Diabetes Mellitus in Children

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- Diabetes mellitus (DM) is 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

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

- Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake.

- Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term **complications** (usually in adulthood) that affect small and large blood vessels resulting in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities.

- The acute clinical manifestations are caused by hypoinsulinemic hyperglycemic ketoacidosis; the genesis of T1DM owes to autoimmune mechanisms; and the long-term complications are related to metabolic disturbances (hyperglycemia).

- 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.

- In the next slide you will find the classification of diabetes and other categories of glucose intolerance.

- Three major forms of diabetes and several forms of carbohydrate intolerance are identified.

Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
   A. Immune mediated
   B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
   A. Typical
   B. Atypical
III. Genetic defects of β-cell function
   A. MODY (maturity-onset diabetes of the young) syndromes
      1. MODY 1 chromosome 20, HNF4α
      2. MODY 2 chromosome 7, glucokinase
      3. MODY 3 chromosome 12, HNF1α, TCF-1
      4. MODY 4 chromosome 13, IPF-1
      5. MODY 5 chromosome 17, HNF1β, TCF-2
      6. MODY 6 chromosome 2q32, neuro-D_1/β_2
   B. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, diabetes mellitus, deafness)
   C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin—chromosome 4p
      1. Wolfram locus 2—chromosome 4q22-24
      2. Wolfram mitochondrial
   D. Thiamine responsive megaloblastic anemia and diabetes
IV. Drug or chemical induced
   A. Antirejection—cyclosporine, sirolimus
   B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
   C. L-Asparaginase
   D. β-Adrenergic blockers
   E. Vacor (rodenticide)
   F. Phenytoin (Dilantin)
   G. α-Interferon
   H. Diazoxide
   I. Nicotinic acid
   J. Pentamidine
V. Diseases of exocrine pancreas
   A. Cystic fibrosis–related diabetes
   B. Trauma—pancreatectomy
   C. Pancreatitis—ionizing radiation
   D. Others
VI. Infections
   A. Congenital rubella
   B. Cytomegalovirus
   C. Hemolytic-uremic syndrome
VII. Variants of type 2 diabetes
   A. Genetic defects of insulin action
      1. Rabson-Mendenhall syndrome
      2. Leprechaunism
      3. Lipoatrophic diabetes syndromes
      4. Type A insulin resistance—acanthosis
   B. Acquired defects of insulin action
      1. Endocrine tumors—rare in childhood
   C. Pheochromocytoma
   D. Cushing
   E. Others
      1. Antiinsulin receptor antibodies
VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency
   A. Prader-Willi syndrome, chromosome 15
   B. Down syndrome, chromosome 21
   C. Turner syndrome
   D. Klinefelter syndrome
   E. Others
      1. Bardet-Biedel
      2. Alström
      3. Werner
   F. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
   G. Celiac disease
   H. Autoimmune polyendocrinopathy
IX. Gestational diabetes
X. Neonatal diabetes
   A. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1β, others
   B. Permanent—agenesis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others

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TYPE 1 DIABETES MELLITUS (T1DM)

- Formerly called *insulin-dependent diabetes mellitus* (IDDM) or *juvenile diabetes*, T1DM is 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 natural history includes 4 distinct stages:

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

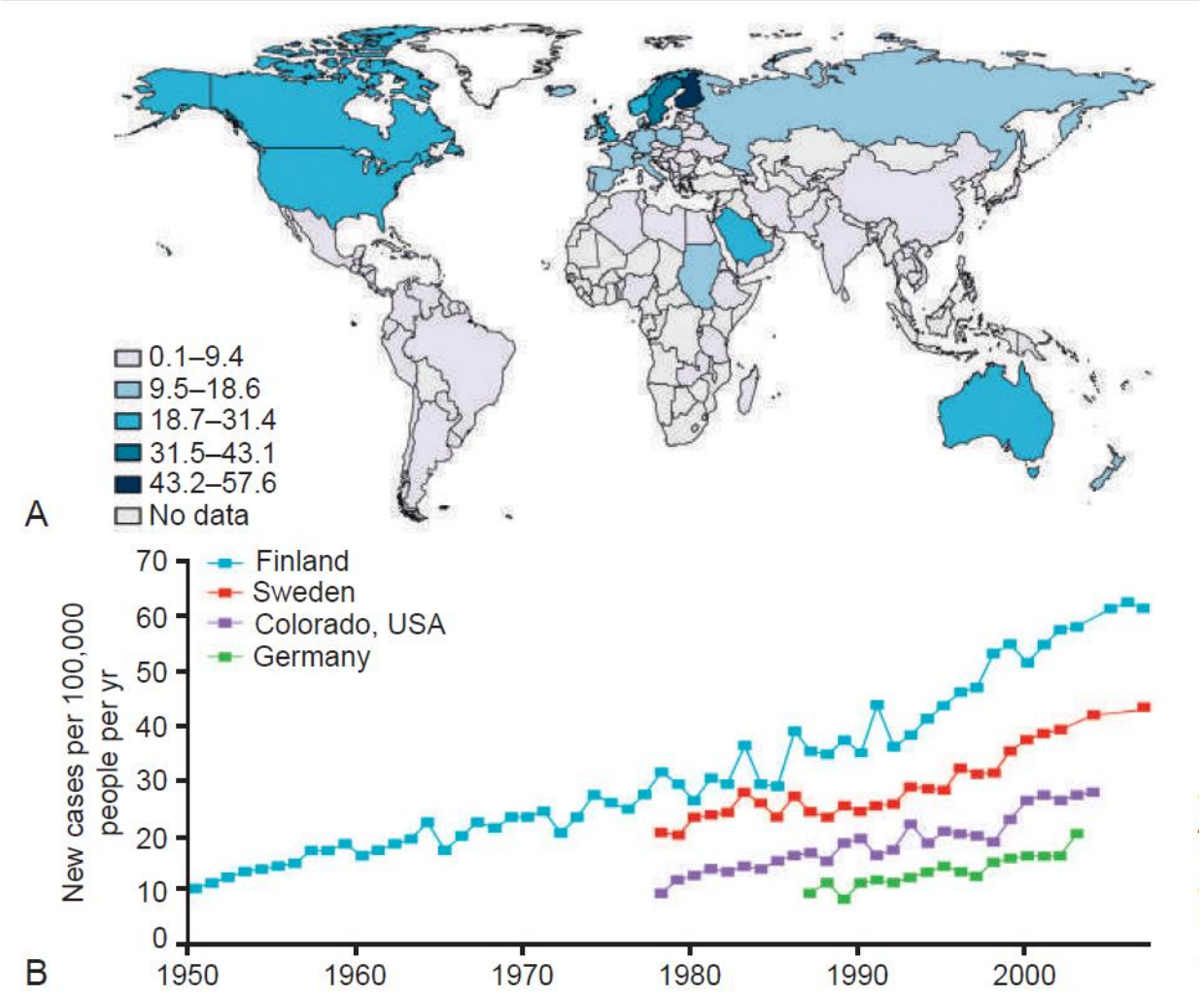
(2) onset of clinical diabetes,

(3) transient remission “honeymoon period,” and

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

Incidence of type 1 diabetes in children ages 0-14 yr, by geographical region and over time

- 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



A, Estimated global incidence of type 1 diabetes, by region, in 2011.

B, Time-based trends for the incidence of type 1 diabetes in children ages 0-14 yr in areas with high or high-intermediate rates of disease.

T1DM

- 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 major histocompatibility complex 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, and ICA512 are detected in serum from affected subjects.
- These can be detected months to years prior to clinical onset of T1DM.

T1DM

- T1DM is associated with other **autoimmune** diseases such as thyroiditis, celiac disease, and Addison disease.
- 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.

