Childhood and Juvenile Diabetes

2.0 Contact Hours

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Diabetes mellitus is the third most prevalent severe chronic disease of childhood. Until recently, diabetes diagnosed in children and adolescents was almost entirely considered to be Type 1 (insulin dependent) diabetes, formerly known as ‘‘juvenile diabetes’’ or ‘‘IDDM.’’ Now, as youth are becoming increasingly overweight, we are seeing more obese children with a clinical phenotype of Type 2, or ‘‘adult onset’’ diabetes. Childhood diabetes, similar to adult diabetes, is now acknowledged to be a complex and heterogeneous disorder.

Diabetes mellitus is a complex disorder with profound consequences, both acute and long-term, for the health of the affected individual and for the cost of health care in society at large. There is also a worldwide increase in childhood Type 1 diabetes, and the reasons for this increase are still not known. The increase in T2DM clearly is related to the epidemic of obesity sweeping both the developed and developing world. The ability to predict T1DM is highly advanced, but preventing or delaying its clinical appearance is a problem that remains to be solved. By contrast, T2DM probably is preventable, though how and why obesity and lifestyle exert such a profound effect remains enigmatic.

Upon completion of this course, the learner will be able to:

1. Define diabetes mellitus
2. Discuss the diagnostic criteria of diabetes mellitus
3. Discuss the epidemiology and types of diabetes mellitus
4. Explain the pathology and pathogenesis of diabetes mellitus
5. Discuss its clinical features
6. Elaborate the various investigations to be done
7. Discuss the treatment & outcome of the disease
8. Discuss the various complications and their management

Introduction

Diabetes mellitus (DM) has affected human beings since ancient times. Sushruta and Charaka (1000 BC) described diabetes as a fatal disease. According to them, this disease caused the affected persons to 'urinate honey' leading to rapid death. The term diabetes means "to run through a siphon" and mellitus means "honey sweet".

Definition

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (ADA expert committee 1997).

The 1997 American Diabetes Association Diagnostic Criteria

For the diagnosis of diabetes at least one of the following 3 criteria must be present:

- Symptoms of diabetes with a random plasma glucose level ≥ 200mg/dL
- Fasting plasma glucose level ≥ 126 mg/dL with no caloric intake for at least 8 hours
- 2 hours plasma glucose level ≥ 200 mg/dL during an oral glucose tolerance test

Diagnostic criteria for diabetes mellitus serve the following main purposes:

- To identify and classify individuals who have diabetes and to provide appropriate treatment
- To provide a tool for epidemiological study

Nomenclature

The terms insulin dependent diabetes mellitus and non-insulin type diabetes mellitus and their acronyms IDDM and NIDDM are obsolete. These terms are confusing and have resulted in classifying the patient based on treatment rather than etiology. The terms Type 1 and Type 2 diabetes mellitus

are used with Arabic numerals. Roman numerals are avoided as Type II can be easily confused by the patients as 11.

Classification

DM is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance. A classification of diabetes and other categories of glucose intolerance is given below.

Etiologic Classifications of Diabetes Mellitus

- Type I diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
    - Immune mediated
    - Idiopathic
- Type II diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
- Other specific types
    - Genetic defects of β-cell function
        - Chromosome 12, HNF-1α (formerly MODY-3)
        - Chromosome 7, glucokinase (formerly MODY-2)
        - Chromosome 20, HNF-4α (formerly MODY-1)
        - Mitochondrial DNA
    - Genetic defects in insulin action
        - Type A insulin resistance
        - Leprechaunism
        - Rabson-Mendenhall syndrome
        - Lipoatrophic diabetes
    - Diseases of the exocrine pancreas
        - Pancreatitis

