METHODS

Urine glucose screening program at schools in Japan. Together with the screening for hematuria and proteinuria to detect chronic renal disease, urine glucose testing was started in Tokyo in 1974 (5). Thereafter, some local governments and cities like Yokohama (6), Fukuoka, and Niigata (7) also adopted this screening program to detect childhood diabetes. In 1994, the school health law was revised in Japan to mandate urine screening of all primary and junior high school students for glucosuria.

In regard to the method of testing, the participants are instructed to collect midstream urine samples from the first urination in the morning at home after emptying their bladder the previous night. Urine samples are then transported in refrigerated containers to the test center for analysis of urine glucose together with that of urine protein and red blood cells. Urine glucose is determined using a glucose oxidase tape. The minimum sensitivity for positive glucose testing is 100 mg/dL or, in some areas, 50 mg/dL. Those children who are found to be positive for both glucose and ketone bodies in the urine are advised to visit a hospital for an immediate clinical evaluation to rule out diabetic ketoacidosis. If one urine sample is positive for glucose, a repeat urine test is requested on another morning. If the second test is also positive, an OGTT is performed to confirm the diagnosis of diabetes (Model A, adopted in Tokyo, etc.). In some local governments and cities, OGTT is performed even after a positive result of the first urine glucose test (Model B, adopted in Yokohama, Niigata, etc.). For the OGTT, 1.75g/kg (maximum 75g) of glucose is used, and WHO criteria (12) are currently followed for the diagnosis of glucose intolerance. The diagnostic accuracy of Model A and Model B for detection of diabetes has been reported to be almost the same by adopting either Model A or Model B (5,6). In most governments and cities, HbA1c, serum insulin, serum cholesterol, serum triglyceride, etc. are also examined at the same time. Children showing diabetic patterns on OGTT are eventually referred to a specialized hospital for detailed examination and treatment of diabetes (Fig. 1).

RESULTS

Positive Rate for Urine Glucose

The positive rate for glucosuria in the first test has been reported to be approximately 0.05–0.1% in primary school children and 0.12–0.2% in junior high school children (6,7). Thus, the positive rate in junior high school children is about twice as high than that in the primary school children. The positive rate for glucosuria in the second test has been reported to be approximately 0.05% in both primary and junior high school children in Tokyo (7). This result indicates that a positive result cannot be reproduced in the second test in about half of the children who show a positive result in the first test. The vast majority of these children are, therefore, considered to have renal glucosuria.

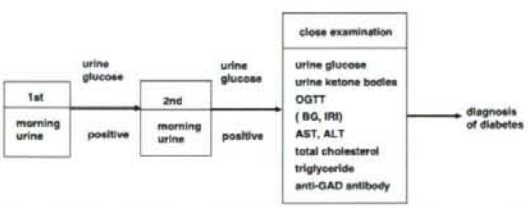

Figure 1. Urine glucose screening system at school in the Tokyo metropolitan area.

Approximately 30–60% of children who show positive test for urine glucose are eventually diagnosed to have renal glucosuria. These children have no symptoms of diabetes and some have a family history of renal glucosuria. They exhibit normal glucose tolerance in the OGTT. Renal glucosuria is an isolated disorder of proximal tubular glucose transport, characterized by abnormal urinary excretion of glucose in the presence of normal blood glucose levels. Marble (13) defined renal glucosuria as a condition characterized by a normal fasting blood glucose level, normal glucose tolerance as assessed by OGTT, and a daily urinary glucose excretion of 10–100g. Laurence (14) defined renal glucosuria as a condition characterized by normal glucose tolerance as assessed by OGTT, regardless of the presence of glucosuria in the fasting state. Cases satisfying Marble's criteria appear to be few, whereas, Desjeux (15) reported that about 60% of the subjects with positive test results for urine glucose were diagnosed as having renal glucosuria in accordance with the criteria proposed by Laurence. The prevalence of renal glucosuria as determined by the urine glucose screening program is consistent with this result.

Incidence of Type 2 Diabetes as Detected by the Screening Program

Result in Tokyo. Between 1974 and 2004, a total of 9,242,259 school children including 6,225,971 primary school children and 3,016,288 junior high school children underwent urinary testing for glucosuria. Of these, a total of 236 children including 47 primary school children and 189 junior high school children were diagnosed as having type 2 diabetes through this screening program. The numbers of the target population were fluctuated according to the students' numbers residing in the Tokyo metropolitan area for each year. However, the participation rate in the urine test was scarcely changed and almost 100% of the students during the study period. The number of school children screened has decline since 1990 because of the decreased birth rate in Japan including the Tokyo metropolitan area.

The overall incidence of type 2 diabetes was estimated to be 2.55/100,000/y. Junior high school children had a significantly higher incidence of diabetes than primary school children (0.75 *versus* 6.27/100,000, $p < 0.0001$). Table 1 shows the annual number and incidence of type 2 diabetes as detected by the screening program for 5-y periods from 1974 to 2004 in Tokyo. The annual incidences over the six consecutive 5-y periods from 1974 to 2004 were 1.73, 3.23, 3.05, 2.90, 2.70, and 1.41/100,000, respectively. The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 and tended to be lower than that

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Table 1. *Annual number and incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2000 in Tokyo*

Year	School students examined (*n*)	Type 2 diabetes (*n*)	Overall frequency of type 2 diabetes/10^5	PSC examined (*n*)	Type 2 diabetes in PSC (*n*)	Frequency of type 2 diabetes in PSC/10^5	JHSC examined (*n*)	Type 2 diabetes in JHSC (*n*)	Frequency of type 2 diabetes in JHSC /10^5
1974–1980	2,076,767	36	1.73	1,466,801	4	0.27	609,966	32	5.25
1981–1985	1,827,870	59	3.23	1,204,262	11	0.91	623,608	48	7.70
1986–1990	1,636,969	50	3.05	1,032,514	8	0.77	604,455	42	6.95
1991–1995	1,481,518	43	2.90	992,771	8	0.81	488,747	35	7.16
1996–2000	1,296,521	35	2.70	880,199	13	1.48	416,322	22	5.28
2001–2004	922,614	13	1.41	649,242	3	0.46	273,190	10	3.66
Total	9,242,259	236	2.55	6,225,971	47	0.75	3,016,288	189	6.27

PSS, primary school children; JHSC, junior high school children.

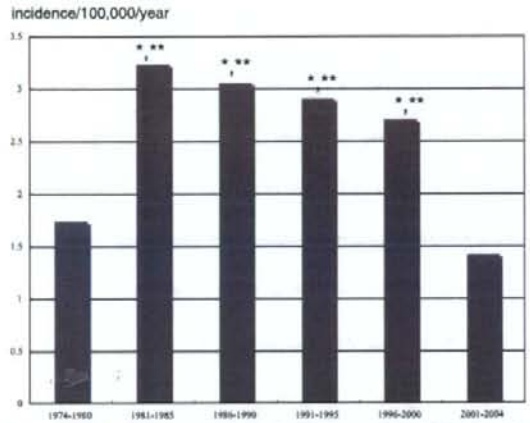

Figure 2. Overall incidence of type 2 diabetes as detected by the urine glucose screening program for 5-y periods from 1974 to 2004 in Tokyo. *The incidence in 1974–1980 was significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0038$, 0.0091, 0.0226, respectively) and tended to be lower than that recorded in 1996–2000 ($p = 0.0672$). **The incidence in 2001–2004 was also significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 ($p = 0.0056$, 0.0120, 0.0194, respectively) and tended to be lower than that recorded in 1996–2000 ($p = 0.0557$).

recorded in 1996–2000. The incidence in 2001–2004 was also significantly lower than that recorded in 1981–1985, 1986–1990, and 1991–1995 and tended to be lower than that recorded in 1996–2000 (5,16) (Fig. 2).

The annual incidence of diabetes from 1974 to 2004 in junior high school children was 5.25, 7.70, 6.95, 7.16, 5.28, and 3.66/100,000, respectively. The incidence in junior high school children in 2001–2004 was significantly lower than that recorded in 1981–1985 ($p = 0.0315$) and tended to be lower than that recorded in 1991–1995 ($p = 0.0622$). There were no significant changes in the incidence of diabetes in primary school children over the corresponding periods (16). Therefore, the overall trend of decreasing incidence of childhood type 2 diabetes in 2000–2004 was most strongly associated with the decrease in the incidence of the disease in junior high school children.

