Diabetes mellitus in Pediatrics

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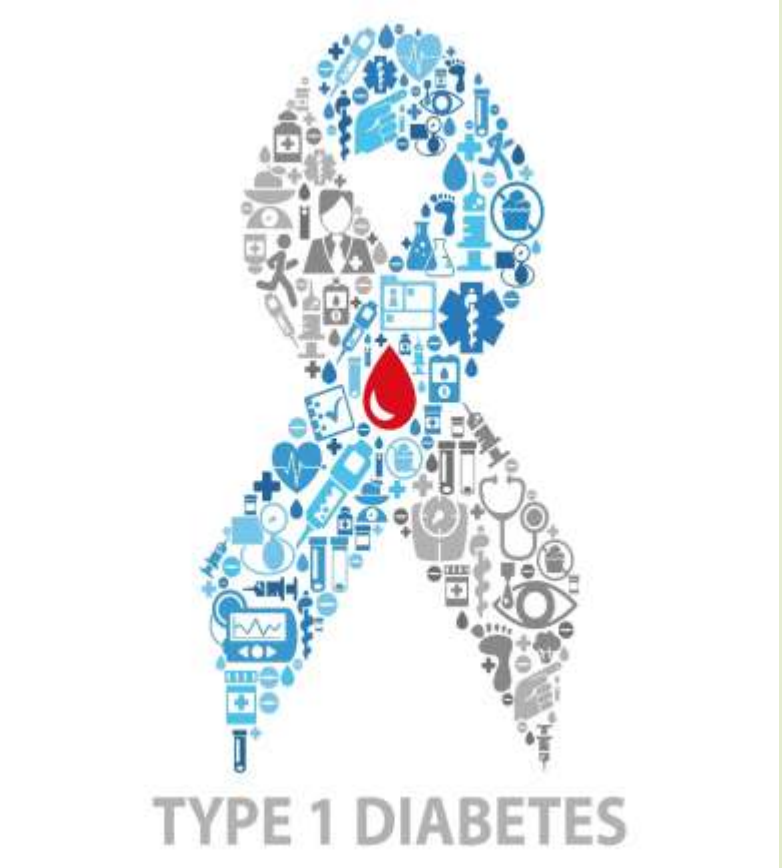
2021/2022



Diabetes mellitus (DM)

- a common, chronic, metabolic disease characterized by hyperglycemia as a cardinal biochemical feature.
- The major forms of diabetes are differentiated by insulin deficiency vs insulin resistance:
- Type 1 diabetes mellitus (T1DM) results from deficiency

of insulin secretion because of pancreatic β-cell damage;

- Type 2 diabetes mellitus (T2DM) is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment.

Classification:

Type 1 diabetes :
Type 2 diabetes:
Other specific types:
- specific genetically defined forms of diabetes (MODY)
- diabetes associated with other diseases or drugs.
-Neonatal DM

Table 2: Types of diabetes

Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes
Slowly evolving immune-mediated diabetes of adults
Ketosis prone type 2 diabetes
Other specific types (see Tables)
Monogenic diabetes
- Monogenic defects of β-cell function
- Monogenic defects in insulin action
Diseases of the exocrine pancreas
Endocrine disorders
Drug- or chemical-induced
Infections
Uncommon specific forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes
Unclassified diabetes
This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes
Hyperglyacemia first detected during pregnancy
Diabetes mellitus in pregnancy
Gestational diabetes mellitus

- T1DM is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development.

- Less common types of diabetes result from genetic defects of the insulin receptor or inherited abnormalities in sensing of ambient glucose concentration by pancreatic beta cells

TYPE 1 DIABETES MELLITUS

- Formerly called *insulin-dependent diabetes mellitus* (IDDM) or *juvenile*

diabetes,

- characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM.

- The onset occurs predominantly in childhood, with a median age of 7-15 yr, but it may present at any age.
- The incidence of T1DM has steadily increased in nearly all parts of the world

Type 1 diabetes

- One-fourth of cases are diagnosed in adults in their late 30s and early 40s. .

- T1DM remains the most common form of diabetes in childhood, accounting for approximately two-thirds of new diagnoses of diabetes in patients ≤19 years of age in the United States, despite the increasing rate of type 2 diabetes

- The natural history includes 4 distinct stages:

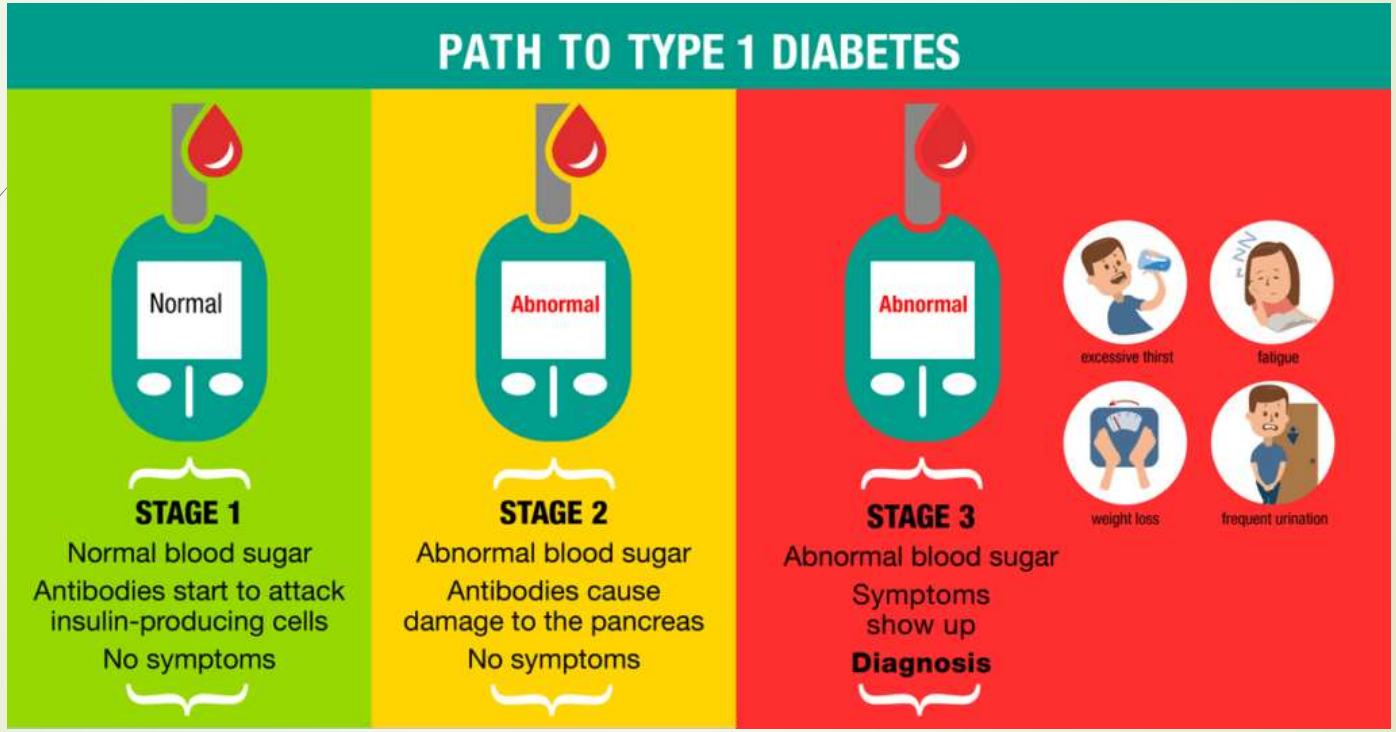
(1) preclinical β-cell autoimmunity with progressive defect of insulin

secretion,

(2) onset of clinical diabetes,

(3) transient remission "honeymoon period," and

(4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy.


PATH TO TYPE 1 DIABETES
Normal
Abnormal
Abnormal
STAGE 1
Normal blood sugar
Antibodies start to attack insulin-producing cells
No symptoms
STAGE 2
Abnormal blood sugar
Antibodies cause damage to the pancreas
No symptoms
STAGE 3
Abnormal blood sugar
Symptoms show up
Diagnosis
excessive thirst
fatigue
weight loss
frequent urination

Etiology:

- T1DM is characterized by autoimmune destruction of pancreatic islet β cells.
- Both **genetic susceptibility** and **environmental factors** contribute to the pathogenesis.
- Susceptibility to T1DM is genetically controlled by alleles of the MHC class II genes expressing human leukocyte antigens (HLAs).
- Autoantibodies to β-cell antigens such as islet cell cytoplasm (ICA), insulin autoantibody (IAA),antibodies to glutamic acid decarboxylase GAD, and ICA512 are detected in serum from affected subjects.
- These can be detected months to years prior to clinical onset of T1DM.

Genetic factors

- Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM.
- Approximately 95% of patients with type 1 DM have either HLA-DR3 or HLA-DR4
- Polygenic
- Siblings or offspring of patients with diabetes have a risk of 2% to 8% for the development of diabetes;
- an identical twin has a 30% to 50% risk.

Cont. genetic factors

for the child of a parent with type 1 DM, the risk varies according to whether the mother or the father has diabetes

Children whose mother has type 1 DM have a 2-3% risk of developing the disease, whereas those whose father has the disease have a 5-6% risk. When both parents are diabetic, the risk rises to almost 30%.

- the risk for children of parents with type 1 DM is slightly higher if **onset of the disease** occurred before age 11 years and slightly lower if the onset occurred after the parent's 11th birthday.

Cont.genetic factors

ethnic populations.

- Type 1 DM is most prevalent in European populations
- people from northern Europe are more often affected than those from Mediterranean regions.
- The disease is least prevalent in East Asians.

Environmental factors

Potential triggers for immunologically mediated destruction of the beta cells include:

- viruses (eg, enterovirus,mumps, rubella, and coxsackievirus B4),
- toxic chemicals

- Early exposure to cow's milk in infancy
- Others: ●Immunizations
- ●Higher socioeconomic status
- ●Obesity
- ●Vitamin D deficiency
- ●Perinatal factors such as maternal age, history of preeclampsia, and neonatal jaundice.