        - Trauma, pancreatectomy
        - Neoplasia
        - Cystic fibrosis
        - Hemochromatosis
        - Fibrocalculous pancreatopathy
        - Pancreatic resection
    - Endocrinopathies
        - Acromegaly
        - Cushing disease
        - Glucagonoma
        - Pheochromocytoma
        - Hyperthyroidism
        - Somatostatinoma
        - Aldosteronoma
- Gestational diabetes mellitus
- Neonatal diabetes mellitus
    - Transient—without recurrence
    - Transient—recurrence 7–20 yr later
    - Permanent from onset
- Drug- or chemical-induced
    - Vacor
    - Pentamidine
    - Nicotinic acid
    - Glucocorticoids
    - Thyroid hormone
    - Diazoxide
    - β-Adrenergic agonists
    - Thiazides
    - Dilantin
    - β-Interferon
    - Cyclosporine, tacrolimus

- Infections
    - Congenital rubella
    - Cytomegalovirus
    - Hemolytic uremic syndrome
- Uncommon forms of immune-mediated diabetes
    - “Stiff-man” syndrome
    - Anti-insulin receptor antibodies
- Other genetic syndromes sometimes associated with diabetes
    - Down syndrome
    - Klinefelter syndrome
    - Turner syndrome
    - Wolfram syndrome
    - Friedreich ataxia
    - Huntington chorea
    - Laurence-Moon-Biedl syndrome
    - Myotonic dystrophy
    - Porphyria
    - Prader-Willi syndrome

Epidemiology

Vast geographic variation occurs in the incidence of diabetes mellitus. Incidence is highest in Scandinavian countries and lowest in some provinces of China. Incidence increases 3% per year. Incidence increases during winter and is lesser in warm months. Incidence of Type 1 diabetes mellitus will be about 40% higher in 2010.

In children, diabetes usually presents in two age groups:

- At 5-7 years of age
- At puberty

The first peak corresponds to the time of increased exposure to infectious agents and the second peak at puberty due to gonadal steroids which may

antagonize insulin action, and also due to the emotional stress of puberty. These possible cause and effect relationships remain to be proved. Boys are affected more than girls.

Both genetic and environmental factors play a role. Familial clustering of cases occurs in 15-20% of cases with Type 1 diabetes. Environmental factors found from clues obtained from epidemiological studies are viral infection, diet, toxins, maternal age over 40 years, low birth weight, stress, etc. Environmental factors may serve as modifiers of disease pathogenesis rather than as triggers.

Etiopathogenesis

Type I diabetes

Type 1 diabetes is the form of the disease caused primarily by β-cell destruction. This condition is characterized by severe insulin deficiency and dependence on exogenous insulin to prevent ketosis and to preserve life. Although the onset is predominantly in childhood, the disease may occur at any age.

It is possible that non-autoimmune and autoimmune destruction of β-cell could coexist, but the current classification considers two subtypes. In Type 1a there is evidence suggesting an autoimmune origin of β-cell destruction, mostly determined by the presence of circulating antibodies against islet cells. Patients with Type 1a are also more likely to have other concomitant autoimmune disorders, such as autoimmune thyroiditis, Addison's disease, and celiac disease.

The Type 1b form of diabetes is characterized by low insulin and C peptide levels similar to those in Type 1a, although there is no evidence of an autoimmune etiology of the b-cell destruction. This idiopathic diabetes reflects the still limited knowledge of the etiology of many forms of diabetes.

Type 2 diabetes mellitus

Type 2 DM is the most common form of diabetes in adults, and its prevalence in children is increasing. It is characterized by insulin resistance and defective insulin secretion, either of which can be the predominant feature. Patients with type 2 DM usually have insulin resistance and relative rather than absolute insulin deficiency. Pediatric patients with type 2 DM are likely to be overweight or obese and present with glycosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss. Up to 33% have ketonuria at diagnosis, and 5% to 25% of patients who are subsequently classified as having type 2 diabetes have ketoacidosis at presentation. Children with type 2 diabetes usually have the metabolic syndrome, have a family history of type 2 diabetes, and are more likely to be of non- European ancestry (African, Hispanic, Asian, and American Indian descent).

