
United States	18.1	16.5	3.3	4.0

Data are percent.

socioeconomic status (67). In the Canadian Ojibwa-Cree community, 48–51% of children aged 4–19 years were found to have a weight >90th percentile (17). Changes in traditional lifestyles among indigenous communities, such as a reduction in hunting and gathering and the adoption of a more sedentary life with a westernized diet, are thought to contribute to rising obesity levels (68).

Physical inactivity

Inactivity is one of the major contributors to overweight and obesity. A recent longitudinal study of girls in the U.S. showed a marked decline in physical activity over 10 years, such that by the age of 16–17 years, 56% of black and 31% of white girls reported no habitual leisure-time physical activity (69). Pregnancy, cigarette smoking, higher BMI, and lower parental education at baseline were all associated with a subsequent decline in physical activity. Participation in physical education in U.S. schools fell from 41.6% in 1991 to 24.5% in 1995 (70). Another study found that white students in the U.S. have higher physical activity levels than other ethnic groups, with boys usually more active than girls, regardless of race (71).

Television-viewing time has been linked with childhood obesity (72), which may be related to the associated consumption of high-energy foods (73). On average, children's programming in the U.S. includes 10 food advertisements hourly (74), more than twice that in adult viewing (75).

Insulin resistance

Published studies linking insulin resistance directly with type 2 diabetes in adolescents and children are very limited. However, observations about the typical age of onset of diabetes, evidence of insulin resistance in normoglycemic children from high-risk ethnic groups, and the vast literature on insulin resistance in adults make a compelling case. Most observations in youth with type 2 diabetes would suggest that insulin resistance is an early feature in these children. Initially, insulin resistance manifests itself in compensatory hyperinsulinemia. Over time there is β-cell failure, resulting in the clinical expression of type 2 diabetes (76) (77).

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 found to have greater insulin resistance. Furthermore, they had higher visceral and lower subcutaneous abdominal fat and decreased first-phase insulin secretion and glucose disposition index (78). Intramyocellular fat content (as measured by nuclear magnetic resonance spectroscopy) showed a strong positive correlation with insulin resistance and with 2-h postload plasma glucose (78), suggesting that it may be important in pathogenesis. Further evidence of the importance of insulin resistance can be drawn from the observation that the onset of type 2 diabetes frequently occurs around the time of puberty, when insulin sensitivity declines (79–81). Even in healthy, prepubertal African-American children, a family history of diabetes is associated with an ~20% reduction in insulin sensitivity (82). The hyperinsulinemia and reduced insulin sensitivity observed in Hispanic and black children has been associated with both increased insulin secretion and reduced insulin clearance (83,84).

In a variety of ethnic groups, obesity is associated with evidence of insulin resistance and impaired insulin secretion among children, as in adults (85,86). Central obesity is of particular importance as a determinant of hyperinsulinemia (87). Compared with white children with obesity and similar insulin sensitivity levels, black children have lower hepatic glucose output, lower total and LDL cholesterol, and lower triglyceride levels, with considerably lower visceral fat levels. Visceral adiposity was associated with lower insulin sensitivity in both groups. This was compensated by higher insulin secretion in whites, but not in blacks (88). These findings suggest a greater diabetogenic risk of obesity among African Americans but greater atherogenic risk among whites. The dietary fat-to-carbohydrate ratio correlates significantly with insulin resistance and may partly explain the metabolic differences seen between black and white children (83). Indeed, a number of studies have shown that African-American children have higher total fat and cholesterol intake, prefer greater sweetness in liquids, are physically less active, and spend more time watching television (59,89).

It is possible to ameliorate insulin resistance by increasing the level of physical activity. This has been demonstrated in obese children and more recently in non-diabetic, normal weight children (90), where more active subjects had lower fasting insulin values and greater insulin sensitivity, as measured by a glucose clamp.

