Overview of childhood diabetes mellitus

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Introduction

Diabetes mellitus is the common end-point of a variety of disorders of insulin production and/or insulin action resulting in hyperglycaemia with associated abnormalities of carbohydrate, fat, and protein metabolism.[1,2] The aetiology of diabetes is heterogeneous, but most cases of diabetes can be classified into two broad aetiopathogenetic categories: type 1 and type 2. However, the American Diabetes Association (ADA) classifies diabetes into: type 1 diabetes, type 2 diabetes, gestational, and acquired disorders.[2] In children, the most common form of diabetes is type 1, due to destruction of the β cells of the pancreas, with eventual complete lack of insulin secretion.[3] The second most common form of diabetes in children is type 2 diabetes, which has been increasing worldwide in children in association with the increase in childhood obesity.[4] It results from peripheral and hepatic resistance to insulin coupled with inability of the pancreatic β cells to compensate.[3,4] Recently a new classification of diabetes has been proposed, the β cell-centric classification.[5] This model pre-supposes that all diabetes originates from a final common denominator, the abnormal pancreatic β cell. It recognises that interactions between genetically predisposed β cells with a number of factors, including insulin resistance (IR), susceptibility to environmental influences, and immune dysregulation/inflammation, lead to the range of hyperglycaemic phenotypes within the spectrum of diabetes.

Diabetes is a serious and costly disease and it is associated with acute and chronic complications that contribute to excess morbidity and mortality in individuals, especially in developing countries.[6]

Epidemiology

Worldwide, diabetes is one of the most common chronic diseases in children and type 1 diabetes accounts for over 90% of the cases.[7] Annually about 80 000 children (age <15 years) are estimated to develop type 1 diabetes worldwide.[8] The incidence of type 1 diabetes in children varies widely, and the incidence rates are correlated with the frequency of human leukocyte antigen (HLA) susceptibility genes in the general population.[9,10] It is higher in Caucasian populations and in populations at a distance from the equator.[3] Countries with the highest annual incidence rates of type 1 diabetes in children are Finland, with 36.5 per 100 000, Sweden with 27.5 per 100 000, Canada (Prince Edward Island) with 24.5 per 100 000, and Norway (eight counties) with 21.2 per 100 000.[8] In Asia, the incidence of type 1 diabetes is low compared with Caucasians.[11] Likewise in Africa, the reported incidence is also low, even though diabetes overall is not rare in Africa, but there is limited information from the region.[12] Generally a rise in type 1 diabetes incidence has been observed globally in recent decades.[13–15] In some reports there has been a disproportionately greater increase in those under the age of five years,[15,16] and in developing countries or those undergoing economic transition in recent decades.[15,17]

Type 2 diabetes is becoming more common and accounts for a significant proportion of young-onset diabetes in certain at-risk populations.[18] However, population-based epidemiological data are more limited compared with type 1 diabetes, even though investigators from various countries like USA,[19,20] Canada, Japan, Austria, UK, and Germany, have reported increased rates of type 2 diabetes.[21–25]

There are generally no significant gender differences in the incidence of diabetes, even though some differences are observed in some populations. However, a male gender bias is often observed in older adolescents and young adults.[26–28]

Type 1 diabetes

Type 1 diabetes is a life-long medical condition and is the leading cause of diabetes in children of all ages.[7] It is an autoimmune disease in which the immune system destroys the insulin-producing β cells of the pancreas that help regulate blood glucose levels.[7] Type 1 diabetes usually begins in childhood or young adulthood, but can develop at any age. Combinations of genetic and environmental factors put people at increased risk for type 1 diabetes. The presence of any of the antibodies, GAD-65, ICA, IAA and IA-2 increase the risk of type 1 diabetes.[29] In general, 70% of people with new-onset type 1 diabetes will have a positive antibody if only one antibody is measured, whereas 90% will have at least one antibody when all four are measured.[29]