Low birth weight decreases the risk of developing T1DM

- In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated.
- This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation.
- These individuals may have ketoacidosis, but they have extensive periods of remission with variable insulin deficiency, similar to patients with T2DM.

epidemiology

- Although most autoimmune diseases are more common in females, there appears to be no gender difference in the overall incidence of childhood T1DM.
- However, in select populations, T1DM occurs more frequently in males (3:2)
- In US, Type 1 DM is the most common metabolic disease of childhood. About 1 in every 400-600 children and adolescents has type 1 DM.
- In adults, type 1 DM constitutes approximately 5% of all diagnosed cases of diabetes

- The **age** of presentation of childhood onset T1DM has a bimodal distribution, with one peak at four to six years of age and a second in early puberty (10 to 14 years of age).
- Overall, about 45 percent of children present before 10 years of age [19].
- usually starts in children aged 4 years or older, appearing fairly abruptly, with the peak incidence of onset at age 11-13 years (ie, in early adolescence and puberty).
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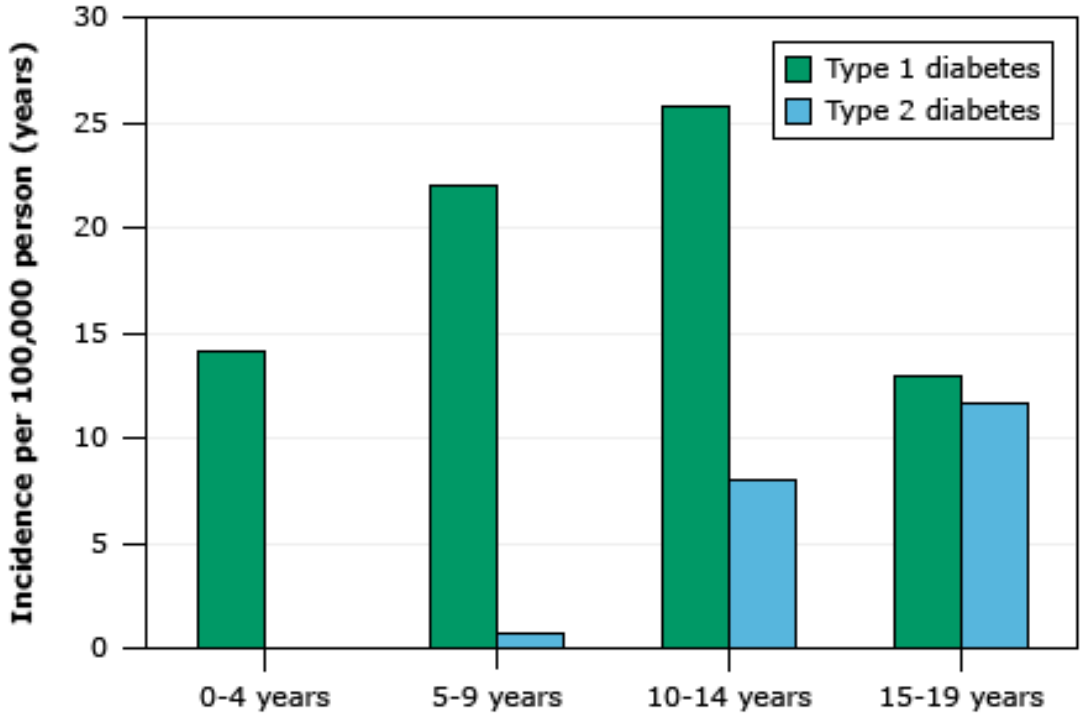
Incidence of diabetes mellitus in youth by age group



Incidence of type 1 and type 2 diabetes mellitus in youth in the United States, from the SEARCH for Diabetes in Youth Study Group, 2002-2003. For type 1 diabetes, there are two peaks in incidence, in mid-childhood and early puberty; this bimodal distribution is not evident from the age categories used for this figure.

Data from: Writing Group for the SEARCH for Diabetes in Youth Study Group, Dabelea D, Bell RA, et al. Incidence of diabetes in youth in the United States. JAMA 2007; 297:2716.

LADA

- high incidence in people in their late 30s and early 40s, in whom the disease tends to present less aggressively (ie, with early hyperglycemia without ketoacidosis and gradual onset of ketosis).

- This slower-onset adult form of type 1 DM is referred to as latent autoimmune diabetes of the adult (**LADA**).

- Internationally, rates of type 1 DM are increasing. In Europe, the Middle East, and Australia, rates of type 1 DM are increasing by 2-5% per year.[41]

- The risk of development of antibodies (anti-islet) in relatives of patients with type 1 DM decreases with increasing age

Pathophysiology

- Type 1 DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas.

- As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels.
- After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed.
- Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism.

Cont. pathophysiology

- Approximately 85% of type 1 DM patients have circulating **islet cell antibodies**, and the majority also have detectable **anti-insulin (** insulin autoantibodies IAA**)** before receiving insulin therapy.