Results in Other Governments and Cities in Japan. The incidences of childhood type 2 diabetes detected by the urine glucose screening program in Tokyo and other cities in Japan are shown in Table 2. Taking into account these results, it is speculated that the overall incidence of childhood type 2 diabetes in Japan is approximately 3.0/100,000/y. The incidence in junior high school children is three to six times higher than that in primary school children.

Kikuchi *et al.* (6) reported the annual incidence of type 2 diabetes in Yokohama city during the 5-y periods 1987–1991 and 1992–1996 were significantly higher than the incidence recorded in 1982–1986. However, Yokota *et al.* (17) demonstrated that the incidence in 1997–2001 was lower than that in 1992–1996 for the same population in Yokohama city. In Fukuoka city, the incidence of type 2 diabetes in junior high school children has been steadily decreasing after 1999 (7). Taking into account these findings and the results obtained in the Tokyo study, it may be deemed that the incidence of childhood type 2 diabetes in big cities of Japan has somewhat decreasing in recent years.

Impaired glucose tolerance. Among children who showed positive test results for urine glucose, a few were diagnosed as having IGT by OGTT. In the Tokyo study, a total of 16 children were identified as having IGTT. Of these, six children finally progressed to type 2 diabetes. In the Yokohama study, 33 children with IGT were found by the screening program, and one third of them developed to type 2 diabetes after 5 y from diagnosis. Obese children showed significantly high incidence of developing diabetes, and all of the diabetic patients showed worsening of obesity at the point of onset of diabetes (18).

Clinical Characteristics of Type 2 Diabetes as Detected by the Screening Program

Gender. Rosenbloom *et al.* (2) reported that gender is an important predisposing factor in the occurrence of type 2 diabetes, with analysis of a large number of studies revealing that girls are 1.7 times more likely to develop diabetes than boys. However, there appears to be no statistically significant gender difference in the incidence of type 2 diabetes among Japanese children (5–7).

Age. The majority of children with type 2 diabetes are junior high school children with the usual pubertal age of 13–15 y at diagnosis (5–7). Puberty is an important risk factor leading to hyperglycemia. Insulin sensitivity decreases by 30% during puberty and is associated with a compensatory increase in the insulin secretion (19,20).

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Table 2. *Incidence of type 2 diabetes as detected by the urine glucose screening program in various areas of Japan*

References	Incidence/100,000/y
Tokyo (1974–2004) (5,16)	Overall: 2.55 (PSC: 0.75; JHSC: 6.27) 1974–1980: 1.73; 1981–1985: 3.23; 1986–1990: 3.05; 1991–1995: 2.90; 1996–2000: 2.70; 2001–2004: 1.41
Yokohama (1982–2001) (6,17)	Overall: 3.19 (PSC: 1.50; JHSC: 6.65) 1982–1986: 1.89; 1987–1991: 3.19; 1992–1996: 4.97; 1997–2001: 4.56
Niigata (1982–2003) (7)	Overall: 3.57 PSC: 1982–1988: 0; 1989–1993: 1.7; 1994–1998: 1.3; 1999–2003: 2.8 JHSC: 1982–1988: 0; 1989–1993: 6.0; 1994–1998: 14.6; 1999–2003: 13.4
Fukuoka (1989–1998) (7)	Overall: 2.77 (PSC: 1.62; JHSC: 5.05)

PSC, primary school children; JHSC, junior high school children.

Obesity. Various studies have reported that greater than 80% of Japanese children with type 2 diabetes are obese at the time of diagnosis (5–7). In the Tokyo study (5), 83.4% were more than 20% overweight and 48.7% had severe obesity defined as more than 40% overweight. On the other hand, some studies have indicated that obesity is significantly more prevalent among males with childhood type 2 diabetes; *e.g.* in the Tokyo study (5), boys showed a higher frequency of obesity than girls (91.5 *versus* 77.0%). Sugihara *et al.* (21) also reported a higher frequency of obesity in males (78% *versus* 63%) based on the results of a survey conducted with the participation of major pediatric departments in Japan. Besides severe obesity being more prevalent among males with childhood type 2 diabetes, nonobesity has also been reported to be more prevalent among females with type 2 diabetes (5,21). This may suggest gender difference in the pathogenesis of type 2 diabetes, whereas obesity, which causes insulin resistance, is highly likely to be involved in the development of hyperglycemia in males, other mechanisms may be involved in females with diabetes.

Several studies have indicated that the observed increase in the incidence of childhood type 2 diabetes is a result of increased frequency of obesity among young people (2–4). The prevalence of obesity in Japanese school children has increased significantly over the past three decades. The prevalence of obesity among Japanese school children in the year 2000 was reported to be approximately 10%, three times as high as the prevalence recorded three decades ago (22). Since the 1970s, the Japanese people, especially Japanese children, have become westernized in relation to their lifestyles and eating habits. Increase in the prevalence of a sedentary lifestyle (watching television and playing TV games) and nutritional problems, such as increased intake of animal protein and fat (23,24), possibly contribute to the increased prevalence of obesity and development of type 2 diabetes among Japanese school children. However, this trend of increasing incidence of childhood obesity appears to have become weaker recently. The Ministry of Education, Culture, Sports, Science and Technology of Japan reported in recent years of a decreasing prevalence of obesity among junior high school children (25). This could be related to the significant increase in awareness and concern regarding childhood obesity and associated metabolic disorders has spread in the Japanese population, especially among children and adolescents residing in big cities. These children, therefore, appear to take sugar-sweetened beverages and snacks as well as high-fat foods less frequently than before. In addition, they seem to have emerged from sedentary lifestyles to actively participate in various sports activities (25). These lifestyle changes may contribute to the decrease in the incidence of type 2 diabetes observed in recent years in big cities of Japan.

Family history of type 2 diabetes. In regard to the role of a family history of diabetes, 56.5% of children with type 2 diabetes in the Tokyo study (5) and 69% of the patients reported by Sugihara *et al.* (21) had a family history of type 2 diabetes in second- and first-degree relatives. The frequency of a positive family history of type 2 diabetes in second- and first- degree relatives has been reported to range from 74 to 100% in Caucasian population (2–4). The frequency of detection of type 2 diabetes in family members may possibly increase after children are diagnosed as having diabetes. Therefore, the family history plays a crucial role in the majority of children developing type 2 diabetes.

Future Prospects

In 1994, when urine glucose screening at schools was made obligatory, no further budgets were allocated for the formation of committees to evaluate cases with positive results. Consequently, no committee for the diagnosis and follow-up of cases showing a positive urine glucose screening test results have been established yet in many governments and cities in Japan (17). In Tokyo, however, all the participants of screening programs with positive test results have undergone adequate evaluation at a unique examination institute and follow-up system established by pediatric diabetes specialists with the support of the Tokyo Health Service Association (5). It is important to constitute such committees composed of pediatric diabetologists for the establishment of a system for confirmation of the diagnosis, treatment and follow-up of cases showing positive screening test results in all areas of Japan.

The major purpose of urine glucose screening is to diagnose the disease in the early stage in children with type 2 diabetes and provide appropriate treatment. However, no guideline for the management of childhood type 2 diabetes has been established as yet in Japan. Moreover, the Japanese government has not approved most of the oral hypoglycemic agents available currently for use in the pediatric population. It is, therefore, extremely important to establish appropriate strategies for the treatment of type 2 diabetes among children at the earliest.

Ritchie *et al.* (26) reviewed the possibility of prevention of type 2 diabetes among youth, and concluded that this disease can be potentially prevented or delayed by improvement of the

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eating habits and physical activity among children (27,28). Several clinical trials in adults have shown that even moderate weight loss can reduce the risk of development of type 2 diabetes (29–31). However, the efficacy of dietary and exercise programs in the prevention of type 2 diabetes among youth still remains to be studied. A recent study by Urakami *et al.* (16) reported a reduction in the incidence of type 2 diabetes in Tokyo during 2001–2004, possibly due to a decreased frequency of childhood obesity associated with improved eating habits and physical activity among children. An interventional trial of the effect of lifestyle alterations should be begun in obese children residing in all areas of Japan to establish its efficacy in the prevention of type 2 diabetes as well as the so-called metabolic syndrome in children.