Acanthosis nigricans and PCOS

Acanthosis nigricans is a well-established physical marker of insulin resistance and is reported to occur in up to 60–90% of young people with type 2 diabetes (91,92). This seems to be especially true for African Americans, Mexican Americans, and some Native Americans, but not in other populations, such as in Japan. PCOS is associated with a state of insulin resistance and compensatory hyperinsulinemia (83). Obese adolescents with PCOS have a 50% reduction in peripheral tissue insulin sensitivity and evidence of hepatic insulin resistance and compensatory hyperinsulinemia (93). Approximately 30% of adolescent girls with PCOS have been found to have IGT, with 4% having type 2 diabetes (28). In these adolescents, glucose intolerance is associated with decreased first-phase insulin secretion, decreased glucose disposition index, and increased hepatic glucose production (94).

Intrauterine environment

Two aspects relating to the intrauterine environment—birth weight and maternal hyperglycemia—may possibly affect the development of type 2 diabetes among the young. There is now abundant evidence that low birth weight predicts type 2 diabetes in middle age (95). Recent data from Taiwan confirm this in children (96). A study of 6- to 18-year-olds showed a U-shaped relationship, in which the risk of type 2 diabetes was lowest in those with a birth weight of 3–3.5 kg, and was significantly increased in those children who had either low (<2.5 kg) or high (>4.0 kg) birth weight, despite adjustment for other factors, including gestational diabetes, family history of diabetes, and socioeconomic status (96). Recent evidence seems to indicate that the greatest risk for obesity and glucose intolerance in adulthood is in those with low birth weight who gain weight rapidly in childhood (97,98). The risk in this group is higher than in those who are overweight from birth.

Gestational diabetes mellitus (GDM) also seems to increase the risk of diabetes developing in offspring (99). A prospec-

Table 3—*ADA recommendations for testing for type 2 diabetes in children (12)*

Criteria for considering screening for diabetes*
Overweight (BMI 85th percentile for age and sex, weight for height 85th percentile, or weight 120% of ideal for height)
Plus any two of the following risk factors:
• Family history of type 2 diabetes in first- or second-degree relative
• Race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander)
• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS)
Age of initiation: age 10 years or at onset of puberty if puberty occurs at a younger age
Frequency: every 2 years
Test: fasting plasma glucose preferred

*Clinical judgment should be used to test for diabetes in high-risk subjects who do not meet these criteria.

tive study (100) found that the prevalence of IGT in the children of mothers with a diabetic pregnancy increased with time from 1.2% at <5 years of age to 19.3% at 10–16 years of age. This was compared with 2.5% at 10–16 years of age in control subjects. Higher levels of amniotic fluid insulin at 33–38 weeks of gestation was a strong predictor of later IGT (100). The specific environmental role of maternal hyperglycemia, as separate from maternal genetics, has been demonstrated in Pima Indians, in whom offspring born after the mother developed diabetes were more obese as children and more likely to have diabetes in their twenties than their siblings born before their mothers developed diabetes (14). No such differences were seen before and after fathers developed diabetes. Age at diagnosis in HNF-1α mutation carriers was >10 years younger when the mother was diagnosed before pregnancy compared with when the mother was diagnosed after pregnancy (101). The father's age at diagnosis did not, however, influence the offspring's age at diagnosis.

Other factors

Family history. Many studies show a strong family history among affected youth, with 45–80% having at least one parent with diabetes and 74–100% having a first- or second-degree relative with type 2 diabetes (12,102). Children with diabetes are also more likely to have a family history of cardiovascular disease (CVD), with one study showing that up to 28% have a positive family history of CVD (103). In a study among Pima Indians, it was shown that the cumulative incidence of type 2 diabetes was highest in offspring if both parents had diabetes (104). 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 have a 48–60% likelihood of having type 2 diabetes (105,106). A lifestyle predisposing to obesity and type 2 diabetes seems to characterize families with adolescents who have type 2 diabetes (26). Specifically, members of such families tend to be overweight and inactive and have a tendency to high-fat intake and even binge eating (107).

Sex. Girls are 1.7 times more likely than boys to develop type 2 diabetes in an analysis of a large set of studies (108). The reason for this is not clear, and it appears to be a special feature of type 2 diabetes in youth, as sex differences in diabetes prevalence are only a very minor feature in adults.