- The most commonly found islet cell antibodies are those directed against glutamic acid decarboxylase **(GAD)**, an enzyme found within pancreatic beta cells.

- Antibodies to tyrosine phosphatase and others.
- The risk for diabetes increases with the number of antibodies detected in the serum.
- In individualswith one detectable antibody only, the risk is only 10% to 15%;
- in individuals with three or more antibodies, the risk is 55% to 90%.

Insulin

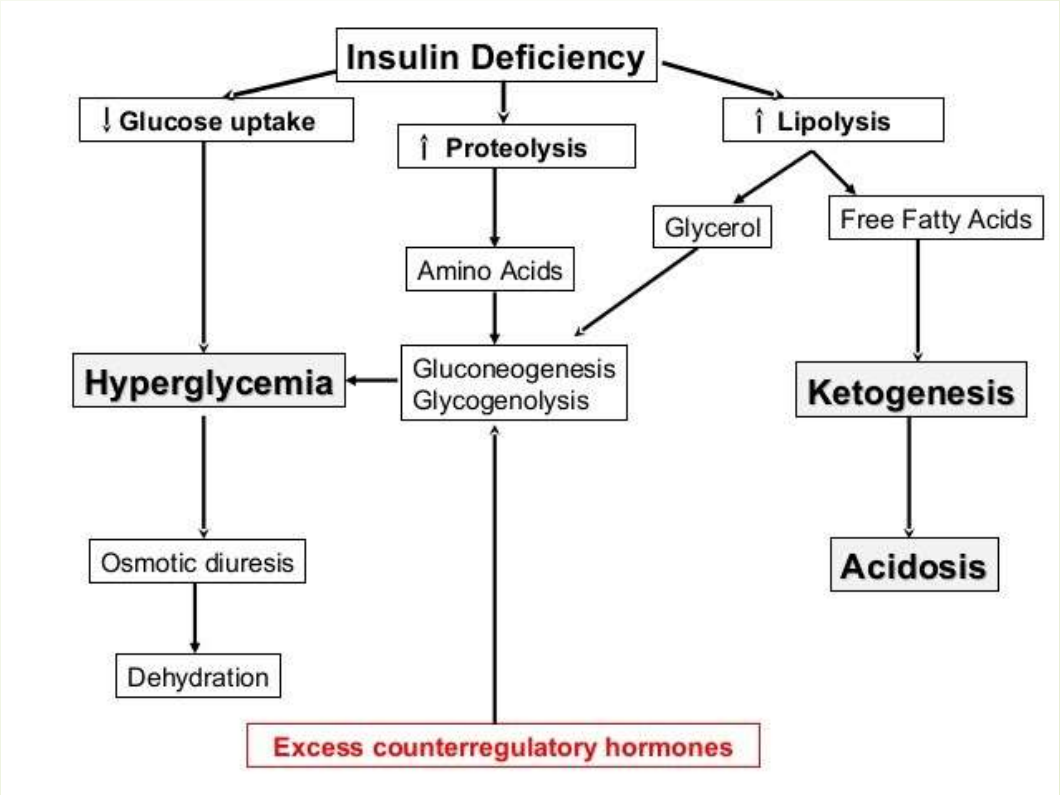
- Secreted by beta cells of pancreas
- Inhibits glycogenolysis and gluconeogenesis in liver
- Stimulates protein synthesis and lipogenesis
- Inhibits lipolysis and proteinolysis

Absence of Insulin

Decrease lipogenesis + increase lipolysis

Decrease protein synthesis + increase proteinolysis

increase glycogenolysis + increase gluconeogenesis


Insulin Deficiency
↓ Glucose uptake
↑ Proteolysis
↑ Lipolysis
Glycerol
Free Fatty Acids
Amino Acids
Hyperglycemia
Gluconeogenesis
Glycogenolysis
Ketogenesis
Osmotic diuresis
Acidosis
Dehydration
Excess counterregulatory hormones

- Hyperglycemia results when insulin secretory capacity becomes inadequate to enhance peripheral glucose uptake and to suppress hepatic and renal glucose production.
- Insulin deficiency usually first causes postprandial hyperglycemia and then fasting hyperglycemia.
- Ketogenesis is a sign of more complete insulin deficiency.
- Lack of suppression of gluconeogenesis and glycogenolysis further exacerbates hyperglycemia while fatty acid oxidation generates the **ketone bodies**: β-hydroxybutyrate, acetoacetate, and acetone.
- Protein stores in muscle and fat stores in adipose tissue are metabolized to provide substrates for gluconeogenesis and fatty acid oxidation.

- **Glycosuria** occurs when the serum glucose concentration exceeds the renal threshold for glucose reabsorption (from 160 to 190 mg/dL).
- Glycosuria causes an **osmotic diuresis** (including obligate loss of sodium, potassium, and other electrolytes), leading to **dehydration**.
- **Polydipsia** occurs as the patient attempts to compensate for the excess fluid losses.
- **Weight loss** results from the persistent catabolic state and the loss of calories through glycosuria and ketonuria.
- The classic presentation of DM1 includes polyuria, polydipsia, polyphagia, and weight loss.