SUMMARY

The increase of childhood type 2 diabetes is observed not only in Japan but is also reported in various countries including the United States, especially among young people with risk factors for type 2 diabetes (*i.e.* pubertal age, obesity, family history of type 2 diabetes, high-risk racial or ethnic group, etc.) (2–4). It is, therefore, principal to establish a screening program to detect children with having type 2 diabetes at the early stage and create a strategy for prevention and treatment of the disease during childhood worldwide.

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Chapter one

Diabetes in children: epidemiology

Challenges

A diagnosis of diabetes in a child has typically been assumed to be type 1 diabetes, formerly classified as juvenile diabetes. However, in the last two decades, type 2 diabetes, once known as adult-onset diabetes, is being diagnosed with increasing frequency in children in countries around the world. The rapidly rising incidence of both type 1 and type 2 diabetes in young people is clear evidence that the 'rules' of diabetes epidemiology as we have known them are being broken. Type 1 is still the major form of diabetes in those under 10 yr old. It is preceded by a dangerous period, including diabetic ketoacidosis (DKA), from which children continue to die, as a result of ignorance and lack of education.

The increasing incidence of type 1 diabetes cannot solely be explained by genetics; environmental factors are influencing those with a genetic predisposition. In addition, type 2 diabetes, while strongly linked to genetics, is certainly attributable to the causative factors of diet, lifestyle and environment. Both forms are clearly linked to genes and environment. Habits of low physical activity coupled with high calorie, nutrient-deficient diets are becoming entrenched early in life.

In both developed and developing countries, common causative factors for both type 1 and type 2 diabetes appear to be converging under lifestyle and environment. The fact that these are modifiable risk factors provides optimism and incentive – to develop and implement comprehensive education and intensive management strategies to provide optimal diabetes treatment while at the same time focusing on arresting the current trend through prevention.

Introduction

Epidemiology describes patterns of disease by causation and geographical region, among other factors. Among developed nations, type 1 diabetes mellitus is one of the leading chronic diseases of childhood (1).

Both type 1 and type 2 diabetes can occur in children and adolescents, although type 1 is in most countries still more common and in fact is still often referred to as childhood or juvenile-onset diabetes. Type 1 and type 2 diabetes present somewhat different disease patterns and require different management; people with type 1 diabetes require daily insulin, which is literally a life-saving treatment. Depending on clinical parameters and treatment success, individuals with type 2 diabetes may require insulin. Whether type 1 or type 2, all forms of diabetes pose potentially grave dangers to health.

In the 19th century, diabetes was uncommon and the incidence of childhood diabetes was relatively low and stable until the middle of the twentieth century. There has been an upturn in the incidence of type 1 diabetes in North America and northern Europe since the mid-1950s, a trend that is now observed in countries around the world. The rise has been too rapid for the explanation to be purely genetic. The causes are not yet completely understood, although various factors have been proposed such as rapid growth in early childhood, early exposure to certain food constituents (e.g. cow's milk hypothesis), enterovirus infection, chemicals and reduced exposure in early childhood to infective agents that contribute to development of a healthy immune system (the 'hygiene hypothesis') (2).

Antenatal risk factors associated with the development of childhood obesity, type 2 diabetes and cardiovascular disease include perinatal factors such as placental insufficiency and food deprivation in early pregnancy, as well as parental history of overweight and maternal overweight during pregnancy (3). Both babies that are small for gestational age and those who are large for gestational age have an increased risk of developing obesity, diabetes and associated cardiovascular disease (3, 4). Initial breastfeeding of the infant appears to protect against obesity in later life (5). Other postnatal factors that influence risk of obesity include infant overnutrition and rapid weight gain during the first few months of life (3). Recent data indicate that among preschool children, current overweight and obesity are stronger determinants of insulin resistance than birth weight (6). Significant differences in the seasonality of birth between children with diabetes and the general population have been observed in Britain, with a peak in early summer

and a trough in winter (7). Early exposure to cow's milk proteins, cereals, and heavy weight during infancy has been implicated as risk factors for type 1 diabetes.

Incidence of diabetes is rising rapidly in children

The incidence of both type 1 and type 2 diabetes is rising rapidly in children. The incidence of type 1 diabetes is increasing in children and youth by about 3% (range about 2–5%) per annum, with the greatest rate of rise in the under 4-yr-old age group (8). Type 2 diabetes was rare in this age group until recently, but the trend towards overweight and obesity is acting as a driver to the development of type 2 diabetes in youth, particularly after onset of adolescence. A rising incidence of type 2 diabetes in adolescents in Japan was first reported in 1990 (9). Further data show that type 2 diabetes is now seven times more common than type 1 in Japanese children, an increase in incidence of more than 30-fold over the past 20 yr, believed to be a function of changing diet and increasing obesity rates (10). Although certain ethnic groups such as South East Asians, Pacific Islanders, Hispanics, African-Americans and the Native North Americas (also called Aboriginals or First Nations in Canada and North American Indians in the USA) are known to be at high risk, the changing patterns are not confined to these groups. The incidence is rising at a greater rate among immigrant populations.

Type 1 diabetes, still the most prominent form of diabetes seen in childhood, is an autoimmune disease characterized by destruction of the insulin-producing beta cells in the pancreas, leading to total or near total insulin deficiency (11). Type 1 diabetes often presents clinically with clear symptoms such as weight loss, excessive thirst, urination and lethargy: ketoacidosis may be observed in the child who has been experiencing these symptoms for some time before medical help is sought. The child with type 1 diabetes will require lifelong insulin replacement.

In type 2 diabetes, the major factor is insulin resistance; diabetes occurs when beta cells are no longer able to produce enough insulin to overcome this resistance. Contributors to insulin resistance include genetic factors, obesity (itself at least partly genetically driven), reduced physical activity, high or low birth weight and infections. The implications of high birth weight, maternal obesity and gestational diabetes for development of metabolic syndrome in childhood are a current subject of research (12). Dietary changes such as greater consumption of high-fat, high-energy foods, lower-fiber and processed foods and foods prepared outside the home are also believed to play a large part in the rapid increase in incidence of type 2 diabetes that we have seen in recent years.

It can be difficult to distinguish type 1 from type 2 diabetes in children and adolescents. Identification of type 1 or type 2 can be supported by the presence of beta cell-related autoantibodies in type 1, but the absence of autoantibodies does not rule out type 1 diabetes as they are lacking in 5–10% of people at diagnosis. Moreover, youth with type 2 diabetes frequently display islet autoantibodies and type 2 diabetes in the young may result from an interplay of insulin resistance and autoimmunity (13–15). Although children with type 1 diabetes are typically not overweight, the population of many countries is becoming more overweight. It is estimated that as many as a quarter of children with type 1 diabetes in these countries may be overweight at the time of diagnosis (16).

This may influence the presentation of diabetes in young people. In addition, there is evidence that type 1 and type 2 diabetes may even be one and the same disorder of insulin resistance; in the case of type 1, beta cell destruction precedes problems in production and resistance, whereas in type 2, insulin production remains intact for a longer period of time and resistance develops on the basis of other (perinatal and weight dependent) cofactors (15).

Table 1 shows the characteristic features of type 1 compared with type 2 diabetes in young people, as derived from the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents (2000) (17).

In addition, there are several other less common forms of diabetes in developing countries, including fibrocalculous diabetes and malnutrition-related diabetes, shown in Table 2. In a paper from Bangladesh that studied children with diabetes under the age of 18 yr, 30.4% had type 1 diabetes, 29.6% had fibrocalculous pancreatitis, 38.5% had malnutrition-modulated diabetes and 1.6% of the children had type 2 diabetes (18).

There are also an increasing number of monogenic conditions associated with diabetes in youth (previously referred to as Maturity Onset Diabetes in the Young) or in the neonatal period that have been recognized. When there is a strong family history of early onset diabetes suggestive of an autosomal dominant inheritance, monogenic forms should be seriously considered, e.g. HNF-1 and 4 mutations, glucokinase mutation (19).