Type 2 DM patients are most likely antibody negative, although in adults a Syndrome of clinical type 2 diabetes with positive autoantibodies has been described as latent autoimmune diabetes. Acanthosis nigricans and polycystic ovarian syndrome, disorders associated with IR and obesity, are common in youth with type 2 diabetes. Currently, children with type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty. With increased obesity and insulin resistance in the population, more and younger individuals with poor b-cell function develop diabetes.

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young comprises a heterogeneous group of disorders of monogenic defects in b-cell function. The maturity-onset diabetes of the young syndromes is characterized by dominant inheritance with at least two and preferably three consecutive generations, and onset before age 25 to 30 years.

Mitochondrial diabetes

Mitochondrial diabetes, also called maternally inherited diabetes and deafness, is characterized by a progressive decline in β-cell function. The diagnosis should be suspected when there is a marked history of diabetes associated with bilateral deafness in most carriers that follows a maternal inheritance. Hearing impairment generally precedes the onset of clinically manifest diabetes by several years and changes in pigmentation of the retina are also present in many.

Diabetes and other syndromes with predominantly insulin resistance

A number of mutations of the insulin receptor resulting in diabetes have been identified. Although these are rare causes of diabetes they should be considered in a patient with marked features of insulin resistance and exceptionally high insulin levels. These mutations lead to at least four clinical syndromes, all of them characterized by findings secondary to insulin resistance. The syndromes include –

- Type A insulin resistance
- Leprechaunism
- Rabson-Mendenhall syndrome
- Lipoatrophic diabetes

Cystic fibrosis–related diabetes

About 5% to 10% of patients with cystic fibrosis have diabetes based on fasting glucose levels. The clinical course of these patients is characterized by a slow progression from normal glucose tolerance to impaired glucose tolerance and ultimately fasting hyperglycemia, with no tendency to ketosis. Patients frequently become glucose intolerant at times of illness. This is presumably caused by limited insulin secretion, which cannot compensate for the stress-induced resistance to insulin action.

Diabetes mellitus in newborn

The syndrome of diabetes mellitus in newborn has its onset in the first week of life and persists only for several weeks to months before spontaneous resolution. It occurs most often in infants who are small for gestational age. It is characterized by hyperglycemia and pronounced glycosuria resulting in severe metabolic acidosis with minimal or no ketonuria or ketonemia. There is a functional delay in the beta cell maturation in this disorder. Treatment is in the form of insulin. 50% of the patients may develop permanent diabetes due to a rare syndrome of pancreatic agenesis. One third has transient diabetes. One third has transient diabetes with recurrence at an older age usually between 7 and 20 years.

Clinical feature

Diabetes and its complications produce a wide range of signs and symptoms. The classical symptoms polyuria, polydipsia, weight loss and polyphagia are usually seen well before the diagnosis of diabetes. But they can occur at any stage of the disease secondary to hyperglycemia.

There are four phases of diabetes. They are –

- **Pre diabetic phase** – This state precedes the clinical onset of diabetes by months or even years and is characterized by the presence of antibodies to islet cell antigens.
- **Overt diabetic phase** – This state is characterized by the onset of classical symptoms. It may be sudden and acute in onset most often.
- **Remission phase (Honeymoon phase)** – The phase occurs after the diagnosis of overt diabetes during which there may be continuing and effective secretion of endogenous pancreatic insulin.
- **Total insulin dependency** – When the beta cell function becomes totally unmeasurable, the individual is said to totally dependent on insulin.

Major symptoms –

- Polyuria
- Polydipsia
- Weight loss
- Polyphagia
- Fatigue

Minor symptoms

- Cramps
- Constipation
- Blurred vision
- Candidiasis
- Skin sepsis
- Poor school performance
- Irritability

Features of ketosis which is a complication of diabetes

- Nausea
- Vomiting
- Drowsiness
- Abdominal pain
- Kussmal respiration
- Ketone breath
- Hypothermia
- Hypotonia
- Uncoordinated ocular movements