Socioeconomic status. Socioeconomic status has been associated with type 2 diabetes and obesity in adults. In developed countries, the risk of diabetes is highest in those with lower socioeconomic status (109,110); however, the opposite appears to apply in developing countries, where higher socioeconomic status is associated with an increased risk of diabetes (111). Physical inactivity probably explains these findings in both settings. In children, no data on diabetes are yet available, but a recent large study of 3-year-olds in the U.K. found that those in the most deprived group were 30% more likely to be obese than those in the least deprived group (112).

SCREENING

A major consequence of the appearance of type 2 diabetes in the younger age-group is that subjects with diabetes will have a longer duration of the disease that increases medical costs and increases the risk that both microvascular and macrovascular complications will develop at an earlier age. This makes the issue of screening in the young a very relevant and, indeed, urgent issue. However, certain criteria need to be met before screening can be considered in the public health arena. These are summarized below.

- The disease is common among the general population or among easily identifiable high-risk subgroups
- The disease is serious in terms of morbidity and mortality
- The disease has a prolonged latency without symptoms
- The screening test is adequately sensitive and specific
- Intervention is available to prevent or delay disease onset or treat at an early stage.

Type 2 diabetes in children appears to meet a number of these criteria, suggesting that it may be an appropriate target for screening. However, even when considering the screening of adults for diabetes, there remains heated debate, as it has been suggested that evidence is not yet available to demonstrate that it fulfills the criteria for population-based mass screening (113). The IDF consensus group noted the recommendations of the 2000 American Diabetes Association (ADA) report on type 2 diabetes in children and adolescents (12), as outlined in Table 3. Consistent with those recommendations, only children at substantial risk for the presence or the development of type 2 diabetes should be considered for screening.

The Third National Health and Nutrition Examination Survey (NHANES III) data suggest that the ADA risk criteria would lead to testing of 10% of youths in the U.S., for a total of ~2.5 million adolescents between 12 and 19 years of age, of whom 5% might be expected to have IFG (fasting plasma glucose 6.1–6.9 mmol/l) or undiagnosed diabetes, while 1.8% of those not tested under such recommendations would be expected to have IFG (114). It should be noted that the ADA has recently recommended lowering the criteria for IFG to 5.7–6.9 mmol/l (115).

The question of what tests to use for the initial screening for type 2 diabetes is difficult. Evidence from adult populations clearly shows that ~30% of all those with undiagnosed diabetes have a nondiabetic fasting glucose (116) but are nev-

ertheless at high cardiovascular risk (117), suggesting that the OGTT should be part of the screening process. Others (118) have questioned this assertion, but the World Health Organization (WHO) and many national diabetes organizations continue to recommend its use for adults, particularly in those with a high but nondiabetic fasting glucose. It should be noted that it is currently unknown whether the diagnostic cut points used for adults are applicable to children. Furthermore, the evidence base for the standard 1.75-g/kg (to a maximum of 75 g) dose of glucose used in the OGTT is not strong, and the evidence needs to be further examined in order to review its validity.

Estimates from the Japan and Taiwan screening programs of the unselected general school population show a cost of approximately $10,000 (U.S.) per case found, indicating the need to focus on high-risk groups. Cost-effectiveness analysis suggests that the optimal approach for screening adults is to use "opportunistic screening" for undiagnosed diabetes at routine medical system contacts (119). Such an approach may not work with children who generally have less frequent contact with health care systems.

The psychosocial impact of diagnosing an asymptomatic disease through screening warrants consideration. The potential for distress to occur when an asymptomatic individual is diagnosed with a lifelong disease is considerable, particularly when the diagnosis occurs during adolescence and when it carries with it implications about an individual's or family's lifestyle habits. Evidence would suggest that in adults there is not a significant detrimental effect of identifying diabetes through screening (120), but there are no such data available for children and adolescents, and it would be particularly dangerous to extrapolate such findings.