Type 1 diabetes: current global data

In 2006, the number of children globally aged 0–14 yr with type 1 diabetes was estimated by the International Diabetes Federation to be 440 000, with an annual increase of 3% per annum and 70 000 newly diagnosed cases a year. More than one quarter of these newly diagnosed cases come from South East Asia and more than one fifth from Europe. The

Table 1. Characteristic features of type 1 compared with type 2 diabetes in young people

Characteristics	Type 1	Type 2
Age	Throughout childhood	Pubertal (or later)
Onset	Most often acute, rapid	Variable: from slow, mild (often insidious) to severe
Insulin dependence	Permanent, total, severe	Uncommon, but insulin required when oral hypoglycaemic agents fail
Insulin secretion	Absent or very low	Variable
Insulin sensitivity	Normal	Decreased
Genetics	Polygenic	Polygenic
Race/ethnic distribution	All groups, but wide variability of incidence	Certain ethnic groups are at particular risk
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% (Japan ~80%)
Associations		
Autoimmunity	Yes	No
Ketosis	Common	Rare
Obesity	No	Strong
Acanthosis nigricans	No	Yes

Source: International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents (17).

increase in incidence of type 1 diabetes has been observed in countries with both high and low prevalence, with an indication of a steeper increase in some of the low-prevalence countries. No region is exempt from type 1 diabetes (Fig. 1) (8). The increase is not readily explained by shifts in genetic susceptibility because it has happened so quickly, but the search continues for explanations.

A 350-fold variation was observed between 1990 and 1994 among 100 populations worldwide in the incidence of type 1 diabetes in children up to the age of 14 yr. The incidence ranged from 0.1 per 100 000 per annum in China and Venezuela to 36.8 per 100 000 in Sardinia and over 40 in Finland. The lowest incidence was generally seen in China and South America. Eighteen of 39 European populations surveyed had an intermediate incidence of diabetes ranging from 5.0 to 9.99 per 100 000 population. A very high incidence, defined as greater than 20 per 100 000, was seen in Sardinia, Sweden, Norway, Portugal, the UK, Canada and New Zealand (20).

European data

The EURODIAB 2000 survey contains data from 44 centres representing most European countries. The data cover new cases in children and adolescents up to the age of 15 yr between 1989 and 1994. In general, the incidence rates are higher in northern and NW Europe and lower in southern, central and eastern Europe; this range is perhaps due to different exposure to infections or other environmental factors. The rates range from 3.2 per 100 000 in Macedonia, 5.0 in Romania and 5.4 in Poland to 40.2 per 100 000 in Finland, 36.6 in Sardinia and 25.8 in Sweden. Pooled incidence rates during this period show a 6.3% increase for children aged 0–4 yr; 3.1% for children aged 5–9 yr and 2.4% for those aged 10–14 yr (21).

In southwest England, an overall crude incidence rate of type 1 diabetes was observed of 14.9 per 100 000 population in youth up to and including the age of 14 yr between 1975 and 1996. During this time there was a marked increase in diabetes in those aged under 5 yr, which is of concern because it can be difficult to maintain good glycaemic control in this age group, a crucial factor in minimizing the risk of development of complications (22). Among children aged 0–14 yr diagnosed with type 1 diabetes and living in the city of Bradford, UK, there was an annual increase in incidence of 6.5% in south Asians compared with an average annual increase in incidence of 4.3% in all children (23).

Data from the Middle East and Australasia

Prospective data collection in Kuwait between 1992 and 1997 showed an incidence in children under the age of 15 yr of 15.4 per 100 000 in 1992, rising dramatically to 20.9 per 100 000 5 yr later. The rise was particularly steep in those aged 5–9 yr (24).

Figures from New South Wales show that the age-standardized incidence of type 1 diabetes among children up to the age of 14 yr rose by 28% between 1992 and 1996. By comparison, the total number of children in this age group rose by 0.5% (25).

In China, data collected for children under 15 yr of age from 22 centers showed an overall corrected incidence of 0.51 per 100 000; this was the lowest incidence recorded in the World Health Organization Multinational Project for Childhood Diabetes (DiaMond) project. There was a 10-fold difference between the different centers, with higher rates in the

Table 2. Other specific types of disorders of glycemia International Society for Pediatric and Adolescent Diabetes (ISPAD)

A. Genetic defects of b-cell function
B. Genetic defects in insulin action Type A insulin resistance, leprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes, others
C. Diseases of the exocrine pancreas Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, others
D. Endocrinopathies Acromegaly, Cushing syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma, others
E. Drug or chemical induced Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, dilantin, alpha-interferon
F. Infections Congenital rubella, cytomegalovirus, coxsackie B4
G. Uncommon forms of immune-mediated diabetes Anti-insulin receptor antibodies, autoimmune polyendocrine syndrome deficiencies I and II, 'stiff-man' syndrome
H. Other genetic syndromes sometimes associated with diabetes Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, Myotonic dystrophy, Porphyria, Prader-Willi syndrome

Source: International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Guidelines for the Management of Type 1 Diabetes Mellitus in Children and Adolescents (17).

north. By ethnic group, there was a sixfold difference between the highest (Mongol) and lowest (Zhuang) incidences. Variations in eating habits and lifestyles could explain some of this diversity but there may also be a genetic element. China is much more genetically diverse than Europe (26).

DKA: a life-threatening but preventable complication

DKA is the leading cause of mortality (usually stemming from cerebral oedema) and morbidity in children with type 1 diabetes. DKA in children develops quickly and is, much more than in adults, related to severe morbidity and sequelae of associated medical complications. There is wide geographic variation in the frequency of DKA at diabetes onset: reported frequencies range between 15 and 67% in Europe and North America and may be more common in developing countries. DKA at onset of type 1 diabetes is more common in children under the age of 4 yr, children without a first-degree relative with type 1 diabetes, and those from low incidence countries, as well as those from families of a lower socioeconomic status (27). The described changing patterns of presentation of diabetes have also changed the incidence and severity of DKA in children (21).

Type 2 diabetes in children and adolescents

Recent data indicate an escalating incidence of type 2 diabetes in children and adolescents worldwide. Although type 2 diabetes used to be a condition in those over 40 yr of age, the increase and decrease of onset-age now hits children even before their teens. Among the primary risk factors for type 2 diabetes are increased weight and lack of physical activity. Over the past decade, there have been profound changes in the quality, quantity and source of food consumed in many developing countries. Processed food, for instance, typically offers greater caloric content but lower nutritional value, at a lower cost. An increasingly sedentary lifestyle and limited physical and sporting activities in school also play a part in the development of overweight and obesity. In addition, less well known factors play an important role such as sleep deprivation, factors that disturb endocrinological pathways, improved conditions of living (such as ambient temperatures in houses) and medicines (28).

Worldwide, overweight and obesity affect an estimated 10–20% of children. Due to the fact that obesity once developed is a chronic condition, there is thus an increasing tendency to develop type 2 diabetes and cardiovascular disease (29).

The complex pathophysiology of type 2 diabetes is not limited to factors of weight and physical activity. Trends in type 2 diabetes are strongly related to environmental factors, some of which are already in effect in the perinatal period. Children with overweight or diabetic mothers are more likely to have diabetes themselves. The nature of foetal and infantile nutrition is associated with later development of type 2 diabetes: poor nutrition at these stages of life is detrimental to the proper development and function of the pancreatic beta cells and insulin-sensitive tissues, potentially leading to insulin resistance under the stress of obesity. The thrifty genotype hypothesis proposes that defective insulin action *in utero* results in decreased foetal growth as a conservation mechanism but at the cost of obesity-induced diabetes in later childhood or adulthood (30). The prevalence of obesity is 50% higher among never-breastfed children compared with breastfed children, and the duration of breastfeeding is inversely correlated with the risk of development of obesity (3).