DDX

- Type 2 DM
- Monogenic DM, previously known as maturity-onset diabetes of youth (MODY)
- Secondary hyperglycemia
- Endocrine disorders - Endocrine tumor causing increased production of growth hormone, glucocorticoids, catecholamines, glucagon, and somatostatin; Addison disease; Graves disease; Hashimoto thyroiditis; acanthosis nigricans (genetic disorders with insulin resistance)

- Drugs - Thiazide diuretics, phenytoin, and glucocorticoids
- Chronic pancreatitis
- Cystic fibrosis
- Prader-Willi syndrome - Mental retardation, muscular hypotonia, obesity, short stature, and hypogonadism associated with DM
- Nondiabetic glycosuria

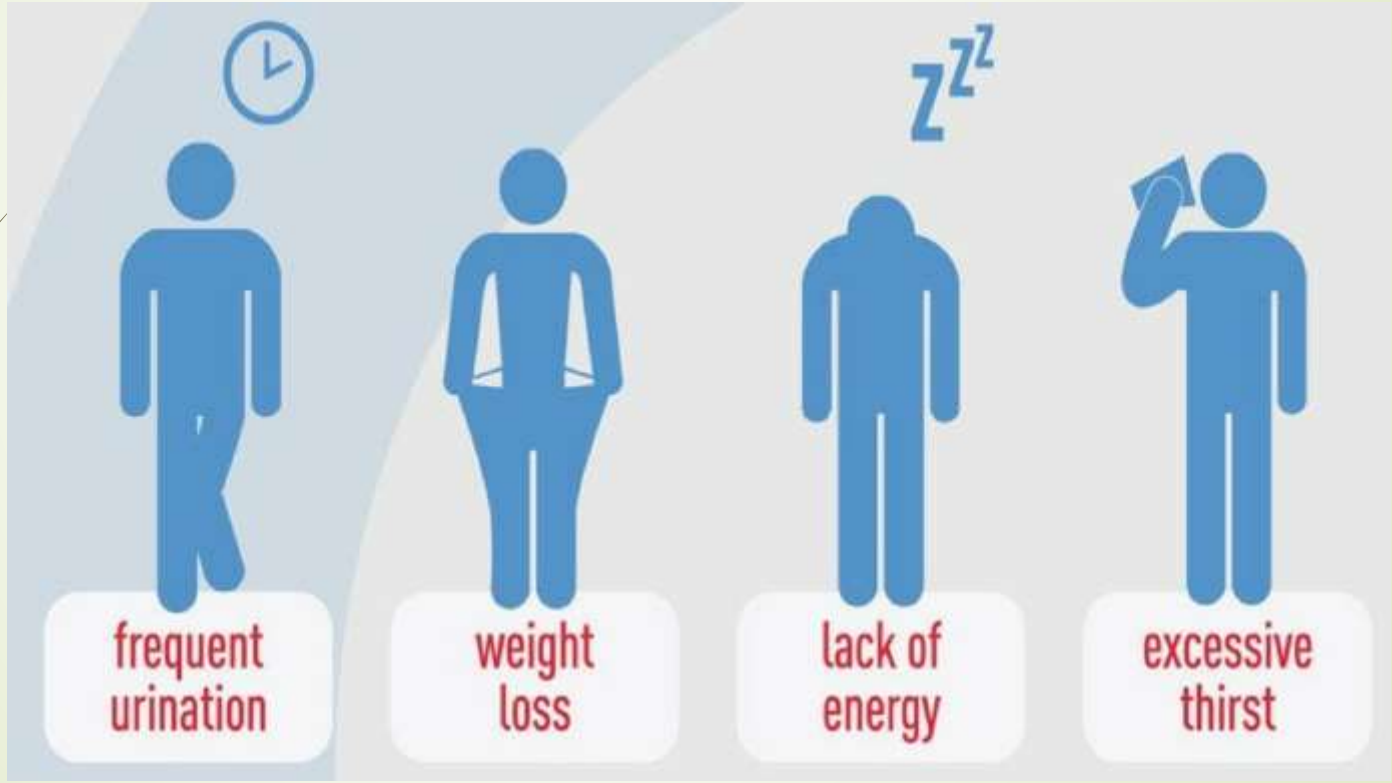
Renal glycosuria - Glucose appears in urine despite normal glucose concentration in blood; this may occur because of an autosomal genetic disorder or dysfunction of the proximal renal tubule (eg, Fanconi syndrome or chronic renal failure), or it may occur during pregnancy as a consequence of the increased glucose load placed on tubules by the elevated glucose filtration rate

Clinical Manifestations:

- Onset is usually sudden
- symptoms at the time of the first clinical presentation can usually be traced back several days to several weeks. However, beta-cell destruction may have started months, or even years, before the onset of clinical symptoms

- Polyuria, polydipsia, polyphagia(The most common symptoms)
- weight loss
- Fatigability
- DKA as first presentation.
- Progression may be accelerated by

intercurrent illness or stress.


frequent urination
weight loss
lack of energy
excessive thirst

presentation

- Classic new onset of chronic polydipsia, polyuria, and weight loss with hyperglycemia and ketonemia (or ketonuria) (the most common with average duration of 10 days of symptoms)

- Diabetic ketoacidosis

- Silent (asymptomatic) incidental discovery

Other presentations

perineal candidiasis, which is a relatively common presenting symptom in young children and in girls .