TYPE 2 DIABETES MELLITUS (T2DM)

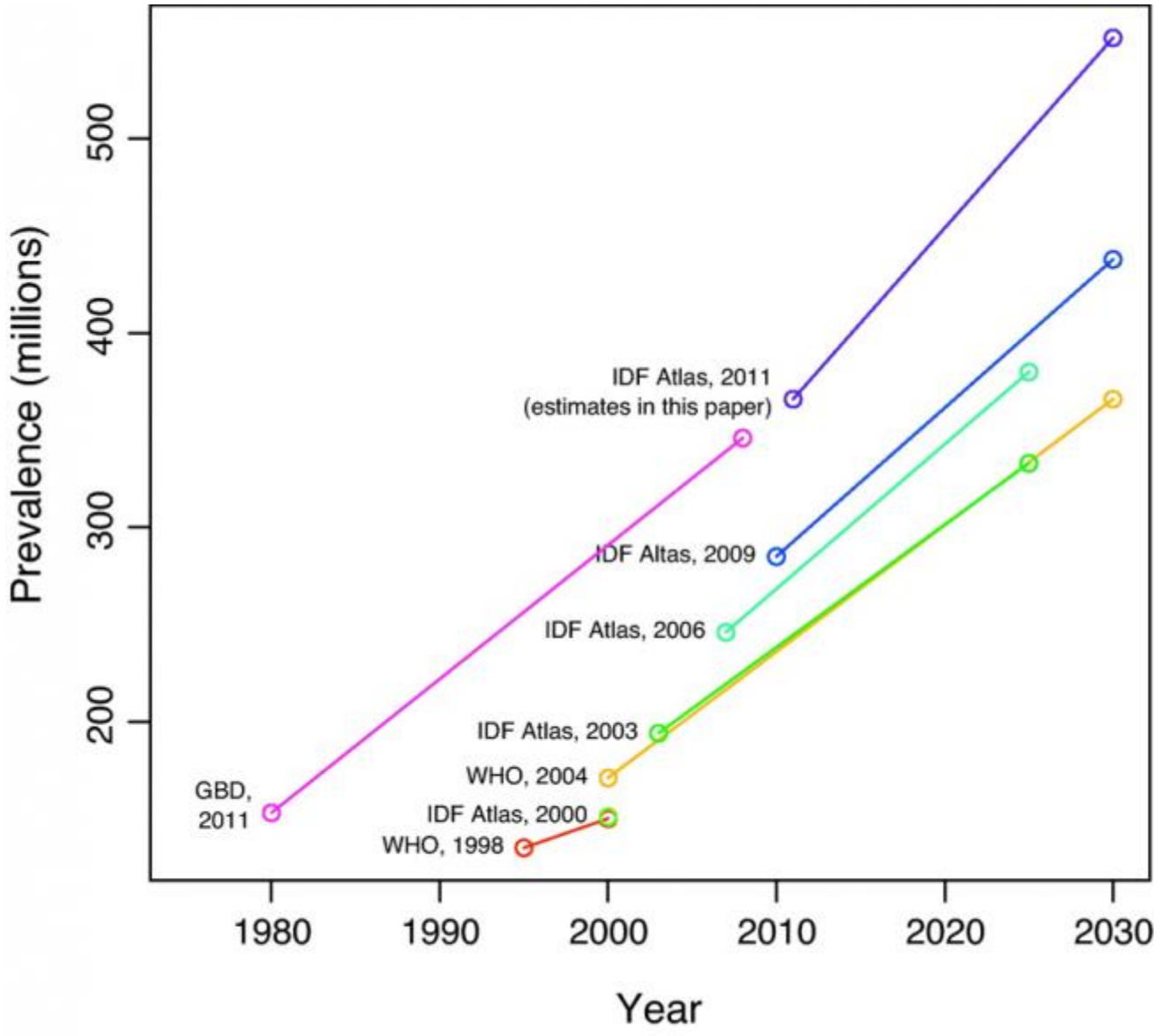
- Children and adolescents with this type of diabetes are usually obese but are not insulin dependent and infrequently develop ketosis.
- Some subjects with T2DM may present with or develop ketosis during severe infections or other stresses and may then need insulin for correction of symptomatic hyperglycemia.
- This category includes the most prevalent form of diabetes in adults, which is characterized by insulin resistance and often a progressive defect in insulin secretion.
- This type of diabetes was formerly known as *adult-onset diabetes mellitus or non–insulin-dependent diabetes mellitus*.

T2DM

- The presentation of T2DM is typically more insidious than that with T1DM.
- In contrast to patients with T1DM who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination.
- A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients.

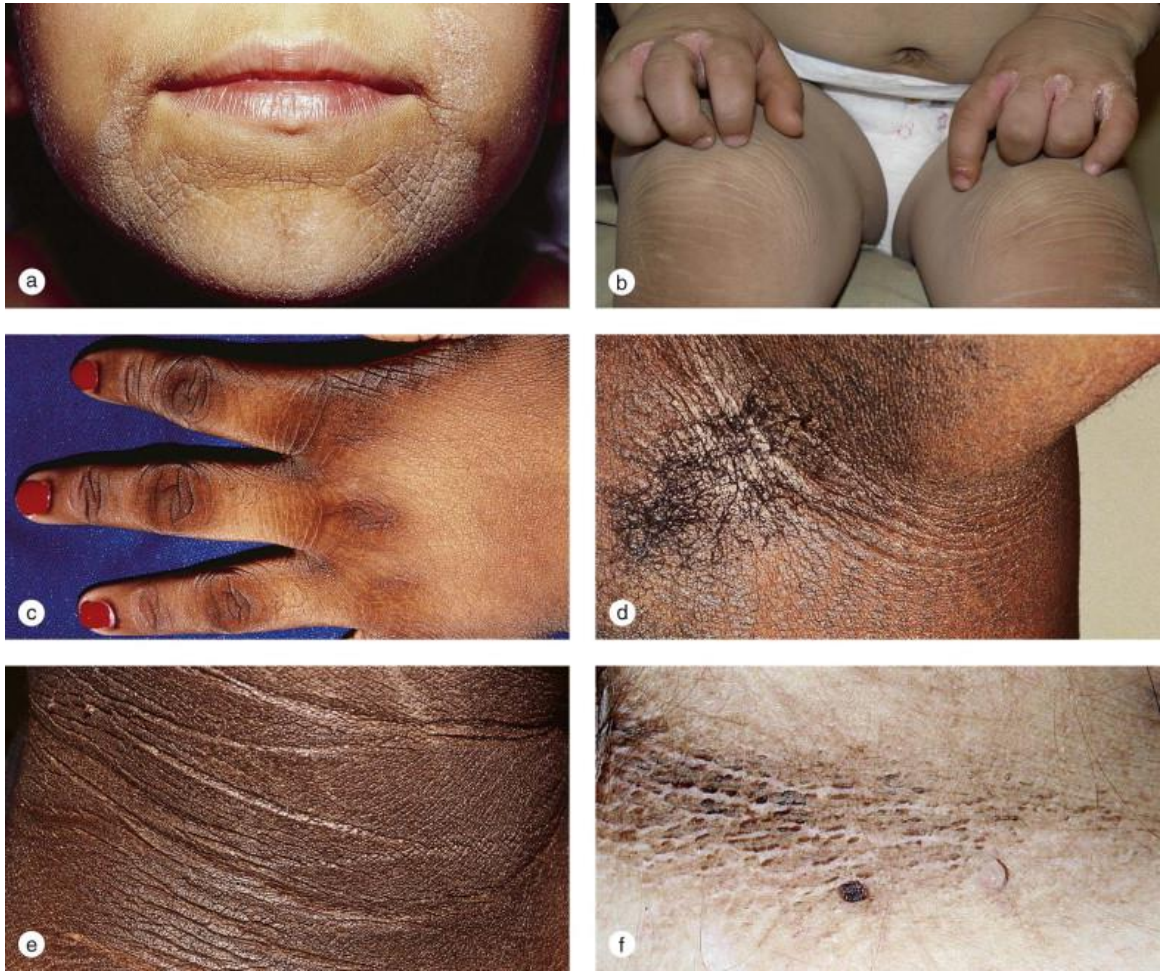
T2DM

- The incidence of T2DM in children has increased by more than 10-fold, depending on geography and mostly as a result of the epidemic of childhood obesity.



T2DM

- **Acanthosis nigricans** (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis.
- However, the serum insulin elevation is usually disproportionately lower than that of age-, weight-, and sex-matched nondiabetic children and adolescents, suggesting a state of insulin insufficiency.
- In some individuals, it may represent slowly evolving T1DM.