Most children with type 2 diabetes are overweight or obese at the time of diagnosis; ethnic background is understood to tie in to the propensity to develop type 2 diabetes in children, thus a child from a high-risk

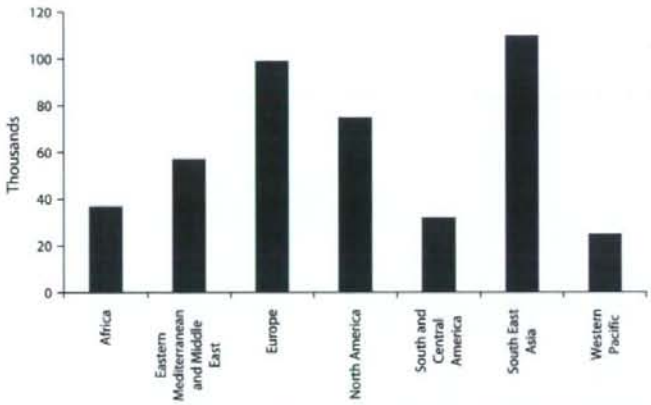

Fig. 1. Estimated number of cases of type 1 diabetes by region. Source: International Diabetes Federation World Atlas of Diabetes (2006) (8).

ethnic group such as South Asian or Pacific Islander may develop type 2 diabetes at a lower Body Mass Index than would a child of Caucasian background. Unlike those with type 1 diabetes, polyuria, polydypsia and weight loss are usually absent or mild. Major risk factors in addition to overweight or obesity include a family history of type 2 diabetes, hypertension, lipid disorders or diagnosis of acanthosis nigricans or polycystic ovary syndrome. The peak age of presentation is mid-puberty, coinciding with a peak increase in growth hormone secretion. This growth hormone tips the balance in individuals with a genetic predisposition to insulin resistance and environmental risk exposure (16).

Recent data on type 2 diabetes show increases in several parts of the world:

North American data

About 94% of children in the USA with type 2 diabetes were found in one survey to belong to minority communities, and the mean age at diagnosis was 12–14 yr. A substantial proportion of type 2 diabetes is estimated to be misclassified, undiagnosed or underreported. The most dramatic figures come from the Pima Indians in Arizona. In the years 1992–1996, the prevalence of type 2 diabetes was 22.3 per 1000 for 10–14 yr olds and 50.9 per 1000 for 15–19 yr olds. Between the years 1967–1976 and 1987–1996, the prevalence increased four- to fivefold for both age groups. Among American Indians and Alaskan Natives aged 15–19 yr, the prevalence increased by 54% between 1988 and 1996. Among white and Hispanic populations of San Antonio, Texas, type 2 diabetes represented 18% of all new cases of diabetes from 1990 to 1997 (31, 32).

Recently new data from the USA became available from the SEARCH for Diabetes Youth Study Group (33). The overall incidence was 24.3 (per 100 000 patient years; previous study 16.5 in early 1990s) confirming the overall increase seen in other countries. Among children younger than 10 yr, most had type 1 diabetes irrespective of their race or ethnicity, with the highest rates in non-Hispanic white youth (18.6, 28.1 and 32.9 for the age groups 0–4, 5–9 and 10–14 yr old respectively). Even in adolescents from non-Hispanic, Hispanic and African-American descent, type 2 diabetes was relatively infrequent, but high rates were found in 15- to 19-yr-old minority groups (17.0–49.4 per 100 000). These data showed the continuous increase of diabetes among US youth and the imminent shift of type 2 diabetes towards younger age. In total, 15 000 youth are diagnosed with type 1 diabetes annually in the USA and 3700 with type 2 diabetes (33).

The First Nations people of Canada represent 3% of the country's population. By 1998, it was estimated that 10–20% of new cases of diabetes were presenting among these people (34).

European data

Data from 2002 estimate that there were a total of 20 000 children with diabetes in the UK at that time, and forecast that the incidence of type 2 diabetes was likely to rise substantially if the UK followed the example of the USA. According to these findings, type 2 diabetes was not limited to high-risk ethnic groups such as South East Asians (35).

Australasian data

Data from Western Australia show an increase of 27% in the incidence of type 2 diabetes in youth between 1990 and 2002. Fifty three per cent of these young people were of indigenous origin. Population-based recommendations include improving dietary intake

and increasing physical activity, including activity during school hours; these strategies should involve the whole family (36).

The incidence of type 2 diabetes is thought to be higher than that of type 1 diabetes among Japanese children. A programme has been in place since 1974 to collect early morning urine samples from schoolchildren. Testing has detected a number of children who have type 2 diabetes but are asymptomatic: 84% of children with type 2 diabetes were 20% or more overweight, and 57% had a family history of type 2 diabetes. Among primary schoolchildren, the incidence is 0.78 per 100 000 children, and among junior high schoolchildren, the incidence rises to 6.43 per 100 000 children (37).

Similarly, a mass screening program for diabetes and proteinuria has been underway for students in Taiwan, using urine testing and blood testing as appropriate. The overall rate of newly identified diabetes, as reported in 2003, was 12.0 per 100 000 students, with considerably higher rates in those aged 13–15 yr compared with those aged 6–9 yr. Compared with controls, those with type 2 diabetes had a higher body mass index, higher blood pressure, were older and were more likely to have a family history of diabetes (38).

A recent review of published data testifies to the global spread of type 2 diabetes in children and adolescents. The issue of type 2 diabetes is not limited to certain ethnic groups or to particular regions but has become almost universal. There appears to be a close relationship between rates of type 2 diabetes in adults and the eventual appearance of type 2 diabetes in adolescents. Therefore, attention to the epidemiology of type 2 diabetes in adults may help to predict the emergence of type 2 diabetes in adolescent populations, with implications for screening programs and obesity prevention programs (39).

Screening for type 2 diabetes

Type 2 diabetes develops in a gradual but persistent manner. A diagnosis of diabetes is preceded by a period of glucose intolerance in which glucose levels increase but remain lower than guideline threshold levels. These threshold levels have been developed in relation to adults, but are also used for children, as specific data for this group are lacking.

From studies in adults it is known that there may be a significant time lag to the onset of type 2 diabetes. The average adult with diabetes has experienced aberrant glucose values for 7–11 yr. During this period, vascular disease with accompanying complications may have already developed. Thus, it is of extreme importance to identify both those at risk for diabetes (primary prevention) and those with diabetes as early as possible, preferably before complications arise and pathophysiological processes become irreversible (secondary prevention). Screening can be applied for primary prevention, but also has a role in secondary prevention.

It is therefore important to screen for diabetes in children and youth at risk. A number of professional organizations around the world, including the American Diabetes Association, recommend testing for type 2 diabetes in children over the age of 10 yr who are overweight (body mass index >the 85th percentile) and who have any two of the following risk factors: a family history of type 2 diabetes in a first or second-degree relative; racial or ethnic high risk (such as American Indian, African-American or South Asian); or signs of insulin resistance or associated conditions.

Several (inter)national guidelines contain similar screening recommendations aimed at primary or secondary prevention; it is important to apply such recommendations as they may reduce the burden of diabetes (40).

Complications of diabetes in children

As described in the previous paragraphs, good diabetes care prevents the development of complications (secondary prevention). Despite screening for diabetes and the availability of adequate treatment guidelines, some people with diabetes (both type 1 and type 2) will unfortunately develop both medical and psychosocial complications due to lack of access to comprehensive care, inadequate practice of care routines, or lack of opportunity or ability to implement available care strategies into daily routines. The early onset of the disease in children places them at a higher risk to develop such complications at an ever younger age.

Complications are being seen at a younger age now that the onset of diabetes is occurring earlier. Thus, in the USA, 40% of children and adolescents with type 2 diabetes were observed to have microalbuminuria (MAU) after a diabetes duration of only 18 months; among Pima Indians diagnosed with diabetes during childhood, 22% had MAU at diagnosis. Studies in these special populations showed that (except for retinopathy) children have no protective or delaying factors that protect them from complications. On average, complications occurred after a similar duration than those in adults (41).

The complications of diabetes can be very severe, leading to early onset of cardiovascular disease and premature death. Other complications that are seriously detrimental to the health and quality of life of people with diabetes include blindness, kidney failure and neurological damage.

Complications are not limited to medical concerns; psychosocial complications can prevent optimal diabetes care and the achievement of treatment goals. Diabetes care poses considerable demands on children

and their families. In addition to the normal developmental challenges of childhood and adolescence, the additional burden of diabetes, and especially intensive management, may be difficult for many children to deal with. More intensive treatment coincides with increased psychological pressure on children with diabetes and family members. This may add to the development of psychosocial complications such as adjustment problems, issues with self-esteem, depression, and particularly in adolescent girls, eating disorders. In one study in adolescents and young adults who had diabetes since childhood, about one-third needed either psychological or psychiatric counselling after (on average) 15 yr following onset of their diabetes (42).

Studies from Sweden showed that, despite the comprehensive care delivered, more than 50% of patients with childhood onset type 1 diabetes developed detectable diabetes complications after an average 12 yr of diabetes. Inadequate glycemic control, including in the first 5 yr of treatment, accelerated this (43).