Investigations

The various investigations that need to done for diagnosing diabetes are –

- Urinalysis – It may show glycosuria and ketonuria
- Serum biochemistry – Glucose, ketones, osmolarity, urea, creatinine, lipids, sodium, potassium, bicarbonate
- Oral glucose tolerance test – A glucose test load of 1.75 g/kg body weight upto a maximum of 75g is given orally. Blood sample is collected 1, 1.5 and 2 hours after the test load. Impaired glucose tolerance test is diagnosed if the fasting blood glucose is less than 126 mg/dl and 2 hour blood glucose level is more than 200 mg/dl.
- Glycosylated hemoglobin (HbA1C) – Glycosylated hemoglobin is formed nonenzymatically wherein the glucose gets attached to beta chain of hemoglobin. Values between 4 and 9 indicate good control over the previous 3 months.
- Fructosamine or glucoprotein test – This is similar to glycosylated hemoglobin (HbA1C) , but measure glucose over the previous 2-3 weeks rather than months
- C peptide level – C peptide is cleaved from the precursor of insulin and is excreted in the urine. Its measurement is very useful in assessing pancreatic beta cell secretory activity.
- Islet cell antibodies – They are markers of ongoing autoimmune beta cell depletion.

Management of diabetes

The management program includes the following –

- Insulin therapy
- Nutrition
- Exercise
- Monitoring
- Education and counseling

Insulin therapy

Insulin is the treatment of choice in Type I diabetes. Maintaining blood glucose concentration as close as normal is essential in order to prevent long term complications. The goals of insulin therapy are –

- Elimination of hyperglycemic symptoms
- Prevention of diabetic ketoacidosis
- Restoration of lean body mass, height velocity and weight
- Improvement in exercise capacity and work performance
- Improvement in immunological defense
- Delay, arrest or prevent microvascular and macrovascular complications

The types of insulin available are –

- Rapid acting
    - Lispro
    - Regular
    - Semilente
- Intermediate acting
    - NPH
    - Lente
- Long acting
    - Ultralente (human)
    - Ultralente (bovine)
    - PZI

Dosage of insulin depends on –

- Age
- Weight
- Stage of puberty
- Duration and phase of diabetes
- Site of injection
- Nutritional intake
- Exercise pattern

- Intercurrent illness

The dose is 0.5 -1 U/kg /day. The dose should be adjusted based on the pattern of blood glucose levels over the previous 3-7 days. The various insulin regimens are –

- Single dose regimen – A combination of regular and intermediate insulin is given 30-45 minutes prior to breakfast
- Twice daily regimen – NPH and short acting insulin are given. Two thirds of the dose is given in the morning and one third in the evening. During each dose two thirds will be NPH and one third will be short acting insulin.

The various devices available to give insulin injections are –

- Pen injector devices
- Automatic injection devices
- Jet injectors
- Subcutaneous insulin injection pumps
- Insulin syringes

The injection sites are –

- Back of arms (for morning injections)
- Buttocks (for morning injections)
- Abdomen (for morning injections)
- Front and sides of thigh (for night injections)

Nutrition

Nutrition management is essential because -

- It provides adequate calories and nutrients for growth and development
- It prevents obesity

The meal should be –

- Carbohydrate – 50-55%

- Protein – 15-20%
- Fat -30%
    - Less than 10% saturated fat
    - Less than 10% polyunsaturated fat
    - Up to 15% monounsaturated fat

Exercise

Exercise is beneficial in children with diabetes by acting in the following ways –

- It lowers blood glucose level by enhancing insulin absorption from the injection site
- It promotes better physical state
- It reduces the risk of cardiovascular complications

Monitoring

Monitoring should include the following-

- Monitoring of blood glucose
- Monitoring of HbA1C
- Monitoring of nutrition
- Growth monitoring
- Monitoring of renal function
- Monitoring of cardiovascular function
- Foot care

Education and counseling

The initial phase of education is very important and should be given to the family soon after the diagnosis. The education should include –

- Basic information about diabetes
- Basic information about insulin
- Blood glucose measurement
- Acceptable blood glucose values

- Information on hyper and hypoglycemia
- Diet counseling

Complications

Complications of diabetes could present as acute or chronic complications. The various complications are –