Maturity-onset diabetes of the young (MODY)

- In some children with a strong family history of diabetes, impaired glucose tolerance (IGT) may occur in a pattern implying dominant inheritance.
- This pattern of diabetes has been termed **maturity-onset diabetes of the young (MODY):** it may require insulin treatment, can be treated with sulfonylureas with varying degrees of success, and is often now referred to as monogenic diabetes.
- MODY may present with hyperglycemia, and consequent polyuria and polydipsia, or may be diagnosed simply by routine screening.

MODY

- In MODY, there is no autoimmune destruction of β cells and no HLA association.
- MODY results from specific genetic disorders involving mutations in the gene encoding either pancreatic β-cell and liver glucokinase or in the nuclear transcription factors hepatocyte nuclear factor (1α, 4α, or 1β).
- A defect in the gene regulating glucose transport into the pancreatic β cell, the GLUT2 transporter, may be responsible for other forms of T2DM.
- The genetic basis of T2DM also includes defects in glycogen synthase, insulin receptors, Rad (Ras associated with diabetes), and possibly apolipoprotein C-III.

OTHER SPECIFIC TYPES OF SECONDARY DIABETES

- Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), and ingestion of certain drugs or poisons.
- In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and posttransplantation DM, ascribed to a number of mechanisms.
- Certain genetic syndromes, including those with abnormalities of the insulin receptor, also are included in this category.
- There are no associations with HLA types, autoimmunity, or islet cell antibodies among the entities in this subdivision.

IMPAIRED GLUCOSE TOLERANCE (IGT)

- The term *impaired glucose tolerance* (IGT) refers to a metabolic stage that is intermediate between normal glucose homeostasis and diabetes.
- A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of “normal.”
- This choice is near the level above which acute-phaseinsulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications.

IGT

- Many individuals with IGT (fasting glucose 100-125 mg/dL) are euglycemic in their daily lives and may have normal or nearly normal glycated hemoglobin levels.
- Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test.
- In the absence of pregnancy, IGT is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease.

IGT

- IGT is often associated with the **insulin resistance syndrome** (also known as *syndrome X* or *metabolic syndrome*), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both, and hypertension.
- Insulin resistance is directly involved in the pathogenesis of T2DM.
- IGT appears as a risk marker for this type of diabetes at least in part because of its correlation with insulin resistance.

Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus

IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLITUS
Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)
	or
2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *or* 2 hr plasma glucose during the OGTT ≥200 mg/dL *or* Hemoglobin A_{1C} ≥6.5%†

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.
†Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.
OGTT, oral glucose tolerance test.

Type 1 Diabetes Mellitus (Immune Mediated)

T1DM - Epidemiology

- T1DM accounts for approximately 10% of all cases of diabetes, affecting up to 3 million people in the United States and more than 15 million people in the world.
- Using population-based estimates of diabetes incidence and prevalence, a recent study indicates that approximately 15,000 youths are diagnosed with type 1 diabetes each year.
- While it accounts for most cases of diabetes in childhood, it is not limited to this age group; new cases continue to occur in adult life and approximately 50% of individuals with T1DM present as adults.
- The incidence of T1DM is highly variable among different ethnic groups

T1DM - Epidemiology

- Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2-5%, whereas some central and eastern European countries demonstrate an even more rapid increase—up to 9%.
- Girls and boys are almost equally affected, but there is a modest female preponderance in some low-risk populations (e.g., the Japanese);
- There is no apparent correlation with socioeconomic status.

T1DM - Epidemiology

- Peaks of presentation occur in 2 age groups: at **5-7 yr of age** and at the time of **puberty**.
- The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school;
- The second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin).

T1DM - Genetics

- There is a clear familial clustering of T1DM, with prevalence in siblings approaching 6%, whereas the prevalence in the general population, for example, in the United States is only 0.4%.
- Risk of diabetes is also increased when a parent has diabetes and this risk differs between the 2 parents;
- The risk is 3-4% if the mother has diabetes but 5-6% when the father has diabetes.
- In monozygotic twins, the concordance rate ranges from 30-65%, whereas dizygotic twins have a concordance rate of 6-10%.

T1DM – Environmental factors

Viral Infections

- It is possible that various viruses do play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM.
- Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts.
- Invoked mechanisms involved direct infection of β cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and “molecular mimicry,” the notion that viral antigens exhibit homology to self-epitopes.

T1DM – Environmental factors

Viral Infections

- **Congenital Rubella Syndrome** - prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children.
- The time lag between infection and development of diabetes may be as high as 20 yr.
- T1DM after congenital rubella is more likely in patients that carry the higher risk genotypes.
- Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

T1DM – Environmental factors

Viral Infections

- **Enteroviruses** - studies show an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM.
- In addition, there are case reports of association between enteroviral infection and subsequent T1DM.
- But the true significance of these infections remains unknown at this time.

T1DM – Environmental factors

Viral Infections

- **Mumps Virus** - it has been variably observed that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases.
- Although mumps may play a role in some cases of diabetes, the fact that T1DM diabetes incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

T1DM – Environmental factors

The Hygiene Hypothesis: Possible Protective Role of Infections

- The hygiene hypothesis states that T1DM is a disease of industrialized countries, where the observation that there are fewer infections implies that the immune system is less-well trained for its main task, namely host defense.
- Some call this theory the “microbial deprivation hypothesis” - the lack of exposure to childhood infections may increase an individual’s chances of developing autoimmune diseases, including T1DM.
- Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed.

T1DM – Environmental factors

Diet

- Breastfeeding may lower the risk of T1DM, either directly or by delaying exposure to cow's milk protein.
- Early introduction of cow's milk protein and early exposure to gluten are implicated in the development of autoimmunity and it has been suggested that this is a result of the "leakiness" of the immature gut to protein antigens.
- Implicated antigens include β-lactoglobulin, a major lipocalin protein in bovine milk, which is homologous to the human protein glycodelin (PP14), a T-cell modulator.

T1DM – Environmental factors

Diet

- Other dietary factors that have been suggested at various times as playing a role in diabetes risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E.

- Vitamin D is biologically plausible (it has a role in immune regulation), deficiency is more common in northern countries like Finland, and there is some epidemiologic evidence that decreased vitamin D levels in pregnancy or early childhood may be associated with diabetes risk.

T1DM – Environmental factors

Psychologic stress

- Several studies show an increased prevalence of stressful psychologic situations among children who subsequently developed T1DM.

- Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity through epigenetic mechanisms remains unknown.