A study reported in 2006 showed that, of 1433 people with type 1 diabetes and 68 with type 2 diabetes, all under the age of 18, those with type 1 diabetes had a longer duration of disease (6.8 vs. 1.3 yr) and a higher median glycated hemoglobin (8.5 vs. 7.3%). Significantly more people with type 2 diabetes were obese (56 vs. 7%). Retinopathy was observed in 20% of those with type 1 diabetes; MAU and hypertension were observed in 28 and 36%, respectively, of those with type 2 diabetes. These high rates of serious complications suggest that children as well as adults with type 2 diabetes should be screened for complications at the time of diagnosis. The data also argue for screening of at-risk adolescents for type 2 diabetes because early treatment may avoid or reverse complications (44, 45).

Clearly, prevention of complications is preferable to treatment of complications. More intensive treatment may contribute to the reduction of complications in children with diabetes. 'Intensive' treatment aims to maintain blood glucose as close to normal as possible on a continuous basis, and is distinguished from 'conventional' treatment by increased vigilance in blood glucose testing, responsive adjustments to insulin dosage based on current blood glucose level as well as food intake and exercise, and regular visits to the diabetes healthcare team. Among those with type 1 diabetes treated intensively, there was a decrease in nephropathy and retinopathy between 1990 and 2002 (46).

Conclusion

(i) The incidence of type 1 diabetes is rising in children and adolescents, and there is a shift in that children are being diagnosed at younger ages.

(ii) Type 2 diabetes is increasing rapidly, largely driven by lifestyle factors such as overweight and obesity, and is being seen in developing countries as lifestyle habits become inappropriately urbanized and modernized.

(iii) Diabetes represents a huge burden to the individual, the family and to society. Early and aggressive treatment must be strived for, and lifestyle changes need to be made possible in order to prevent diabetes from escalating out of control worldwide. Only by achieving good control can the complications be prevented or minimized.

(iv) There are still many gaps in the data on type 1 and type 2 diabetes in children and adolescents. These gaps need to be addressed to understand the epidemiological patterns of disease and the consequences of these patterns to facilitate appropriate management and optimal allocation of health care funding.

Recommendations

(i) Fill in the gaps regarding the incidence and prevalence of type 1 and type 2 diabetes, in order to more fully understand the magnitude and impact of the problem.

(ii) Initiate local, regional or nation-wide studies on the epidemiology of diabetes.

(iii) Fill in the gaps on the incidence and cost of the complications of diabetes.

(iv) Use this more complete knowledge for effective planning for resource allocation, comprehensive education, early detection/intervention and prevention strategies.

(v) Build on this knowledge to formulate prevention messages for children and youth at risk of developing type 2 diabetes and their families, emphasizing nutrition and exercise strategies to maintain a healthy weight and overall health from infancy onward.

(vi) Stimulate education and knowledge on the most important cause of death in (type 1) diabetes: DKA, by implementing education and awareness programmes.

(vii) Develop national plans for diabetes care as suggested by the United Nations Resolution on Diabetes, with specific focus on childhood diabetes.

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Pediatric Diabetes

Review Article

Metabolic syndrome in youths

Amemiya S, Dobashi K, Urakami T, Sugihara S, Ohzeki T, Tajima N. Metabolic syndrome in youths.
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Abstract: The metabolic syndrome (MetS), characterized by a clustering of cardiovascular disease and type 2 diabetes (T2DM) risk factors, has become prevalent in children and adolescents in recent years. However, the reported prevalence data on the MetS in youths has varied markedly, in large part, because of the disagreement among the variously proposed definitions of the MetS. Obesity is defined by using body mass index, waist circumference, or percent overweight, pointing to the need for standardized use of anthropometric variables to define obesity with a well-defined reference year for each ethnic population. In addition, slightly different cutoff values are used for triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting plasma glucose. Therefore, International Diabetes Federation recently proposed unified, easy-to-use criteria for diagnosing the MetS in youths. To provide insight into the mechanisms underlying the MetS in youths, the degree of insulin sensitivity/resistance and its correlation with the serum lipid and blood pressure levels have been evaluated. In addition, the serum levels of adipocytokines, such as adiponectin, leptin, tumor necrosis factor-α, resistin, interleukin-6, plasminogen activator inhibitor-1, and their correlation with childhood obesity have been extensively investigated. Recommendations for future research include exploring ways to assess visceral adiposity, to identify better biochemical markers for prediction of T2DM and disease progression, and to effectively intervene to prevent the MetS in youths.

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Key words: Adiponectin – children – metabolic syndrome – obesity – prevalence

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The metabolic syndrome (MetS) in adults is defined as a clustering of cardiovascular and type 2 diabetes (T2DM) risk factors (1, 2). The recent interest in the MetS was stimulated by Reaven's description of syndrome X in his Banting Lecture in 1988 (3). Other descriptions of the MetS followed: DeFronzo (4) referred to its multifaceted nature while Kaplan (5) referred to it as the deadly quartet, and Matsuzawa (6) described it as the visceral fat syndrome. The constellation of metabolic abnormalities includes glucose intolerance (T2DM, impaired glucose tolerance, or impaired fasting glycemia), insulin resistance, central obesity, dyslipidemia, and hypertension, all of which are well-documented risk factors for cardiovascular disease (CVD). These conditions occur together in an individual more often than what might be expected by chance.

Although the cause of the syndrome is still not certain, numerous groups have attempted to define its

essential components. The World Health Organization (WHO) (7), the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) (8), and the European Group for the Study of Insulin Resistance (9) have all formulated definitions in an effort to provide a diagnostic tool for clinicians and researchers. Although these definitions are not identical, they do agree that the essential components of MetS include measures of glucose intolerance, obesity, hypertension, and dyslipidemia. In 2005, recognizing how difficult it is to have multiple working definitions of the MetS, the International Diabetes Federation (IDF) published its definition for adults (2). Recently, in 2007, the IDF did the same for children (10) (Table 1). The desire to have a single definition for children was driven by the fact that the early identification of children at risk of developing the syndrome, T2DM, and CVD in later life cannot be underestimated.

Prevalence of the metabolic syndrome in youths

The first comprehensive national survey of the MetS in pediatric populations was the National Health and Nutrition Examination Survey (NHANES) III in the USA, conducted by Cook et al. (11). This survey evaluated the prevalence and distribution of the MetS among 2430 adolescents, aged 12–19 yr, using the modified ATP III definition. They defined obesity as being waist circumference (WC) ≥90th percentile for age and gender. The cut-points for blood pressure, lipids, and fasting plasma glucose levels were modified to be suitable for adolescents (Table 2) and the presence of any three of the five criteria made the diagnosis. In this study, the overall prevalence of the MetS was 4.2%, and 6.1% of males and 2.1% of females were affected ($p = 0.01$). While the body mass index (BMI, weight/height^2) is widely used in adult populations, the BMI percentile is suitable for age and gender in pediatric populations. The syndrome was present in 28.7% of obese adolescents (BMI ≥95th percentile) compared with 6.8% of overweight adolescents (BMI >85th to 95th percentile) and 0.1% of those with a BMI below the 85th percentile ($p < 0.001$). The authors argued that the use of WC was more meaningful, as it specifically addresses abdominal obesity, i.e., visceral adiposity, rather than another measurement of obesity.

De Ferranti et al. (12) analyzed the same population that had been previously evaluated by Cook et al. (11) using slightly different criteria. They employed a definition of obesity as a WC ≥75th percentile and different cut-points were also adopted for the lipid criteria (Table 2). Changing these cut-points for the diagnosis increased the prevalence of the MetS from 4.2 to 9.3% in the total population and from 28.7 to 31.2% among the obese population in the total cohort.

Weiss et al. (13) reported the effect of varying degrees of obesity on the prevalence of the MetS in 488 children and adolescents, aged 4–20 yr, in the USA. These other criteria are shown in Table 2 and the presence of any three of the five criteria made the diagnosis. In their moderately obese group (BMI z score 2.0–2.5), the prevalence of the syndrome was 38.7%, increasing to 49.7% in those with severe obesity (BMI z score >2.5). Each half-unit increase in the BMI converted to a z score was associated with an increase in the risk of the syndrome among obese subjects (odds ratio, 1.55). In this study, BMI was used for the assessment of obesity instead of WC. The authors argued that WC was a less reliable tool for detecting variations related to age and race/ethnicity.