- Visual disturbances are common because of alterations in the osmotic milieu of the lens, and to a lesser extent the aqueous and vitreous humors leading to changes in refractive index .
- Children with longstanding hyperglycemia may present with cataracts

- Unlike people with type 2 DM, those with type 1 DM usually are **not obese** and usually present initially with diabetic ketoacidosis (**DKA).**

- The distinguishing characteristic of a patient with type 1 DM is that if his or her insulin is withdrawn, ketosis and eventually ketoacidosis develop. Therefore, these patients are dependent on exogenous insulin**.(insulin dependent)**

Physical Examination

- In new cases of diabetes, physical examination findings are usually normal. Patients with DKA, however, will have Kussmaul respiration, signs of dehydration, hypotension, and, in some cases, altered mental status.
- In established cases, patients should be examined every 3 months for macrovascular and microvascular complications. They should undergo funduscopic examination for retinopathy and monofilament testing for peripheral neuropathy.

labs

- FBS
- RBS
- OGTT
- Islet cell autoantibodies: (GAD-65, insulin, islet cell antibodies)
- Blood gas and ketones
- C-peptide: In a type 1 patient, elevation >2 years after diagnosis should prompt reevaluation of classification
- Insulin and C-peptide: Not helpful in initial classification. At presentation, levels usually low in type 1 but there is significant overlap with type 2
- Screening for associated conditions

Diagnosis:

- FPG ≥ 126 mg/dL , 7 mmol/L (more than one occasion)

or

- Random PG ≥ 200 mg/dL (11.1 mmol/L) + symptoms of

diabetes

or

- 2hr PG in a 75-g OGTT ≥ 200 mg/dL
- HA1c>= 6.5%

- A patient is considered to have **impaired fasting glucose**
- if fasting serum glucose concentration is 100 to 125 mg/dL or
- **impaired glucose tolerance** if 2-hour plasma glucose following
- an OGTT is 140 to 199 mg/dL

HbA1c :

- A reliable index of long-term glycemic control

- the fraction of hemoglobin to which glucose has been nonenzymatically attached in the blood stream.
- A HbA1c measurement reflects the average blood glucose concentration from the preceding 2-3 mo.

Treatment

- Insulin with good glycemic monitoring

Comorbid Conditions of DM Type1

- Autoimmune thyroid disease
  - 15-30% of individuals with type 1 diabetes .
- Celiac disease:
  - 4 to 9% of children with type 1 diabetes.
  - 60 to 70% are asymptomatic.
- Addison disease:
  - rare.

Type 1 versus type 2 diabetes

- Determining whether a patient has type 1 or type 2 DM is an important diagnostic and therapeutic concern because patients with type 1 DM depend on continuous exogenous insulin for survival.
- A patient whose diabetes is controlled with diet or an oral antidiabetic agent clearly has type 2 DM.
- A lean patient who has had diabetes since childhood, who has always been dependent on insulin, or who has a history of diabetic ketoacidosis (DKA) almost certainly has type 1 DM.
- Distinguishing the type of diabetes can be difficult in some patients
- When in doubt, treat the patient with insulin and close monitoring of glucose levels.

TYPE 1 VERSUS TYPE 2 DIABETES AT PRESENTATION

Type 1DM	Type 2DM
Onset Usually prepuberty	Usually postpuberty
Polydipsia and polyuria Present for days to weeks	Absent; or present for weeks to months
Ethnicity : Caucasian	African American, Hispanic, Asian,Native American
	Obese
Weight loss	
Other physical findings: none	Acanthosis nigricans
	Type 2 diabetes
Family history :Autoimmune diseases	Less common
Ketoacidosis More common	75 to 90 percent of those with T2DM have an affected close relative

Type II Diabetes Mellitus

- 1. Prevalence: Increasing among children, especially among African Americans, Hispanics, and Native Americans; increase is related to increased prevalence of **childhood obesity**
- 2. Etiology: Abnormality in glucose levels caused by insulin resistance and insulin secretory defect
- 3. Presentation: Although not typical, can present in ketoacidosis

- 4. Screening:

  Consider screening by measuring fasting blood glucose levels among children who are overweight *and* have two of the following risk factors:

- Family history of type 2 DM in a first- or second-degree relative
- Signs associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian disease)

- 5. Treatment: Primarily diet and exercise; pharmacologic agents are often necessary for those who fail conservative management or are symptomatic at presentation
- a. Metformin
- b. medications other than insulin and metformin in children and adolescents (GLP-1 Analogues).

Maturity-Onset Diabetes of Youth
MODY

- GENETIC DEFECTS OF β-CELL FUNCTION (monogenic)
- Onset 9-25 yr,
- AD inheritance
- A primary defect in insulin secretion.
- **Diagnostic Criteria:**

- Diabetes in at least 3 generations with AD

- Diagnosis before age 25 yr in at least 1 affected subject.