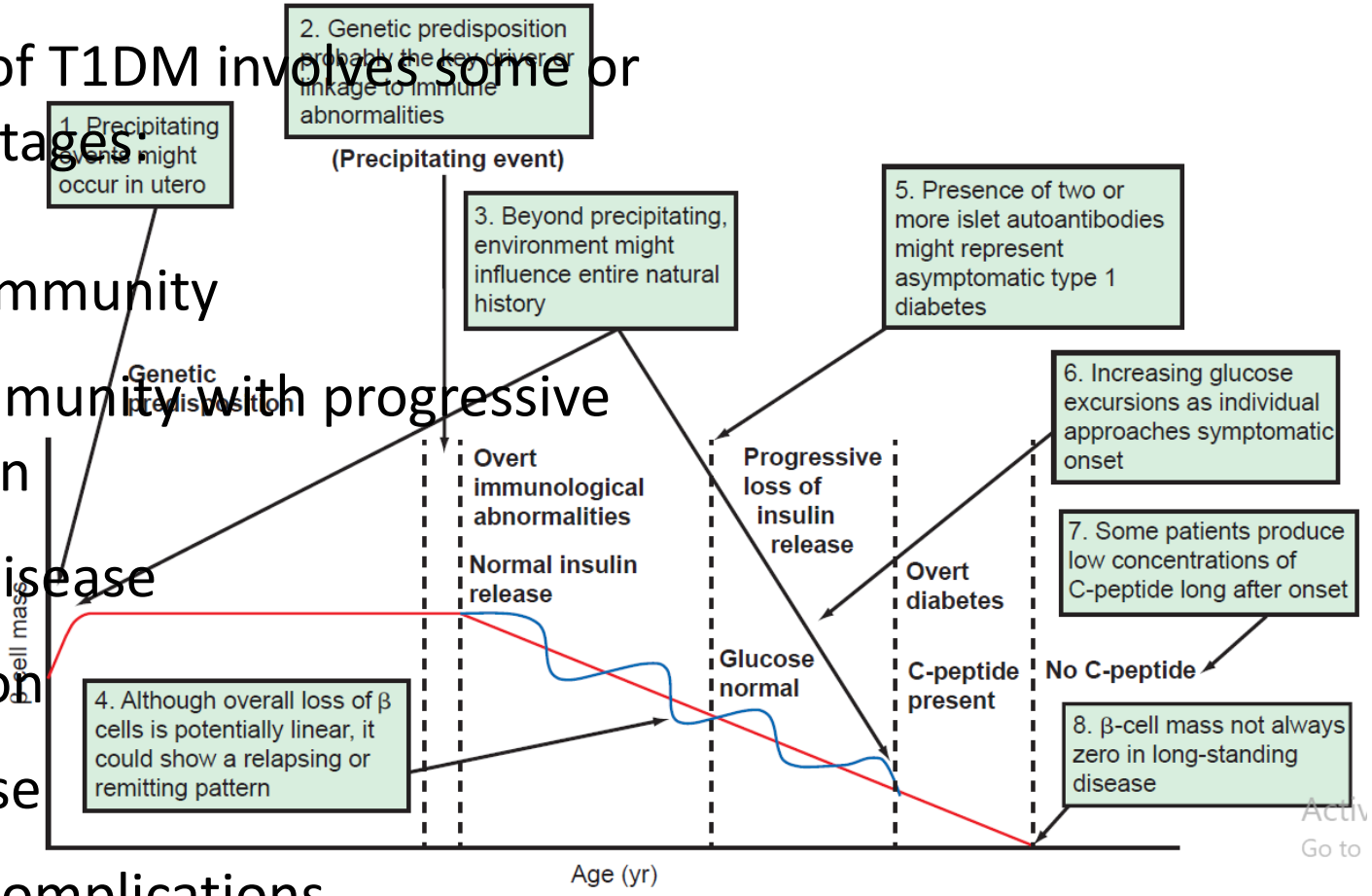
T1DM – PATHOGENESIS AND NATURAL HISTORY

- In T1DM, a genetically susceptible host develops autoimmunity against the host's own β cells.
- What triggers this autoimmune response remains unclear at this time.
- In some (but not all) patients, this autoimmune process results in progressive destruction of β cells until a critical mass of β cells is lost and insulin deficiency develops.
- Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM.
- At the time of diagnosis, some viable β cells are still present and these may produce enough insulin to lead to a partial remission of the disease (honeymoon period) but over time, almost all β cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival.

T1DM – PATHOGENESIS AND NATURAL HISTORY

The natural history of T1DM involves some or all of the following stages:

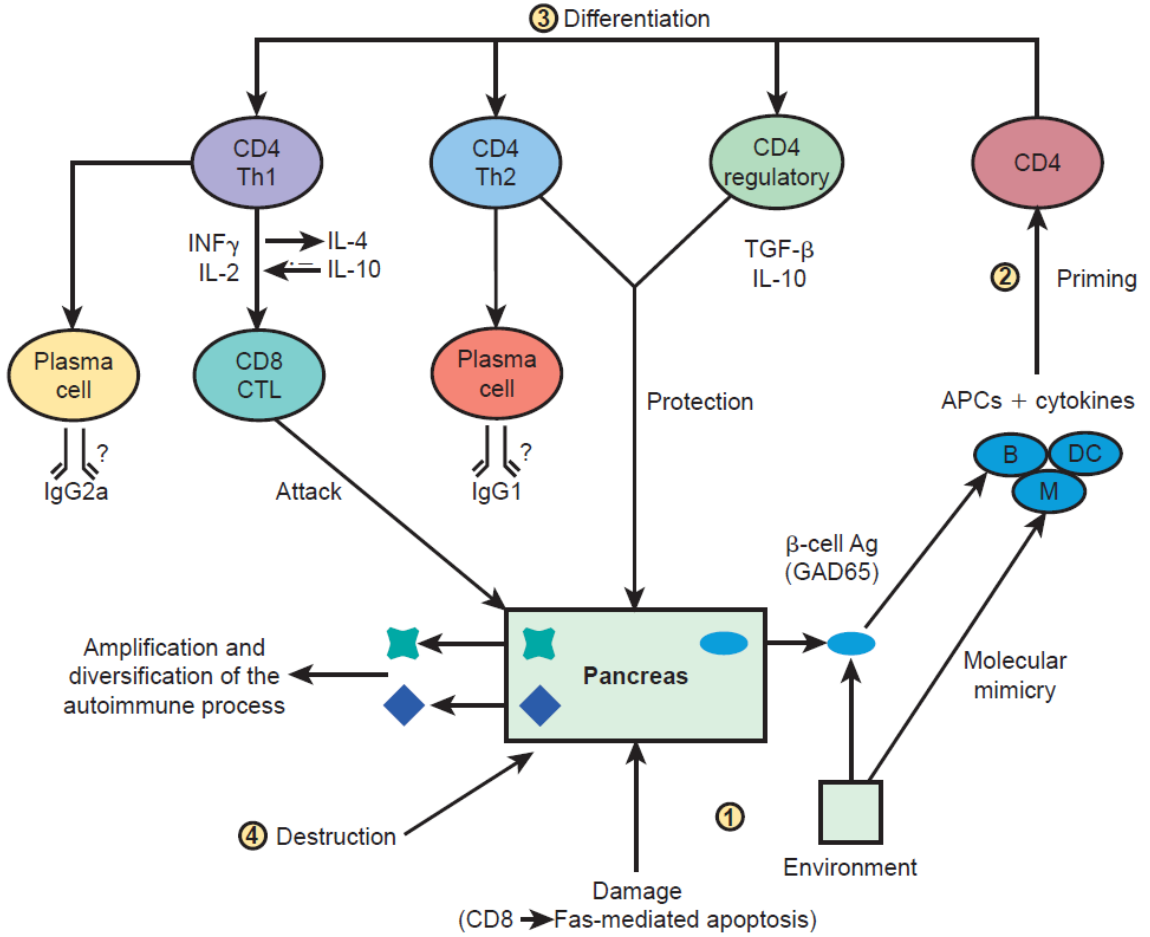
1. Initiation of autoimmunity
2. Preclinical autoimmunity with progressive loss of β-cell function
3. Onset of clinical disease
4. Transient remission
5. Established disease
6. Development of complications



The natural history of type 1 diabetes

T1DM – autoimmune response against pancreatic β cells

- An insult to the pancreas leads to the release of β-cell antigens (GAD65), which are taken up by antigen-presenting cells (APCs) and the epitopes presented to the CD4 T cells.
- Type and stage of activation of APCs as well as the cytokine environment, in which the CD4 T-cell priming takes place, dictate the differentiation of autoreactive T cells toward diabetogenic T-helper type 1 (Th1) cells, T-helper type 2 (Th2) cells, or antigen-specific regulatory T cells.
- A predominant Th1 autoimmune response results in the recruitment and differentiation of cytotoxic CD8 cells, which attack the pancreatic β cells, leading to a massive release of β-cell antigens (Ag), epitope spreading, and destruction of the pancreatic islets.



B, B lymphocyte; CTL, cytotoxic cell; DC, dendritic cell; IL, interleukin; INFγ, interferon-γ; M, macrophage; TGF-β, tumor growth factor β

T1DM – Pathophysiology

- Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use.
- Insulin levels must be lowered to then mobilize stored energy during the fasted state.
- Thus, in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue

Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake	Glucose production
	Glycogen synthesis	Glycogenolysis
	Absence of gluconeogenesis	Gluconeogenesis
	Lipogenesis	Absence of lipogenesis
	Absence of ketogenesis	Ketogenesis
Muscle	Glucose uptake	Absence of glucose uptake
	Glucose oxidation	Fatty acid and ketone oxidation
	Glycogen synthesis	Glycogenolysis
	Protein synthesis	Proteolysis and amino acid release
Adipose tissue	Glucose uptake	Absence of glucose uptake
	Lipid synthesis	Lipolysis and fatty acid release
	Triglyceride uptake	Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

T1DM – Pathophysiology

- T1DM is a progressive low insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes.
- With moderate insulinopenia, glucose utilization by muscle and fat decreases and postprandial hyperglycemia appears.
- At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and fasting hyperglycemia begins.
- Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L).