Several studies have revealed race/ethnic differences in the prevalence of the MetS in children as well as in adults. With a total MetS prevalence of 4.2% in the NHANES study, the lowest prevalence was 2.0% and was found in the African-American cohort (11). However, contrary to the NHANES study, Quintos et al. (14) reported a high frequency of the syndrome in inner-city, obese African-American youth. Thirty-five percent of the total cohort had the MetS. Among

Table 1. The IDF definition of the at-risk group and MetS in children and adolescents

Age group (yr)	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Glucose (mmol/L) or known T2DM
6 to <10	≥90th percentile	MetS cannot be diagnosed, but further measurements should be made if there is a family history of MetS, T2DM, dyslipidemia, CVD, hypertension, and/or obesity			
10 to <16	≥90th percentile or adult cut-off if lower	≥1.7 mmol/L (≥150 mg/dL)	<1.03 mmol/L (<40 mg/dL)	Systolic ≥130 mmHg or diastolic ≥85 mmHg	≥5.6 mmol/L (100 mg/dL) (or known T2DM) (if ≥5.6 mmol/L recommend an OGTT)
16+	Use existing IDF criteria for adults [reference (2)]				

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; MetS, metabolic syndrome; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WC, waist circumference.

Table 2. Comparison of criteria for the diagnosis of the MetS used by different studies in adults [the National Cholesterol Education Program Adult Treatment Panel III (ATP III)] and children and adolescents

Risk factor	ATP III in adults (8)	Cook et al. (11)	De Ferranti et al. (12)	Weiss et al. (13)	MHWL in Japan (33)
Obesity					
WC	102 cm (M), 8 cm (F)	≥90th percentile	>75th percentile		80 cm
BMI *z* score for age and sex				≥2.0	
Triglycerides (mg/dL)	≥150	≥110	≥100	≥95th percentile	≥120
HDL-C (mg/dL)	<40 (M), <50 (F)	≤40	<45 (M), <50 (F)	<5th percentile	<40
Blood pressure	≥130/85 mmHg	≥90th percentile	≥90th percentile	>95th percentile	≥125/70 mmHg
Fasting blood glucose (mg/dL)	≥110	≥110	≥110	IGT*	≥100

F, females; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; M, males; MHWL, Ministry of Health, Welfare, and Labor; OGTT, oral glucose tolerance test.
*IGT, OGTT 2 h glucose ≥ 140 mg/dL and <200 mg/dL.

the morbidly obese children with a BMI *z* score >2.5, the prevalence of the syndrome increased to 44%. On the other hand, Esmaillzadeh et al. (15) reported a high prevalence of the MetS – 10.1% of the overall prevalence – in Iranian adolescents.

Hara (16) reported the change of the annual prevalence of the MetS in Japanese children, aged 9–13 yr. They used percent overweight, which is commonly used in Japan as an index instead of BMI, for the assessment of obesity. In Japan, children with percent overweight ≥20% are classified as obese. In this study, the overall prevalence of the MetS increased from 0.9 to 1.4% during 1992–2002. All the children with the MetS were obese and most showed lipid abnormalities. Some Japanese surveys demonstrated a high prevalence of the MetS in obese children as detected through school-based health screening. It is reported that 15–20% of Japanese children with obesity exhibited the MetS, and the prevalence of the syndrome increased with the degrees of percent overweight.

A need for standardization of MetS in the young

De Ferranti et al. (12) demonstrated different prevalence rates of MetS by using slightly different modifications of the ATP III criteria in the same population using the same dataset. Children with WC >90th percentile are more likely to have multiple risk factors than those with a lower WC (17). Several studies have already used the 90th percentile as a cut-point for WC (18, 19) and this was also recommended by the IDF when it attempted to define a definition of the MetS for children and youth that was both clinically and research relevant (10).

Because standard WC increases in proportion to height and is affected by ethnic factors, the cut-off value of the WC should be set in each country. The waist-to-height ratio (>0.5) can be a good alternative for WC but the age-dependent change of this parameter is a critical problem for use in screening overweight children (20). In Japan, 'obesity disease' is used to indicate an obese condition associated with health problems, and 'obesity' to indicate a mere health risk both in adults (21) and in children (22). The cut-off values of visceral adipose tissue (VAT) area of 100 cm^2 for adults and 60 cm^2 for children with obesity were chosen based on the risk assessment. The WC that corresponded to these VAT cut-off values was estimated as 85 cm for adult men, 90 cm for adult women, and 80 cm for children. In 2006, based on these observations, the Ministry of Health, Welfare and Labor in Japan proposed a definition of childhood (6–15 yr) obesity as a WC ≥ 80 cm (23).

As described, the reported prevalence data on MetS in the young has varied markedly, in large part because of disagreement among the variously proposed definitions of MetS. Therefore, a simple, easy-to-apply clinical definition was proposed by the IDF (Table 1). The new IDF definition is ranked according to age groups 6 to <10 yr, 10 to <16 yr, and ≥16 yr. This was believed to be necessary because of the developmental challenges presented by age-related differences in children and adolescents. Children <6 yr were excluded as a result of insufficient data in this age group. The IDF suggests that below 10 yr of age, the MetS should not be diagnosed, and a strong message for weight reduction should be delivered to parents and caregivers of those with abdominal obesity.

The IDF concluded that early detection, followed by treatment, particularly lifestyle intervention, is vital in halting the progression of this syndrome in this age group. This should reduce morbidity and mortality in adulthood and help minimize the global burden of CVD and T2DM. Governments and society, in general, must be made more aware of the problems associated with obesity and the likelihood of its progression to the MetS in children and adolescents.

Anthropometric variables to define obesity

Childhood obesity is a serious public health problem that is surprisingly difficult to define. The ideal definition of obesity, based on the percentage of body fat, is impracticable for epidemiological use. Although less sensitive than skin fold thickness (24), the BMI is widely used in adult populations, and a cut-point of 30 kg/m^2 is recognized internationally as a definition of adult obesity (25). On the other hand, BMI in childhood changes substantially with age (26, 27). Cole et al. (28) described the development of age-specific and gender-specific cut-points for BMI for overweight and obesity in children, using dataset-specific centiles linked to adult cut-points. Although the 85th and 95th percentile of the US BMI reference has been proposed as cut-points for childhood overweight and obesity (29), like previous definitions, it is far from universally accepted. In its place, Cole et al. proposed a definition of overweight and obesity in childhood, which is based on pooled international data for BMI and is linked to the widely used adult overweight and obesity cut-point of 25 and 30 kg/m^2. These definitions are less arbitrary and more broadly international than others and should encourage direct comparison of trends in child obesity worldwide. They argued that this approach might help to avoid some of the usual arbitrariness in choosing the reference data and cut-point.

More recently, a working party composed of representatives from WHO (Geneva), the International Society for the Study of Obesity, and the International Obesity Task Force re-emphasized the fact that obesity-associated risk is a continuum and that there are inter-ethnic differences in the relationship between various obesity indices and the risks of CVD (30). They noted that among urban Asians, the BMI range of 23–24 had an equivalent risk of T2DM, hypertension, and dyslipidemia as a BMI range of 25–29.9 had in the white population. In addition to BMI, WC has been proposed as the best marker of adiposity. Cook et al. (11) argued that the use of WC is more meaningful, as it specifically addresses abdominal obesity and visceral adiposity better than any other measurement of obesity. This is supported by the fact that among obese youth with similar BMI, insulin sensitivity is lower in those individuals with high VAT (31). It has been widely recognized that central obesity is a basic component of MetS and WC is recognized as its marker in the definition of MetS for adults. Although it is gaining acceptance for children, a global standard for WC in pediatrics is not available, and there are those, including Weiss et al. (13), who argue that WC is less reliable for detecting variations related to age and race/ethnicity.