TREATMENT — The appearance of type 2 diabetes in a younger age-group raises new issues in management of diabetes apart from the difficulty in classification. What therapies are safe in this age-group? Most pharmacologic therapies for diabetes and its associated conditions (apart from insulin) are not approved for use in children, and the same applies for those for blood pressure and dyslipidemia.

The goals of treatment for type 2 diabetes in children and adolescents are to achieve:

- Physical well-being
- Long-term glycemic control
- Prevention of microvascular complications of diabetes
- Prevention of macrovascular disease
- Psychological well-being.

Physical well-being

The attainment of physical well-being has short-term and long-term goals. Short-term goals include treatment of acute metabolic decompensation if present (ketoacidosis), the elimination of symptoms associated with hyperglycemia (polyuria, polydipsia), treatment of acute and chronic infections (vaginal candidiasis is frequent at presentation), and treatment of medical problems associated with obesity (e.g., sleep apnea, steatosis).

The long-term goals for physical well-being include achieving normal growth for the younger adolescent with diabetes, achieving and maintaining a reasonable body weight, maintaining a reasonable level of fitness by a regular physical activity program, avoidance of smoking, and preventing the complications of diabetes.

Glycemic control

The theoretical glycemic goal is to achieve and maintain normoglycemia; however, a more pragmatic target is to maintain HbA_{1c} <7%. Lifestyle intervention (diet, exercise, and weight control) is the cornerstone of management and if successful is likely to benefit blood pressure and lipids as well as glycemia. If diabetes is diagnosed early, lifestyle intervention may suffice, although this only appears to be applicable to ~10% of patients in clinical practice (121).

In principle, there is no reason to suppose that pharmacological treatment of hyperglycemia should be any different in adults and children. What does pose a problem is our lack of knowledge about the long-term implications of drug treatment of diabetes in this age-group.

A proposed therapeutic algorithm for asymptomatic children with type 2 diabetes is to start with lifestyle intervention approaches; then add monotherapy, particularly emphasizing the use of metformin; and subsequently use combinations of two oral medications and, if adequate control is not achieved, the addition of insulin. For symptomatic children, with blood glucose persistently exceeding 17 mmol/l or when DKA is present, insulin therapy is indicated, with subsequent efforts to taper this phenomenon and substitute metformin monotherapy once blood glucose levels are normal (108,121). Many youth maintain near-normal blood glucose levels for months to years after one course of insulin at diagnosis (122).

In clinical practice in the U.S., approximately one-half of young patients with type 2 diabetes receive insulin and one-half receive oral agents, most commonly metformin (108,121). In another analysis of treatment regimens for type 2 diabetes in young persons, 28% began therapy with metformin, with the remainder using insulin alone or the two in combination (123).

Pharmaceutical agents

Insulin. The apparent "overuse" of insulin therapy in adolescent type 2 diabetes is probably multifactorial. It is possible that significant insulin deficiency may be common among the symptomatic adolescents with type 2 diabetes presenting to diabetes centers. Insulin is very familiar to pediatricians and is necessary for treating acute metabolic decompensation. At presentation, there is often uncertainty about whether the patient has type 1 or type 2 diabetes. Experience with oral agents in children is limited and safety data are scant. Formal approval by the Food and Drug Administration (FDA) (and other national therapeutic goods agencies) for their use in childhood and adolescence is limited. Insulin may in addition convey a message of more serious illness, perhaps improving compliance.

The optimum schedule and type of insulin need to be determined in this age-group. It is a priority to study the optimum type of insulin, timing, intensity, duration, and follow-up in multicenter random controlled trials.

Metformin. This is approved in the U.S. for pediatric use. It is recommended as initial pharmacologic treatment in the absence of severe hyperglycemia. Data on metformin in children are limited, but a 16-week study (124,125) showed it to be safe and effective in 10- to 16-year-olds with type 2 diabetes. Long-term outcome studies are needed, as analysis of efficacy of metformin in a small group of Cree in northern Manitoba, Canada, showed little effect of metformin on HbA_{1c} or body

weight after 1 year among adolescents with type 2 diabetes (17). Gastrointestinal side effects were common with treatment. Poor adherence to oral therapy among relatively asymptomatic young persons with type 2 diabetes may be a major barrier to improvement in outcome.