Onset

Type 1 diabetes mostly has an acute onset, with children and adolescents usually able to pinpoint when symptoms began.[30] Some children and adolescents may present with ketoacidosis as the first indication.[31] Others may have post-meal hyperglycaemia, or modest fasting hyperglycaemia that rapidly progresses to severe hyperglycaemia and/or ketoacidosis in the presence of infection or other stress.[30]

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1. Classic symptoms of diabetes or hyperglycaemic crisis, with plasma glucose concentration ≥11.1 mmol/l (200 mg/dl) or
2. Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl). Fasting is defined as no caloric intake for at least 8h* or
3. Two hour post-load glucose ≥11.1 mmol/l (≥200 mg/dl) during an oral glucose tolerance test (OGTT). (The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75g)
4. Haemoglobin A1c (HbA1c) >6.5%†

Table 1. Criteria for the diagnosis of diabetes mellitus

Plasma blood glucose target range		HbA1c	Notes
Before meals	**Bedtime/overnight**		
5.0–7.2 mmol/l	5.0–8.3 mmol/l	<7.5%	A lower goal (<7.0%) is reasonable if it can be achieved without excessive hypoglycaemia
(90–130 mg/dl)	(90–150 mg/dl)		

Table 2. Blood glucose and HbA1c targets for type 1 diabetes across all paediatric age-groups[35]

Symptoms

The immunologic process that leads to type 1 diabetes can begin years before symptoms develop.[30] Symptoms become apparent when most of the β cell population is destroyed and usually develop over a short period of time.[30] Early symptoms, which are mainly due to hyperglycaemia, include polyuria and polydypsia, polyphagia, weight loss, and blurred vision. Elevation of blood glucose, acidosis, and dehydration comprise the condition known as diabetic ketoacidosis or DKA. If diabetes is not diagnosed and treated with insulin at this point, the individual can lapse into a life-threatening coma.

Diagnostic criteria for diabetes in childhood and adolescence

Diagnostic criteria are based on blood or plasma glucose measurements and the presence or absence of symptoms,[1] and different methods can be used for the diagnosis (Table 1).[1,2]

Complications

DKA and hypoglycaemia are the most significant acute complications of diabetes and its treatment, and both complications pose a significant risk of morbidity and mortality. Children with type 1 diabetes are also at risk for the long-term complications of diabetes, most notably microvascular complications such as retinopathy, nephropathy, and neuropathy. Longer term, macrovascular disease may occur, leading to strokes and heart disease.[32]

Management

The main goals of treatment of type 1 diabetes are to achieve glycaemia as close to metabolic normality as possible, avoid acute complications, minimise the risk of long-term micro- and macrovascular complications, and assist the child and family in achieving normal growth and development, as well as normal psychological maturity and independence. The basic elements of management are insulin administration (either by subcutaneous injection or insulin pump), nutrition management, physical activity, blood glucose testing, the avoidance of severe hypoglycaemia, and the avoidance of prolonged hyperglycaemia or DKA.[33]

Most pre-adolescent children need about 0.7–1.0 insulin units/kg/day, while adolescents usually need about 0.8–1.2 units/kg/day. Sometimes requirements may rise substantially above 1.2 units and even up to 2.0 units/kg/day. This increased need in adolescence is due to increased insulin resistance during puberty.[34] However, during the 'honeymoon period', dose requirements may drop to less than 0.5 units/kg/day. The honeymoon period is the period when insulin requirements often decline temporarily, usually starting 1–3 months after diagnosis, and is due to improved function of β cells with removal of the toxic effect of hyperglycaemia. The honeymoon period may last several months, occasionally 12 months or more.[34]

Commonly used insulin regimens are either split/mixed or basal/bolus regimens. Using split/mixed regimens, most children and adolescents require at least two injections per day of short- and intermediate-acting insulin to achieve satisfactory metabolic control. The injections are administered shortly before breakfast and dinner. Using these regimens, patients usually need about two-thirds of their total dose in the morning and one-third in the evening. The doses usually are split between one-third regular/rapid-acting insulin and two-thirds isophane (NPH).[34]