Acute complications –

- Hypoglycemia – Hypoglycemia occurs when the blood glucose level drops below 60 mg /dl. It is often due to mismatch between the use of insulin and diet and activity
- Diabetic ketoacidosis
- Non-ketotic hyperosmolar coma

Chronic complications –

- Retinopathy – It could be either non-proliferative or proliferative retinopathy. Increased capillary permeability is the earliest sign. Proliferative retinopathy is characterized by new vessel formation. All patients should be evaluated annually 3 years after the diagnosis. Treatment consists of photocoagulation and pars plana vitrectomy.
- Nephropathy –This is the most common cause of death in type 1 diabetes. It is characterized by microalbuminuria which is defined as protein excretion of30-300 mg /day. Overt nephropathy occurs in 30% and renal failure may result after about 20 years. Meticulous control of diabetes can reverse microalbuminuria.
- Neuropathy – Diabetic neuropathy, both autonomic and peripheral is rare in children and is seen in only about 10% of the children diagnosed with diabetes.
- Coronary artery disease – Symptomatic cardiac disease like coronary artery disease is rare in children with diabetes.
- Cerebrovascular disease – Cerebrovascular disease is rare.

- Peripheral arterial disease – Peripheral arterial disease is rare in children
- Dyslipidemia –In type 1 diabetes there is an elevated level of triglyceride levels in children with poor control of diabetes. Borderline values for total cholesterol is 170-199mg/dl and for LDL is 110-129 mg/dl. Treatment goal is to achieve LDL cholesterol below 100mg/dl. The treatment includes high fiber diet, resins and statins.

Pediatric Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is an important complication of childhood diabetes mellitus and the most frequent diabetes-related cause of death in children. In various population-based studies, reported rates of DKA at presentation of type 1 diabetes have ranged from as low as 15% to as high as 83%, with most North American and European studies reporting rates of approximately 40%. Although DKA occurs less frequently in children with type 2 diabetes, case series have documented frequencies of DKA at diagnosis of type 2 diabetes in children ranging from 6% to 33%. A diagnosis of type 2 diabetes cannot be excluded based on the occurrence of DKA.

In children who have established diabetes, DKA may occur with episodes of infection or other illnesses or with insulin omission or malfunction of diabetes care equipment, such as insulin pumps. In children who have established diabetes, DKA occurs at a rate of approximately 1% to 8% per year. DKA in patients who have established diabetes occurs more frequently in persons with lower socioeconomic status, lack of adequate health insurance, higher HbA1c levels, and psychiatric disorders. Insulin omission is the most frequent cause of DKA in children who have known diabetes.

Classic symptoms of DKA include polyuria, polydipsia, weight loss, abdominal pain, nausea, and vomiting. Abdominal tenderness, absence of bowel sounds, and guarding may be present and may mimic the acute abdomen.

Tachycardia is frequent, and signs of hypoperfusion, such as delayed capillary refill time and cool extremities, are also common.

Other signs of dehydration also may be present, including dry mucous membranes, absence of tears, and poor skin turgor. Hypothermia also has been described. Tachypnea occurs in response to metabolic acidosis as a result of stimulation of chemoreceptors in the central nervous system (CNS). Tachypnea may be extreme and may cause DKA to be initially misdiagnosed as respiratory illness. Acetone (produced from nonenzymatic decarboxylation of acetoacetate [AcAc]) typically causes a fruity breath odor, which may be a helpful initial clue to the diagnosis of DKA. Despite profound systemic acidosis, most children who have DKA present with normal mentation or only minimal depression of mental status.

Nonketotic hyperosmolar coma

Nonketotic hyperosmolar coma is also called hyperglycemic hyperosmolar nonketotic coma (HONK). This complication is more common in adults. It is characterized by –

- Severe hyperglycemia (blood glucose more than 600 mg / dL)
- Absence of ketosis
- Severe dehydration
- Depressed sensorium
- Neurological signs like seizures, hyperthermia, hemiparesis and positive Babinski sign

Treatment is directed against rapid repletion of blood volume and very slow correction of hyperosmolar state.