Percentiles, rather than absolute values of WC, must be used to compensate for the changes that occur as a result of age, gender, growth, pubertal development, and ethnicity. Ethnic-specific WC percentile data are becoming increasingly available (32). WC measurement has several limitations for clinical use as well as in population-based studies (33). In order to achieve a reliable means for international comparison, it will be necessary to standardize the process for measuring WC. For example, WC should be measured at the horizontal level of the umbilicus both in boys and girls, as the narrowest point in the waist girth of an adolescent girl may be different from that in an adolescent boy and accounts for a significantly smaller value than that measured at the level of the umbilicus. The reference year for the dataset used should also be noted, as the rising rate of obesity over the past decades could result in an underestimation of the obese population, if the most recent dataset is used instead of the dataset from two decades ago. The real values at the 90th percentile of the WC in the dataset for 2000 could be much larger than those in the dataset for the 1980s in each ethnic population as stratified by age or gender. Thus, we should ensure that the reference year for the dataset is well defined and established for each ethnic population examined.

Mechanism underlying the metabolic syndrome

Insulin resistance in children with the metabolic syndrome

For the assessment of insulin resistance, the glucose clamp test is the gold standard for quantifying insulin sensitivity or resistance *in vivo*. However, as it requires intravenous infusion of insulin and glucose and frequent blood samples over a 3-h period, fasting immunoreactive insulin levels, the homeostasis model assessment insulin resistance index (HOMA-R) (34), and the quantitative insulin sensitivity check index (35) are acceptable alternatives for estimating insulin resistance.

Increased adiposity, including increased visceral fat has been demonstrated to be associated with lower insulin sensitivity, i.e. higher insulin resistance, in children as well as in adults (36–38). Epidemiological studies have shown insulin resistance (measured indirectly as fasting serum insulin level) clustered with several features of the MetS in both white and black children (39, 40). A Finnish pediatric prospective study showed higher baseline fasting insulin levels in children who later developed the MetS (39). The results of this study suggest that insulin resistance in obese children precedes the metabolic and atherogenic complications.

Weiss et al. (13) investigated the effect of insulin resistance on the prevalence of the MetS. They classified the subjects into three insulin resistance

categories by using the 33rd and 66th percentiles of the HOMA-R values as cut-offs and found that the prevalence of the MetS increased significantly with the degree of insulin resistance ($p < 0.001$) after adjustment for race or ethnic background and obesity group. Each unit of increase in insulin resistance by the HOMA-R was associated with an increase in risk of the MetS (odds ratio, 1.12; 95% confidence interval (CI), 1.07–1.18 for each additional unit of HOMA-R).

Cruz et al. (41) examined the relation between insulin sensitivity/resistance determined by the frequently sampled intravenous glucose tolerance test and minimal modeling and features of the MetS in overweight Hispanic youth with a family history of T2DM. After controlling for body composition, insulin sensitivity was positively correlated with the serum high-density lipoprotein cholesterol level ($p < 0.01$) and negatively correlated with the serum triglyceride level ($p < 0.001$) and both systolic ($p < 0.01$) and diastolic blood pressure ($p < 0.05$). Insulin sensitivity significantly decreased ($p < 0.001$) as the number of features of the MetS increased. Druet et al. (42) reported that the frequency of the MetS was independently influenced by HOMA-R (odds ratio 1.10; 95% CI, 1.00–1.21) in overweight and obese French children.

The effect of lifestyle intervention on metabolic derangements, including insulin resistance in youth, has been examined in several studies (43–45). Kang et al. (43) found an improvement in measures of insulin resistance in 80 obese youths between 13 and 16 yr of age who participated in 8 months of lifestyle education and intense physical activity compared with those who underwent lifestyle education alone. A 3-yr study of Zuni Pueblo American Indian high-school students showed that diet education and increased physical activity reduced their fasting and 30-min insulin levels (44).

Chen et al. (45) examined the effects of lifestyle modification in 16 overweight children placed on a high-fiber, low-fat diet, and daily aerobic exercise in a 2-wk residential program. They reported that the fasting insulin level, HOMA-R values, and body weights decreased significantly and that a reversal of the MetS was noted in seven subjects after the 2-wk intervention. All these changes occurred even with only modest improvements in the percentage of body fat and BMI. Their results documented that drastic reductions in the incidence of the MetS and insulin resistance in children can be achieved in a very short period through changes in diet and exercise alone.

Visceral fat accumulation and the metabolic syndrome in children and adolescents

Recent advances have provided insight into the role of the adipose mass and the possible mechanisms of obesity-related metabolic abnormalities. Imaging techniques that measure VAT have highlighted the importance of excess accumulation of VAT in obese children as well as in adults.

Obesity-related metabolic abnormalities, such as liver dysfunction, hyperinsulinemia, and hypertriglyceridemia are relatively common even in childhood. Recent studies on the topic of adipocytes and adipocytokines (adipokines) have helped explain the mechanisms for metabolic derangements (humoral theory) associated with obesity (46). Adipocytokines such as leptin, tumor necrosis factor-α (TNF-α), resistin, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1) are physiologically active substances that are secreted from adipocytes and increase in obesity. Their expression and secretion are modulated by the hypertrophy of adipocytes and inflammatory factors surrounding adipose tissue (46, 47). Leptin is considered as the master regulator of appetite. TNF-α, resistin, and IL-6 are key inducers of insulin resistance. PAI-1 accelerates atherosclerosis by inhibiting fibrinolysis (47). On the other hand, the secretion of adiponectin is decreased with obesity (48). The obesity-induced changes in the levels of these adipocytokines in children are essentially similar to those in adults. The expression profile of respective adipocytokines varies in subcutaneous adipose tissue (SAT) and VAT. Their serum levels change depending on the body fat distribution. The accumulation of VAT itself results in an increased flux of free fatty acids directly from the portal system into the liver (49). Fontana et al. (50) suggested that increased secretion of IL-6 from VAT is involved in the pathogenesis of systemic inflammation and metabolic abnormalities. Thus, visceral obesity is more closely linked to metabolic derangements than subcutaneous obesity. Genetic factors also play a role in determining the obesity phenotype (51). Asian children appear to carry more risk of VAT accumulation at lower body fatness than Caucasians (52). In African-American children, various genetic and/or lifestyle factors show more impact on insulin resistance than VAT accumulation (53).

Adiponectin is now considered to be a key adipocytokine, because of its anti-atherogenic, anti-diabetic, and anti-inflammatory effects (48). Asayama et al. (54) reported that plasma adiponectin concentrations decreased with obesity and that it was restored toward normal by dieting in obese children. Although the basic molecular structure of adiponectin is a trimer, various multimers exist in circulating blood (48). Recently, a new immunoassay method has been developed to selectively measure the high molecular weight (12–18 mer; HMW), medium molecular weight (6 mer), and low molecular weight (3 mer) fractions. Among the different plasma adiponectin fractions, HMW-adiponectin is predominantly decreased in obese children (55). The plasma HMW-adiponectin level is closely correlated with VAT area and inversely

so with plasma insulin level and HOMA-R. Decrease in HMW-adiponectin more specifically reflects the number of abnormal values in clinical biochemistry because of obesity than that of total adiponectin (55). Thus, HMW-adiponectin is a better metabolic marker than total adiponectin in both adults and children.

The serum level of a new adipocytokine can predict fat distribution in obesity. Serum leptin concentration is closely correlated with percentage overweight and percentage body fat (56) and reflects the size of the SAT depot better than total or VAT in children (57). Barbeau et al. (58) reported that serum level of PAI-1, which is more preferentially expressed in VAT than in SAT, was significantly correlated with VAT in obese teenagers. Recently, visfatin has been identified as a VAT-specific adipocytokine by a differential display method (59). Further studies are needed to evaluate whether we can use visfatin as a predictor of VAT amount in clinical practice.

Future research

Areas of research interest include ways to assess visceral adiposity and liver fat, with methodologies such as tomography. Studies determining the relevance of certain biomarkers derived from adipose tissue including adiponectin, leptin, apolipoprotein-B and low-density lipoprotein particle size also need to be performed. The most effective ways to determine insulin resistance, endothelial dysfunction, inflammation with C-reactive protein, TNF-α, IL-6, and thrombosis with PAI-1, fibrinogen need to be considered. These markers should be combined with an assessment of CVD outcome and the development of diabetes so that better predictors of the MetS and disease progression can be developed.

Recommendations for future research include exploring ways to assess visceral adipocity, to identify better biochemical markers for prediction of T2DM and disease progression, and to effectively intervene to prevent the MetS in youth.

Conflict of interest

The authors have declared no conflicts of interest.

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