Sulfonylureas. This class is well studied in adults; they are effective, safe, and inexpensive, although sulfonylureas have the potential to cause weight gain and hypoglycemia. They are the treatment of choice in patients with mutations in HNF1α and HNF4α, but only very low doses may be required (47).

Thiazolidinediones. This newer class of drugs is not yet approved for use in childhood and adolescence. Clinical studies for pediatric use are in progress, and although associated with weight gain, their reduction of visceral fat suggests overall benefit if long-term safety concerns can be addressed. Their safety profile with regard to edema and weight gain may be more favorable in children than adults, although this needs to be determined.

α-Glucosidase inhibitors. They have been used infrequently but are safe agents, although, like metformin, their gastrointestinal side effects may decrease acceptance among young persons.

Lipid-lowering therapy

The ADA has recently published consensus-based guidelines for the management of dyslipidemia in children (126). The recommendations for type 2 diabetes are that lipids should be measured every 2 years; optimal levels are as follows: LDL <2.6 mmol/l, HDL >0.9 mmol/l, and triglycerides <1.7 mmol/l. When optimal levels are not present, dietary advice should be provided and blood glucose should be treated aggressively. If after 6 months, LDL is >4.1 mmol/l, medication should be started (resins should be considered and if not accepted or tolerated, statins can be used). If LDL is 3.4–4.1 mmol/l after 6 months of diet and blood glucose management, medication should be considered in those with additional cardiovascular risk factors (including blood pressure, family history, and smoking status). Medication is not advised for the specific treatment of triglycerides (unless >11.2 mmol/l) or HDL.

Hypertension

Hypertension is a comorbidity of type 2 diabetes in youth and is a major risk factor for nephropathy and atherosclerosis. Hypertension is defined in pediatric patients as an average systolic or diastolic blood pressure ≥95th percentile for age, sex, and height, taken on three occasions. Blood pressure measurement should be obtained in all children with type 2 diabetes during diabetes health care visits. If hypertension does not respond to lifestyle changes, first-line pharmacological therapy for hypertension is an angiotensin-converting enzyme inhibitor, with angiotensin II receptor antagonists being reserved as second-line therapy due to little primary data in pediatric subjects.

Hypercoagulability

The risk of Reye's syndrome, which is extremely rare after puberty, has led the ADA to recommend against the use of aspirin in those <20 years of age.

Barriers to treatment

Attainment of treatment goals poses challenges, especially for the adolescent age-group when the developmental stage of moving toward independence is frequently marked by risk-taking behavior, lack of long-term planning, noncompliance, and resistance to lifestyle changes. Additional problems affecting the treatment of type 2 diabetes include family and/or psychosocial dysfunction and ethnic influences. Depression due to the high family burden of illness, poverty and isolation, and substance abuse are also not uncommon in lower socioeconomic groups and in many indigenous populations, leading to difficulties in the treatment of type 2 diabetes.

For young individuals, the important role of the family in diabetes management cannot be overestimated, as involvement of the family has been shown to lower HbA_{1c} (127).

PREVENTION — There is now very clear evidence supporting both lifestyle intervention and pharmaceutical agents in the prevention of type 2 diabetes in adults (128). However, the only evidence on diabetes prevention in children relates to breast-feeding, which may minimize excessive energy intake and perhaps improve insulin sensitivity by its higher polyunsaturated fat content. Studies of Pima Indians (129) and Native Canadian children (68) have shown a lower prevalence of type 2 diabetes among children and adolescents who were breast-fed during infancy. Compared with formula feeding, breast-feeding has been associated with a lower weight for length and smaller skinfold thickness up to the age of 2 years (130) and with a lower plasma glucose in infants undergoing elective surgery (131).