T1DM – Pathophysiology

- The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon).
- These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

T1DM – Pathophysiology

- The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids.
- The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral utilization and renal excretion.

T1DM – Pathophysiology

- Accumulation of these keto acids results in metabolic acidosis (diabetic ketoacidosis [DKA]) and compensatory rapid deep breathing in an attempt to excrete excess CO2 (Kussmaul respiration).
- Acetone, formed by nonenzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath.
- Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability.
- With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

T1DM – Clinical manifestations

- The decreasing β-cell mass with worsening insulinopenia, progressive hyperglycemia, and eventual ketoacidosis all imply that symptoms steadily increase, from early intermittent polyuria to DKA and coma, over weeks usually, rather than months.
- Initially, when only insulin reserve is limited, occasional postprandial hyperglycemia occurs.
- When the serum glucose increases above the renal threshold, intermittent polyuria or nocturia begins.
- With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, often with nocturnal enuresis, and polydipsia becomes more apparent.

T1DM – Clinical manifestations

- Calories are lost in the urine (glycosuria), triggering a compensatory hyperphagia.
- If this hyperphagia does not keep pace with the glycosuria, loss of body fat ensues, with clinical weight loss and diminished subcutaneous fat stores.
- An average, healthy 10 yr old child consumes approximately 50% of 2,000 daily calories as carbohydrate. As that child becomes diabetic, daily losses of water and glucose may be 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake.
- Despite the child's compensatory increased intake of food, the body starves because unused calories are lost in the urine.

T1DM – Clinical manifestations

- When extremely low insulin levels are reached, ketoacids accumulate. At this point, the child quickly deteriorates.
- Ketoacids produce abdominal discomfort or true pain, nausea, and emesis, preventing oral replacement of urinary water losses.
- Dehydration accelerates, causing weakness or orthostasis—but polyuria persists.
- Ketoacidosis exacerbates prior symptoms and leads to Kussmaul respirations (deep, heavy, nonlabored rapid breathing), fruity breath odor (acetone), prolonged corrected Q-T interval, diminished neurocognitive function, and possible coma.
- Approximately 20-40% of children with new-onset diabetes progress to DKA before diagnosis.

T1DM – Clinical manifestations

- This entire progression happens much more quickly (over a few weeks) in younger children, owing to either more aggressive autoimmune destruction of β cells and/or to lower β-cell mass compared to older subjects.
- In infants, most of the weight loss is acute water loss because they will not have had prolonged urinary loss of calories from glycosuria, and there will be an increased incidence of DKA at diagnosis.
- In adolescents, the course is usually more prolonged (over a few months), and most of the weight loss represents fat loss from prolonged starvation.
- Additional weight loss from acute dehydration may occur just before diagnosis.
- In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counterregulatory (stress) hormones overwhelm the limited insulin secretory capacity.

T1DM – Diagnosis

- The most important clue is an inappropriate polyuria in any child with dehydration, poor weight gain, or “the flu.”
- Hyperglycemia, glycosuria, and ketonuria can be determined quickly.
- Nonfasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria.
- In the obese child, T2DM must be considered.

IMPAIRED GLUCOSE TOLERANCE	DIABETES MELLITUS
Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)
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2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *or* 2 hr plasma glucose during the OGTT ≥200 mg/dL *or* Hemoglobin A_{1C} ≥6.5%†

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria; †Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia; OGTT, oral glucose tolerance test.

T1DM – Diagnosis

- Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) and to evaluate electrolyte abnormalities—even if signs of dehydration are minimal.
- A baseline hemoglobin A1c (HbA1c) will be confirmatory and allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy.
- Falsely low HbA1c levels are noted in hemolytic anemias, pure red cell aplasia, blood transfusions, and anemias associated with hemorrhage, cirrhosis, myelodysplasias, or renal disease treated with erythropoietin.

T1DM – Diagnosis

- Other autoimmunities associated with T1DM should be sought, including celiac disease (by tissue transglutaminase IgA and total IgA) and thyroiditis (by antithyroid peroxidase and antithyroglobulin antibodies).
- Fifteen to 30% of subjects with T1DM have elevated thyroid-stimulating hormone (TSH) and antithyroid antibodies and close to 5-10% have evidence for celiac disease.
- These diseases share common genes and likely the same interplay between environmental and immunologic factors.
- Because significant physiologic distress can disrupt the pituitary–thyroid axis, free thyroxine and TSH levels should be checked after the child is stable for a few weeks.

T1DM – Diabetic Ketoacidosis

- DKA is the end result of the metabolic abnormalities resulting from a severe deficiency of insulin or insulin effectiveness.
- The latter occurs during stress as counterregulatory hormones block insulin action.
- DKA occurs in 20-40% of children with new-onset diabetes and in children with known diabetes who omit insulin doses or who do not successfully manage an intercurrent illness.

T1DM – Risk factors for Diabetic Ketoacidosis

- Young children
- Poor diabetes control
- Previous episodes of DKA
- Missed insulin injections
- Insulin pump failure
- Infection or other illnesses
- Low socioeconomic status
- Lack of adequate health insurance
- Psychiatric disorders (i.e., eating disorders)

Hypoglycemia

- **Low blood glucose: treated when less than 60 mg/dL**
- **Develops because the body doesn't have enough glucose to burn energy**
- **Can happen suddenly**
- **Can be treated quickly and easily by eating or drinking a small amount of glucose rich food**

The signs and symptoms include:

Low blood glucose

Hunger

Headache

Confusion, shakiness, dizziness

Sweating

If hypoglycemia is suspected, check the blood glucose concentration

Hyperglycemia

- High blood glucose: **treated when greater than 200 mg/dL**
- Develops when the body has too much glucose in the blood
- Serious problem if not treated
- A major cause of many of the complications in children with diabetes

The signs and symptoms include:

High blood glucose

High levels of glucose in the urine

Frequent urination

Increased thirst

If hyperglycemia is suspected, check the blood glucose concentration

Hypoglycemia vs. Hyperglycemia

Low blood glucose

(less than 60 mg/dL)

Signs and symptoms include:

- Shakiness
- Dizziness
- Sweating
- Hunger
- Headache
- Pale skin color
- Mental or behavior changes
- Lethargy
- Clumsy or jerky movements
- Seizure
- Difficulty concentrating
- Tingling sensations around the mouth

High blood glucose

(greater than 200 mg/dL)

Signs and symptoms include:

Classic symptoms:

- **Polyphagia** (excessive hunger)
- **Polyuria** (excessive urine/urination)
- **Polydipsia** (excessive thirst)

Other symptoms might include:

- Blurred vision
- Fatigue
- Weight loss
- Slow-healing cuts and sores
- Headaches
- Difficulty concentrating
- Vaginal and skin infections

Ketosis

Ketones

- Acidic substances that are made when the body breaks down fat for energy

Ketosis

- Presence of excess ketones in the body
- Blood ketone concentration between 0.3 and 7.0 mmol/L

Ketoacidosis

- Severe form of ketosis
- Reflects levels of 7.0 mmol/L or higher
- Lowers the pH to 7.3 or lower

Acidosis

- **Increased acidity of the blood**

- **Acidemia is a pH below 7.35**

Signs & Symptoms

- ***Deep, rapid breathing (known as Kussmaul's respirations)***
- ***confusion or lethargy***
- ***abdominal pain***

- **Blood tests to diagnose metabolic acidosis may include:**
  - **Arterial or venous blood gas**
  - **Electrolytes: Na^+ (sodium), K^+ (potassium), Cl^- (chloride) and HCO_3^- (bicarbonate) (total CO_2 content)**

DKA is a complex metabolic state of: *hyperglycemia, ketosis, and acidosis*

Symptoms include:

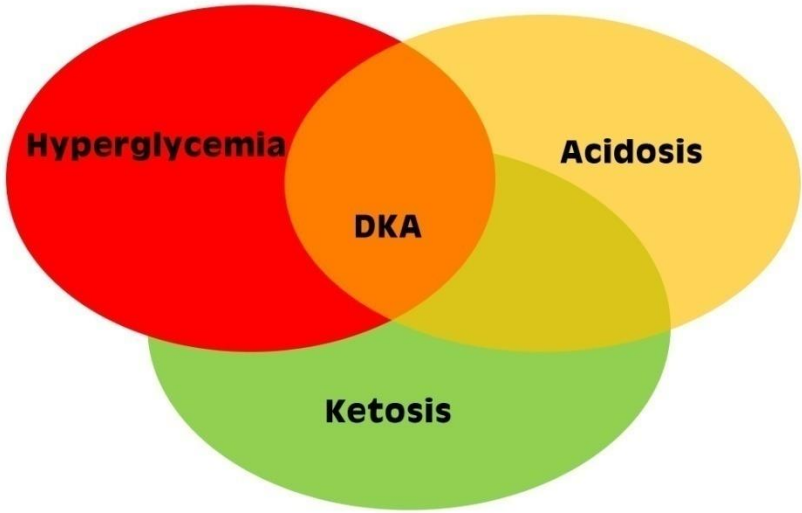
- Deep, rapid breathing
- Fruity breath odor
- Very dry mouth
- Nausea and vomiting
- Lethargy/drowsiness

DKA is life-threatening and needs immediate treatment

Classic Triad of DKA

The biochemical criteria for the diagnosis of DKA[3,4]

- **Hyperglycemia - blood glucose greater than 200 mg/dL**
- **Ketosis - ketones present in blood and/or urine**
- **Acidosis - pH less than 7.3 and/or bicarbonate less than 15 mmol/L**



Classification of DKA

DKA is generally categorized by the severity of the acidosis.

- **MILD** – Venous pH less than 7.3 and/or
  bicarbonate concentration less than 15 mmol/L

- **MODERATE** – Venous pH less than 7.2 and/or
  bicarbonate concentration less than 10 mmol/L

- **SEVERE** – Venous pH less than 7.1 and/or
  bicarbonate concentration less than 5 mmol/L

Classification of DKA

Diagnostic Criteria for Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

	Mild DKA	Moderate DKA	Severe DKA	HHS
Blood glucose	>200 mg/dL	>200 mg/dL	>200 mg/dL	>600 mg/dL
Venous pH	< 7.3	< 7.2	< 7.1	> 7.3
Serum bicarbonate	< 15 mEq/L	< 10 mEq/L	< 5 mEq/L	> 15 mEq/L
Urine ketones	Positive	Positive	Positive	Small or none
Blood ketones	Positive	Positive	Positive	Small or none
Beta-hydroxybutyrate	High	High	High	Normal or elevated
Serum osmolality	Variable	Variable	Variable	> 320 mOsm/kg H2O
Alteration in mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

Thorough History is Imperative!

New onset diabetes

- Recent history of
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Weight loss
- Past medical history
  - Family history of diabetes
- History/duration of symptoms
  - Headache
  - Blurry vision
  - Nausea/vomiting/ abdominal pain
  - Difficulty in breathing
  - Changes in behavior
- Precipitating factors
  - Concurrent illness or infection

Preexisting diabetes

- History of diabetes and duration
  - Last meal/carbohydrate intake
  - Current and routine blood glucose levels
- Standard insulin regimen
  - Last insulin dose
  - Type of insulin and route
- Past hospitalization history
- Duration of symptoms
  - Nausea/vomiting/abdominal pain
- Precipitating factors
  - Physical exertion
  - Change in eating habits/diets
  - Stress
  - Missed insulin dose
  - Illness

Physical Assessment

- Assess for dehydration
  - Vital signs, mucous membranes, capillary refill, skin (color, temperature and turgor)
- Assess for acidosis
  - Fruity breath odor
  - Deep, rapid breathing → Kussmaul's respirations
- Assess mental status → watch for cerebral edema!
  - AVPU
  - PGCS
- Assess for signs/symptoms of possible infection

Primary Assessment

- **Assess Airway, Breathing, and Circulation**
- Perform a clinical evaluation
- Obtain vital signs and weight (kg)
- Assess clinical severity of dehydration
- Assess neurological status
  - AVPU
  - PGCS
- Apply cardiac monitor

Laboratory Evaluation

- **Initial Labs**
  - **Blood glucose**
  - **Urine ketones**
  - **Venous blood gas**
  - **Basic blood chemistry**
    - Electrolytes
    - BUN, creatinine
    - Magnesium, calcium, phosphorus
- **Additional labs**
  - CBC
  - Osmolality
  - Serum beta-hydroxybutyrate (β-OH)
  - Hemoglobin A1c (HgbA1c)
  - Pancreatic antibodies
  - Additional testing as indicated
    - CXR, non-contrast Head CT, Cultures (blood, urine, throat)

Blood Glucose Testing

- A blood glucose test measures the amount of glucose in the blood
- Blood glucose tests are done to screen and monitor treatment
- Normal glucose range is between 80 and 120 mg/dL

Ketone Testing

Blood Ketone Reading Indications

Above 1.5 mmol/L
Readings above 1.5 mmol/L in the presence of hyperglycemia indicate the child may be at risk for developing diabetic ketoacidosis (DKA).

0.6 to 1.5 mmol/L
Readings between 0.6 and 1.5 mmol/L may indicate the development of a problem that may require medical assistance.

Below 0.6 mmol/L

Readings below 0.6 mmol/L are in the normal range.

Urine Ketone Testing

Out-dated or expired test strips may cause a false-positive reading.

Blood Gases

ABG arterial blood sample or VBG venous blood sample are both adequate to determine blood pH.

VBG is sufficient unless altered level of consciousness

- *Remember: arterial puncture is a painful procedure; consider using topical anesthetic as a pain reducing therapy*

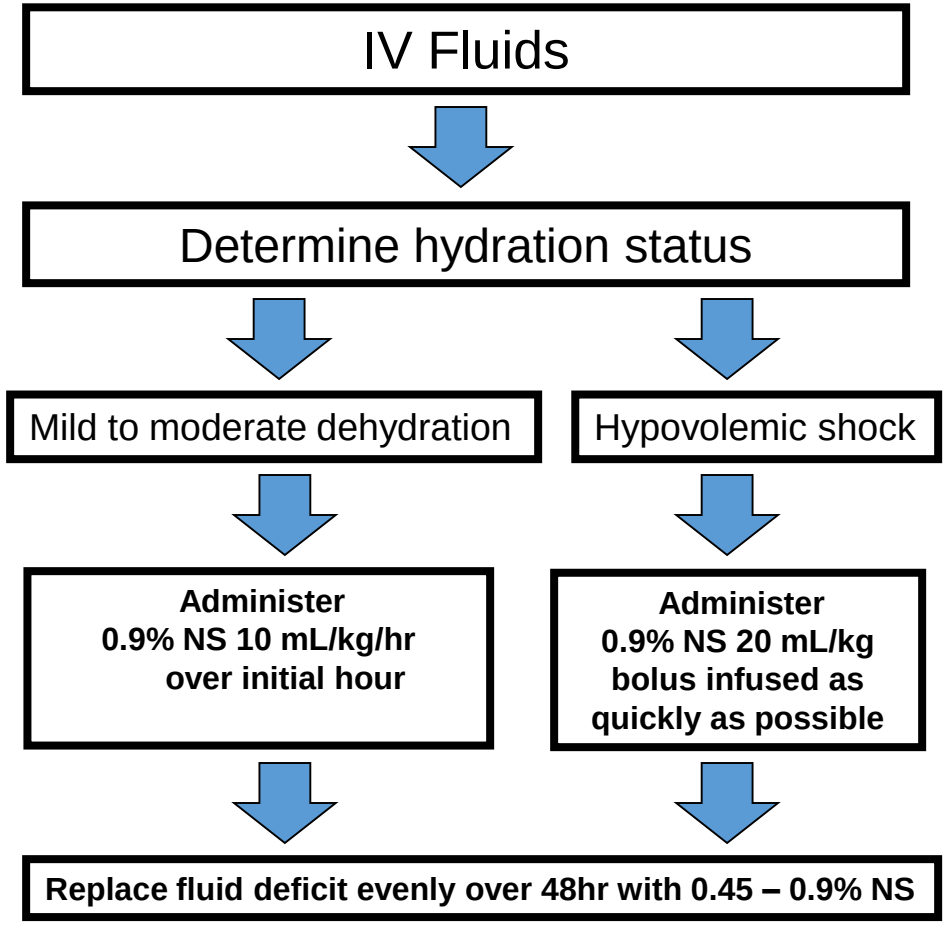
- An ABG provides a snapshot of the blood's pH + PO_2 + PCO_2 = HCO_3
  - pH – indicates if acidotic or alkalemic
  - PO_2 – the amount of oxygen dissolved in the blood
  - PCO_2 – the amount of carbon dioxide dissolved in the blood
  - HCO_3 – the amount of bicarbonate in the blood