Basal/bolus regimens aim to achieve more physiological insulin concentrations with less between-meal insulin action. The basal insulin provides baseline or fasting insulin needs; the bolus doses provide insulin to cover food requirements and to correct postprandial hyperglycaemia. The basal insulin is provided by either rapid-acting insulin given with the basal rate of an insulin pump or with once or twice-daily injections of long-acting insulin analogues such as detemir or glargine. The bolus insulin is provided by acute doses of rapid-acting insulin, either through injections or through bolus doses given by an insulin pump.[34]

Physical activity helps to lower blood glucose levels in addition to maintaining cardiovascular fitness and controlling weight. To maintain blood glucose levels within the target range during extra physical activity, patients will need to adjust their insulin and food intake. They also may need to check their blood glucose levels more frequently to prevent hypoglycaemia while engaging in physical activity.

To control diabetes and prevent complications, blood

glucose levels in children with type 1 diabetes should be managed as indicated in Table 2. However, goals should be individualised and different goals may be reasonable based on benefit–risk assessment. Furthermore, families need to work with their healthcare team to set target blood glucose levels appropriate for the child.

Type 2 diabetes

Type 2 diabetes used to occur mainly in adults who were overweight and older than 40 years. Now, as more children and adolescents in most societies become overweight or obese and inactive, type 2 diabetes is occurring more often in young people.[36] Type 2 diabetes is a complex metabolic disorder of heterogeneous aetiology with social, behavioural, and environmental risk factors unmasking the effects of genetic susceptibility.[37] There is a strong hereditary (likely multigenic) component to the disease, with the role of genetic determinants illustrated when differences in the prevalence of type 2 diabetes in various racial groups are considered.[38] Type 2 diabetes is more common in certain racial and ethnic groups such as African-Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans.[39] In Japanese school children, type 2 diabetes is now more common than type 1.[40] The diagnosis of type 2 diabetes in children is made on average between 12 and 16 years of age, and rarely before age 10. However, the youngest patient reported was diagnosed at four years of age.[41]

Onset

The first stage in the development of type 2 diabetes is often insulin resistance, requiring increasing amounts of insulin to be produced by the pancreas to control blood glucose levels.[4] Initially, the pancreas responds by producing more insulin, but after several years, insulin production may decrease and diabetes develops.[3] Type 2 diabetes usually develops slowly and insidiously in children.

Symptoms

Some children or adolescents with type 2 diabetes may show no symptoms at all. In others, symptoms may be similar to those of type 1 diabetes. Sometime symptoms may include weight loss, blurred vision, frequent infections, and slow healing of wounds or sores. Some may present with vaginal or penile candidiasis. Extreme elevation of blood glucose levels can lead to DKA as a presenting feature. Because symptoms are varied, it is important for healthcare providers to identify and test those who are at high risk for the disease.[42]

Signs of diabetes

Physical signs of insulin resistance include acanthosis nigricans, where the skin around the neck or in the armpits appears dark and thick, and feels velvety. It is present in up to 50–90% of children with type 2 diabetes. It is recognised more frequently in darker-skinned obese individuals. Girls can have polycystic ovary syndrome with infrequent or absent periods, excess hair and/or acne. Lipid disorders and hypertension also occur more frequently in children with type 2 diabetes.[43]

Diabetes risk factors and testing criteria

Current diabetes risk factors and testing criteria in Table 3 may help identify type 2 diabetes in children before the onset of complications.

Co-morbidities

Children with type 2 diabetes are also at risk for the long-term complications of diabetes and the co-morbidities associated with insulin resistance (lipid abnormalities and hypertension).

Management

The American Academy of Pediatrics has, very recently, published management guidelines on how to treat children and adolescents with type 2 diabetes.[44] The ideal goal of treatment is normalisation of blood glucose values and HbA1c.[42] Therefore, it may be reasonable to use the values in Table 2 (for children with type 1) as a guide. All aspects of the regimen need to be individualised.

The cornerstone of diabetes management for children with type 2 diabetes is healthy eating with portion control, and increased physical activity.[45] If this is not sufficient to normalise blood glucose levels, glucose-lowering medication and/or insulin therapy are used as well.[42,44] Many drugs are available for individuals with type 2 diabetes, although only metformin and insulin are currently licensed for use in patients under 18 years old.[42] Advantages of oral agents include potentially greater compliance and convenience for the patient. Clinical features suggesting initial treatment with insulin include dehydratation, presence of ketosis, and acidosis.