Further relevant findings can be found in studies of overweight and obese children. In a 20-week study of 50 obese adolescents, those randomized to a weight loss program had, at the end of the study, lower serum insulin levels and blood pressure than those in the control group (132). In a similar study of 29 obese, hyperinsulinemic adolescents with a positive family history of type 2 diabetes randomized to metformin or placebo, BMI and fasting insulin improved modestly with metformin, but no change could be demonstrated in insulin sensitivity, HbA_{1c}, lipids, or glucose disposal (133).

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, with 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 during the 6-month study (134).

The "Trim and Fit" program in Singapore integrated nutrition education into the school curriculum, controlled the school canteens, encouraged water drinking by providing water coolers, targeted obese children for additional assistance, and rewarded schools achieving good health outcomes. Over 8 years of the program, from 1992 to 2000, the prevalence of obesity fell from 16.6 to 14.6% in 11- to 12-year-olds and from 15.5 to 13.1% in 15- to 16-year olds (135). An exercise intervention in Japan decreased the prevalence of overweight from 40 to 37% among boys and to 32% among girls between the ages of 10 and 13 years, with no change in a control group (136).

A school-based program among Mexican-American children has shown the importance of creating a network of social support in the classroom, the home, the school cafeteria, and among friends and classmates. In comparison to children in a control setting, those in the program have shown improved physical fitness, reduced numbers with fasting plasma glu-

cose >6.1 mmol/l, and reduced body fat (137,138).

Beyond individual and community-based interventions, to successfully prevent lifestyle diseases such as diabetes, changes in government policies and legislation are essential. Government intervention can include mandating a greater emphasis on more exercise and dietary education in schools, banning the advertising of unhealthy products, and subsidizing healthy food at the expense of less healthy food.

CONCLUSIONS — Until recently, type 2 diabetes has been viewed as a disease of older adults. With increasing rates of obesity, it is clear that the age of disease onset is falling in all ethnic groups and that type 2 diabetes is occurring in childhood (39). While much of the information is currently based on case reports and clinic-based series, and any generalizations should therefore be very guarded, the underlying problem of childhood obesity is, unfortunately, well documented. It would indeed be surprising if type 2 diabetes does not follow in its wake. The challenge to epidemiologists is to define its extent.

The pathophysiology of type 2 diabetes in children and adolescents appears to be very similar to that of adults. Insulin resistance (often exacerbated by puberty) is initially compensated by increased insulin secretion, but over time, β-cell function declines and hyperglycemia ensues. The pancreatic islet β-cell failure may occur very rapidly but the reasons for this are unclear.

The management of type 2 diabetes in the younger age-groups presents several major challenges. First, differentiation from type 1 diabetes can be difficult, notably when those presenting with DKA subsequently manifest many features typical of type 2 diabetes. Agreement on classification is required, and the framework needs to be useful in the clinical (both at the time of presentation and later on) and research settings. Successful treatment will require intensive efforts to alter lifestyle, which will need to focus on families as well as the individual. There do not appear to be any reasons why pharmacological treatment should differ from that used in adults, but more evidence is needed is about long-term safety and efficacy in relation to currently available oral hypoglycemic agents.

Prevention must remain a high priority and is only likely to be successful if governments and communities provide the environment within which individuals can make lifestyle changes that will prevent and, when necessary, reverse obesity. The school systems provide an ideal setting for prevention of obesity and diabetes, because the whole target population is available and both diet and physical activity can be influenced. In an ideal world, it would be possible to implement the proposed wide-reaching recommendations. In reality, this may be difficult given the socioeconomic contraints and the already tight health budgets of many governments. In addition, achieving good pregnancy outcomes with regard to avoiding low birth weight and treating gestational diabetes also provides an important prevention opportunity.

A consequence of urbanization is the parallel emergence of CVD, obesity, and type 2 diabetes, which until recently was mainly a problem of the developed world. Therefore, governments are going to be forced to deal with the problem of type 2 diabetes in children. As such, it would be better to address the problem as a public health issue under the heading of primary care and prevention instead of dealing with the consequences of an entrenched condition and its complications in a young population.

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