- **Metabolic acidosis** is defined as a low pH and decreased HCO_3
- **Metabolic alkalosis** is defined as a high pH and increased HCO_3

Treatment Overview

- Follow established guidelines
- Consider need for consultation and transfer to higher level of care
- Recognize and prevent serious complications such as cerebral edema
- Maintain strict NPO
- IV fluids
  - Phase I
    - Initial volume expansion
  - Phase II
    - Replacement of fluid deficit
    - Maintenance fluids
- Insulin administration (begins after the initial fluid resuscitation)
  - Continuous IV insulin infusion
  - Subcutaneous/Intramuscular
- Electrolyte replacement
- Reassessment and ongoing monitoring

IV Fluid Administration



The goal of the first hour of treatment

- fluid resuscitation
- confirmation of DKA by laboratory studies

The goals of the second and succeeding hours

- slow correction of hyperglycemia, metabolic acidosis and ketosis
- continued volume replacement

This usually requires several hours and meticulous attention to the patient's response to therapy

Adapted from:

Kitabchi AE, Umpierrez GE, Murphy MB, et al; American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(Suppl. 1):S94-S102

IV Fluid Key Points

- **Start IV fluids: 10-20 mL/kg of 0.9%NS over the first hour**
  - In a severely dehydrated patient, this may need to be repeated
  - Fluids should not exceed 50 mL/kg over first 4 hours of therapy

- **Clinical assessment of dehydration to determine fluid volume**
  - Children with DKA have a fluid deficit in the range of 5-10%
    - Mild DKA 3-4% dehydration
    - Moderate DKA 5-7% dehydration
    - Severe DKA 10% dehydration
  - Shock is rare in pediatric DKA

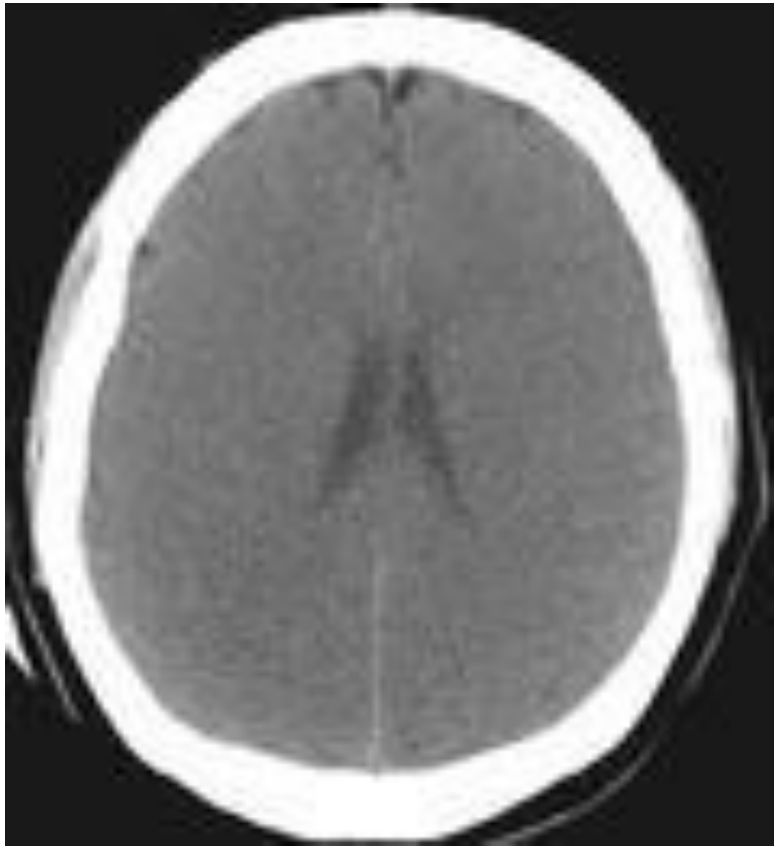
- **Replace fluid deficit evenly over 48 hours**

- **REMINDER:** Serum sodium decreases by 1.6mEq/L for every 100-mg/dl increase in serum glucose concentration above 100mg/dl, therefore no electrolyte correction is needed

ALL PATIENTS WITH DKA REQUIRE SUPPLEMENTAL FLUIDS

Cerebral Edema: Facts

- Occurs in less than 1% of Pediatric DKA episodes
- Accounts for 60% to 90% of all DKA deaths
- 10% to 25% of survivors have permanent neurological injury



Cerebral Edema: Presentation

- May develop without warning symptoms
- Asymptomatic cerebral swelling is believed to occur more frequently
- Occurs most frequently 4-12 hours after therapy initiation
- May occur before treatment is initiated.

Cerebral Edema: Risk Factors

- Younger age (e.g., infants and children < 5 yrs)
- New-onset diabetes
- High glucose levels
- Severe dehydration (elevated BUN/creatinine)
- Severe acidosis (lower pH, HCO_3, pCO_2)
- Treatment with bicarbonate

Cerebral Edema: Warning Signs & Symptoms

- **Major criteria:**[14]
  - Altered mental status/fluctuating LOC
  - Sustained HR deceleration (not due to sleep or improved intravascular volume)
  - Age-inappropriate incontinence

- **Minor criteria:**
  - Vomiting
  - Headache
  - Lethargy
  - Diastolic B/P > 90 bpm
  - Age < 5 years

Cerebral Edema: Treatment

- Reduce rate of intravenous fluids

- Elevate head of bed to at least a 30° angle
- Give mannitol 0.25 - 1 gram/kg IV over 20 minutes
  - May repeat if no initial response in 30 minutes to 2 hours
  - Have mannitol ready at bedside and calculate dose beforehand

Initiate treatment as soon as cerebral edema is suspected

Cerebral Edema: Treatment (cont.)

- Intubation for impending respiratory failure
  - **avoid aggressive hyperventilation**

- CNS imaging studies (non-contrast CT scan)
  - **treatment should not be delayed while waiting results.**

- Transfer and or admit to PICU.

These measures may be life-saving when initiated promptly (before coma) and may prevent neurologic sequelae.

T1DM – Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
CO_2 (mEq/L, venous)†	20-28	16-20	10-15	<10
pH (venous)†	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.
†CO_2 and pH measurement are method dependent; normal ranges may vary.

- Therapy is tailored to the degree of insulinopenia at presentation.
- Most children with new diabetes have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis.
- Once DKA has resolved in the newly diagnosed child, therapy is transitioned to that described for children with nonketotic onset.
- Children with previously diagnosed diabetes who develop DKA are usually transitioned to their previous insulin regimen.

T1DM – Treatment

- Diabetes control involves many goals:
  - to maintain a balance between tight glucose control and avoiding hypoglycemia,
  - to eliminate polyuria and nocturia,
  - to prevent ketoacidosis, and
  - to permit normal growth and development with minimal effect on lifestyle

- Therapy encompasses initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines.