When to suspect MODY?

- a strong family history of young onset diabetes mellitus (DM)
- mild persistent hyperglycemia with a HbA1c

at the upper limit of normal,

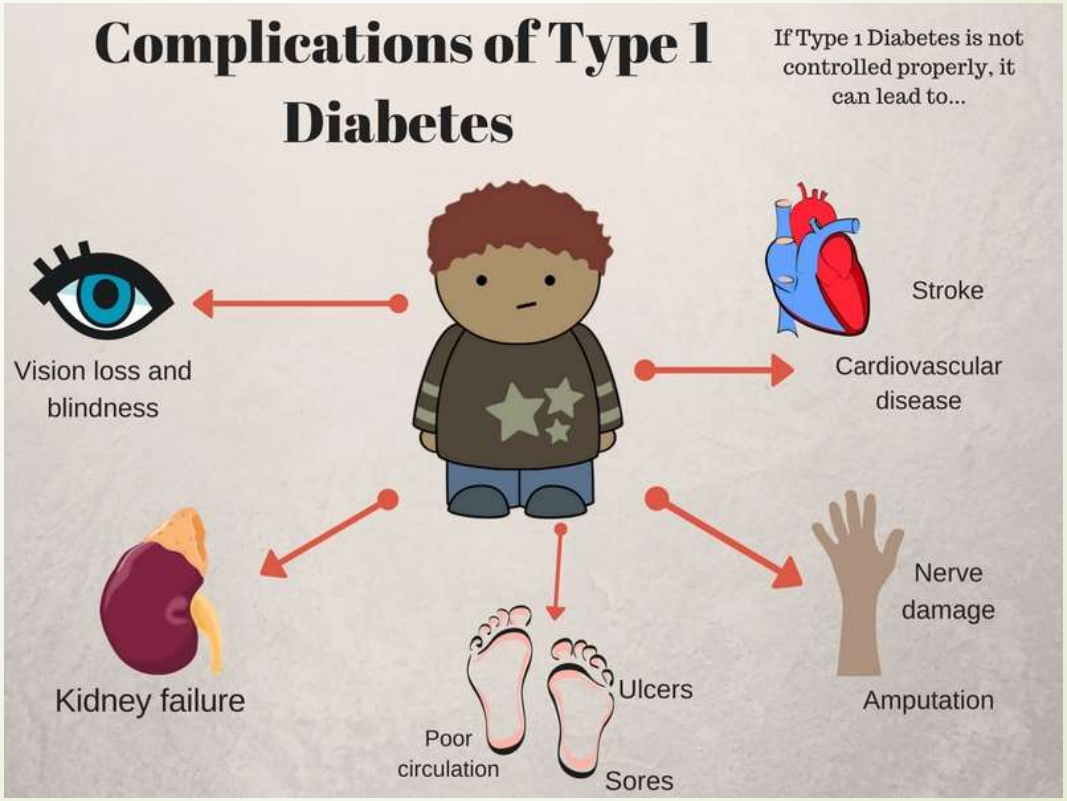
- glucosuria at low blood glucose
- Type II-like disease in a nonobese host, or type I-like disease in a host who has never had DKA or is still producing insulin beyond the honeymoon phase (up to 3 years)

Complications of DM

short- and long-term complications.

- Hypoglycemia from management errors
- Increased risk of infections
- Microvascular complications (eg, retinopathy and nephropathy)
- Neuropathic complications
- Macrovascular disease

- The long-term complications are related to metabolic disturbances (hyperglycemia)
- These complications result in increased risk for IHD, cerebral vascular disease, peripheral vascular disease with gangrene of lower limbs, chronic renal disease, reduced visual acuity and blindness, and autonomic and peripheral neuropathy.
- Diabetes is the major cause of blindness in adults aged 20-74 years, as well as the leading cause of nontraumatic lower-extremity amputation and ESRD.


Complications of Type 1 Diabetes
If Type 1 Diabetes is not controlled properly, it can lead to...
Vision loss and blindness
Stroke
Cardiovascular disease
Kidney failure
Nerve damage
Amputation
Ulcers
Poor circulation
Sores

- a lifelong challenge to achieve and maintain blood glucose levels as close to the normal range as possible.
- With appropriate glycemic control, the risk of both microvascular and neuropathic complications is decreased markedly.
- In addition, aggressive treatment of hypertension and hyperlipidemia decreases the risk of macrovascular complications.

Cont. Diabetes Complications:

- Nephropathy
- Retinopathy:

The risk after 15 yr duration of diabetes:

- 98% T1DM

- 78% T2DM.

- Neuropathy:

The risk after 20 yr duration of diabetes:

- 20-30% T1DM

- 15-20% T2DM

- Dyslipidemia
- Hypertension

Up to 16% of adolescents with type 1 diabetes

Prognosis

- Type 1 DM is associated with a high morbidity and premature mortality.
- More than 60% of patients with type 1 DM do not develop serious complications over the long term, but many of the rest experience blindness, ESRD, and, in some cases, early death.
- The risk of ESRD and proliferative retinopathy is twice as high in men as in women when the onset of diabetes occurred before age 15 years.[42]

Cont. prognosis

- Patients with type 1 DM who survive the period 10-20 years after disease onset without fulminant complications have a high probability of maintaining reasonably good health.