Other types of diabetes

In a small proportion of cases, diabetes has a simple inheritance pattern, suggesting causation by a single gene (monogenic diabetes), and clinical manifestations depend on the gene involved. In some cases, diabetes is secondary to a particular disease entity or a particular drug.[2] Rare monogenic forms of diabetes (neonatal diabetes or maturity-onset diabetes of the young) that occur in less than 5% of children are due to one of six gene defects that result in faulty insulin secretion.[33] These are discussed in detail below.

Maturity-onset diabetes of the young (MODY)

Maturity-onset diabetes of the young (MODY) is a group of diseases characterised by inherited young-onset diabetes (usually in adolescence or early adulthood) from a single gene mutation.[46] It is an autosomal dominant condition due to a defect in insulin secretion. About six genes are involved (MODY 1 to MODY 6).[47] MODY

patients are usually not obese and are not insulin resistant. The severity of the diabetes symptoms associated with MODY varies depending on the type of MODY diagnosed. MODY 2 appears to be the mildest form of the disease, often only causing mild hyperglycaemia and impaired glucose tolerance.[47] MODY 1 may require treatment with insulin, much like type 1 diabetes. Family members of people with MODY are at greatly increased risk for the condition.[46]

MODY is often misdiagnosed initially as the more common type 1 or type 2 syndromes, but diagnosis should be considered in any of the following circumstances:[33]

- Children with a strong family history of diabetes but without typical features of type 2 diabetes (non-obese, low-risk ethnic group).
- Children with mild fasting hyperglycaemia (i.e. 5.5–8.2 mmol/l; or 100–150 mg/dl), especially if young and non-obese.
- Children with diabetes but with negative autoantibodies and without signs of obesity or insulin resistance.

Neonatal diabetes

This is a rare form of monogenic diabetes usually diagnosed within the first six months of life. Onset of diabetes in infancy should raise the possibility of neonatal diabetes. It is due to mutations in the genes encoding the adenosine triphosphate-sensitive potassium channel of the β cell (*KCNJ11*, encoding the Kir6.2 subunit, and *ABCC8*, encoding the SUR1 subunit) or a mutation in the insulin gene.[48] It is rare, estimated at 1:400 000 live births, and it can be transient or permanent.[49] In approximately half the cases it is transient (TNDM) and insulin requirements drop to zero by a few weeks or months of age. In permanent neonatal diabetes, problems tend to persist, requiring lifelong treatment usually with sulphonylureas.[50]

Treatment varies: some children respond to diet therapy, exercise, and/or oral anti-diabetes medications that stimulate endogenous insulin secretion through binding to the sulphonylurea receptor (SUR1). However, in some instances long-term insulin is required for therapy.[49]

Secondary diabetes

Secondary diabetes can occur in children with other diseases such as pancreatic diseases, Cushing's disease, cystic fibrosis, etc., or those using drugs such as glucocorticoids. These causes may account for 1–5% of all diagnosed cases of diabetes.[2]

Conclusion

Diabetes is the common end-point of a variety of disorders of insulin production and/or insulin action resulting in hyperglycaemia. It results from inadequate insulin secretion, which can be absolute or relative to increased requirements because of the defects of insulin action. Diabetes typically presents with increased urination, increased thirst, fatigue, and weight loss, although children and adolescents with type 2 diabetes may be asymptomatic. It may also present with acute metabolic decompensation, with hyperosmolar dehydration and/or ketoacidosis. There is no single regimen to manage diabetes that fits all children. Blood glucose targets, frequency of blood glucose testing, type, dose and frequency of insulin, use of insulin injections with a syringe or a pen or pump, use of oral glucose-lowering medication, and details of nutrition management all may vary among individuals. The family and diabetes care team determine the regimen that best suits each child's individual characteristics and circumstances.

Author declaration

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