T1DM – Treatment

Insulin Therapy

- The dose is usually higher in pubertal children.
- It is also higher in those who are in DKA at the time of presentation.
- The optimal insulin dose can only be determined empirically, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team.
- Many children with new-onset diabetes have some residual β-cell function (the honeymoon period), which is associated with reduced exogenous insulin needs shortly after starting on treatment.
- Residual β-cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

T1DM – Treatment

Insulin Therapy

Starting Doses of Insulin (units/kg/day):

	NO DIABETIC KETOACIDOSIS	DIABETIC KETOACIDOSIS
Prepubertal	0.25-0.50	0.75-1.0
Pubertal	0.50-0.75	1.0-1.2
Postpubertal	0.25-0.50	0.8-1.0

T1DM – Treatment

Insulin Therapy

- The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell.
- There are inherent limits to our ability to mimic the β cell.
- Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose; absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin release ceases and serum levels quickly lower with a normally rapid clearance.
- The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation.
- Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a basal-bolus regimen, that is, with slow-onset, long-duration background insulin for between-meal glucose control and rapid-onset insulin at each meal.

T1DM – Treatment

Insulin Therapy

- All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation.
- A detectable effect for **regular insulin** is delayed by 30-60 min after injection. This, in turn, requires delaying the meal 30-60 min after the injection for optimal.
- Regular insulin has a wide peak and a long tail for bolus insulin.
- This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia.
- These unwanted between-meal effects often necessitate “feeding the insulin” with snacks and limiting the overall degree of blood glucose control.

T1DM – Treatment

Insulin Therapy

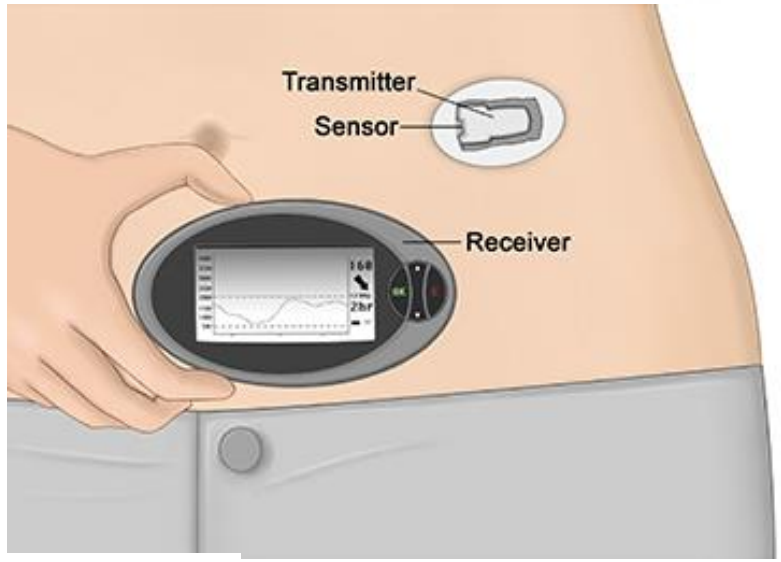
- Frequent blood glucose monitoring and insulin adjustment are necessary in the 1st weeks as the child returns to routine activities and adapts to a new nutritional schedule, and as the total daily insulin requirements are determined.
- The major physiologic limit to tight control is hypoglycemia.
- Use of insulin analogs moderates but does not eliminate this problem.
- Some families may be unable to administer 4 daily injections. In these cases, a compromise may be needed. A 3 injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control.
- Further compromise to a 2 injection regimen may occasionally be needed and frequently involves use of premix insulin (e.g., 70/30).

T1DM – Treatment

Insulin Pump Therapy

- Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens.
- Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the insulin to carbohydrate ratio and the correction scale for premeal glucose levels.
- The patient can enter the patient's blood glucose level and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose.

T1DM – Treatment



Continuous Glucose Monitoring Systems

- These devices do not directly control insulin administration but provide glucose readings to permit finer control of insulin administration by patients and families.

- To avoid hypoglycemia the glucose sensor sounds an alarm.

T1DM – Nutritional guideline

NUTRIENT RECOMMENDATIONS AND DISTRIBUTION

NUTRIENT	(%) OF CALORIES	RECOMMENDED DAILY INTAKE
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber	>20 g/day	
Protein	12-20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6-8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive

T1DM – Nutritional guideline

- *Energy:* If using measured diet, reevaluate prescribed energy level at least every 3 mo.

- *Protein:* High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.

T1DM – Nutritional guideline

- *Alcohol:* Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.

- *Snacks:* Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).

T1DM – Nutritional guideline

- *Alternative sweeteners:* Use of a variety of sweeteners is suggested.

- *Educational techniques:* No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.

T1DM – Nutritional guideline

- *Eating disorders:* Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.

- *Exercise:* Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.

T1DM – Monitoring

- Self-monitoring of blood glucose is an essential component of managing diabetes.
- Monitoring often also needs to include insulin dose, unusual physical activity, dietary changes, hypoglycemia, intercurrent illness, and other items that may influence the blood glucose.
- These items may be valuable in interpreting the self-monitoring of blood glucose record, prescribing appropriate adjustments in insulin doses, and teaching the family.

T1DM – Monitoring

- For monitoring is used a small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion.
- Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper, and at bedtime.
- When insulin therapy is initiated and when adjustments are made that may affect the overnight glucose levels, self-monitoring of blood glucose should also be performedat 12 midnight and 3 am to detect nocturnal hypoglycemia.

T1DM – Monitoring

- Ideally, the blood glucose concentration should range from approximately 80 mg/dL in the fasting state to 140 mg/dL after meals.
- In practice, however, a range is acceptable, based on age of the patient:

AGE GROUP (yr)	TARGET PREMEAL BG RANGE (mg/dL)	30-DAY AVERAGE BG RANGE (mg/dL)	TARGET HbA_{1c} (%)
<5	100-200	180-250	7.5-9.0
5-11	80-150	150-200	6.5-8.0
12-15	80-130	120-180	6.0-7.5
16-18	70-120	100-150	5.5-7.0

In our laboratory, the nondiabetic reference range for HbA_{1c} is 4.5-5.7% (95% confidence interval).
BG, blood glucose; HbA_{1c}, hemoglobin A_{1c}.

- Blood glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose.

T1DM – Long-term complications

- Complications of DM can be divided into 3 major categories:

(1) microvascular complications, specifically, retinopathy and nephropathy;

(2) macrovascular complications, particularly accelerated coronary artery disease, cerebrovascular disease, and peripheral vascular disease; and

(3) neuropathies, both peripheral and autonomic, affecting a variety of organs and systems

T1DM – Long-term complications

Screening Guidelines

	WHEN TO COMMENCE SCREENING	FREQUENCY	PREFERRED METHOD OF SCREENING	OTHER SCREENING METHODS	POTENTIAL INTERVENTION
Retinopathy	After 5 yr duration in prepubertal children, after 2 yr in pubertal children	1-2 yearly	Fundal photography	Fluorescein angiography, mydriatic ophthalmoscopy	Improved glycemic control, laser therapy
Nephropathy	After 5 yr duration in prepubertal children, after 2 yr in pubertal children	Annually	Spot urine sample for albumin : creatinine ratio	24 hr excretion of albumin, urinary albumin : creatinine ratio	Improved glycemic control, blood pressure control, ACE inhibitors
Neuropathy	Unclear in children; adults at diagnosis in T2DM and 5 yr after diagnosis in T1DM	Unclear	Physical examination	Nerve conduction, thermal and vibration threshold, pupillometry, cardiovascular reflexes	Improved glycemic control

ACE, angiotensin-converting enzyme; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone

T1DM – Long-term complications

Screening Guidelines

	WHEN TO COMMENCE SCREENING	FREQUENCY	PREFERRED METHOD OF SCREENING	OTHER SCREENING METHODS	POTENTIAL INTERVENTION
Macrovascular disease	After age 2 yr	Every 5 yr	Lipids	Blood pressure	Statins for hyperlipidemia Blood pressure control
Thyroid disease	At diagnosis	Every 2-3 yr or more frequently based on symptoms or the presence of antithyroid antibodies	TSH	Thyroid peroxidase, thyroglobulin antibodies	Thyroxine
Celiac disease	At diagnosis	Every 2-3 yr	Tissue transglutaminase, endomysial antibody	Transglutaminase antibodies	Gluten-free diet

ACE, angiotensin-converting enzyme; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone

Thank you for the attention!