- Other factors affecting long-term outcomes are the patient's education, awareness, motivation, and intelligence level.

Monitoring of All Diabetics

- 1. Glucose control: Daily blood glucoses; HbA1c level every 3 months

- 2. Other involved organ systems: Frequent eye examinations and screening for hypertension, proteinuria, and hyperlipidemia (Monitor q2 years with goals of low-density lipoprotein [LDL] <100 mg/dL, high-density [HDL] >35 mg/dL, triglycerides [TGs] <150 mg/dL)

Patient Education

- Education is a vital aspect of diabetes management.
- the clinician should educate the patient—and, in the case of children, the parents—about the disease process, management, goals, and long-term complications.
- Make patients aware of the signs and symptoms of hypoglycemia and knowledgeable about ways to manage it.
- Help patients understand and acknowledge the course of diabetes that requires lifestyle modification and that they are likely to have chronic complications if they do not take control of their disease

Cont. patient education

- Reassure patients about the prognosis in properly managed type 1 DM
- Education about an appropriate treatment plan and encouragement to follow the plan are especially important in patients with diabetes.
- All necessary laboratory tests, examinations (eg, foot and neurologic examinations), and referrals to specialists (eg, an ophthalmologist or podiatrist).
- A dietitian should provide specific diet control education to the patient and family. A nurse should educate the patient about self–insulin injection and performing fingerstick tests for blood glucose level monitoring.

Honeymoon Period

- A period of stable blood glucose control, often with nearly normal glucose concentrations.
- Usually starts in the first weeks of therapy, often continues for 3 to 6 months, and can last 2 years

Explanation:

- In some patients with new onset of DM1, the beta cell mass has not been completely destroyed.
- The remaining functional beta cells seem to recover function with insulin treatment.
- When this occurs, exogenous insulin requirements decrease.

Neonatal Diabetes

- also termed congenital diabetes, or diabetes of infancy, is highly likely to be due to an underlying monogenic defect when it occurs under 6 months of age.
- Mutations in *KCNJ11* and *ABCC8* (affecting the pancreatic beta-cell K-ATP channel) may be treated with oral sulfonylureas and account for about 40 percent of these patients.
- Oral sulfonylureas stimulate endogenous insulin secretion through binding to sulfonylureas receptor.
- Transient (but can recur later in life) VS. permanent

Outpatient Type 1 Diabetes Mellitus Management

- Management of DM1 in children requires a comprehensive approach with attention to medical, nutritional, and psychosocial issues.
- Therapeutic strategies should be flexible with the individual needs of each patient and the family taken into account.
- Optimal care involves a team of diabetes professionals,including a physician, a diabetes nurse educator, a dietitian,and a social worker or psychologist.

Goals

- The Diabetes Control and Complications Trial established that intensive insulin therapy, with the goal of maintaining blood glucose concentrations as close to normal as possible, can delay the onset and slow the progression of complications of diabetes (retinopathy, nephropathy, neuropathy).

- Attaining this goal using intensive insulin therapy can increase the risk of hypoglycemia.
- The adverse effects of hypoglycemia in young children may be significant because the immature CNS may be more susceptible to glycopenia.

- Although the risk for diabetic complications increases with duration of diabetes, there is controversy as to whether the increase of risk is slower in the prepubertal years than in adolescence and adulthood.
- The goals of therapy differ, depending on the age of the patient.
- For children younger than 5 years old, an appropriate goal is maintenance of blood glucose concentrations between 80 and 180 mg/dL.
- For school-age children, 80 to 150 mg/dL is a reasonable target range.
- For adolescents, the goal is 70 to 130 mg/dL.
- Goals of therapy also should take into account other individual characteristics, such as a past history of severe hypoglycemia and the abilities of the patient and family.


S
M

Hypoglycemia

Symptoms of Low Blood Sugar Include:

- Hunger
- Trembling
- Sweating
- Extreme Mood changes
- Extreme tiredness
- Pale
- Dizziness
- Blurred Vision
- Headaches

Cont. hypoglycemia

- These symptoms will always precede NEUROGLYCOPENIA except in long standing type 1 diabetes/hypoglycemia unawareness.

- Action : confirm blood sugar is less than 72 mg/dL and TREAT WITH CARBOHYDRATE

Dawn phenomenon

- Normal event with hyperglycemia between 5 and 9 am without a preceding hypoglycemia
- Due to increased clearance of insulin and to nocturnal increases of GH
- Rx: increase the evening dose of insulin.

Somogy phenomenon

- Hypoglycemic episodes followed by hyperglycemia
- Late nocturnal or early morning sweating night terrors, alternating with ketosis, hyperglycemia, ketonuria and excessive glucosuria
- Insulin induced hypoglycemia followed by outpouring of counterregulatory hormones
- Rx: reduce insulin dose