

Diabetes mellitus in children

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

TYPE 1 DIABETES MELLITUS

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:

- preclinical β -cell autoimmunity with progressive defect of insulin secretion
- onset of clinical diabetes,
- transient remission “honeymoon period,”
- established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy.

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).

Autoantibodies to β -cell antigens such as islet cell cytoplasm (ICA), insulin autoantibody (IAA), and antibodies to glutamic acid decarboxylase are detected in serum from affected subjects. These can be detected months to years prior to clinical onset of T1DM.

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

GENETICS

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 6%.

Risk of T1D 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%

85% of newly diagnosed type 1 diabetic patients do not have a family member with T1DM.

the known associations include the HLA DR3/4-DQ2/8 genotype.

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.

- **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.
- **Mumps Virus, enterovirus**

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.

VIT D, C, ZINC

Role of Autoantibodies

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies.

- ; only 30% of children with 1 antibody will progress to diabetes, but this risk increases to 70% when 2 antibodies are present and 90% when 3 are present

PATHOPHYSIOLOGY

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.

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)

The resulting loss of calories and electrolytes with the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, GH, and glucagon). These hormones contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine

-), by antagonizing its action (epinephrine, cortisol, GH), and by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, GH, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, GH, cortisol).

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.).

Patients with progressive β -cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β -cell mass is destroyed by the time clinical disease develops, but later studies have revealed that this is not always the case. It now appears that β -cell destruction is more rapid and more complete in younger children

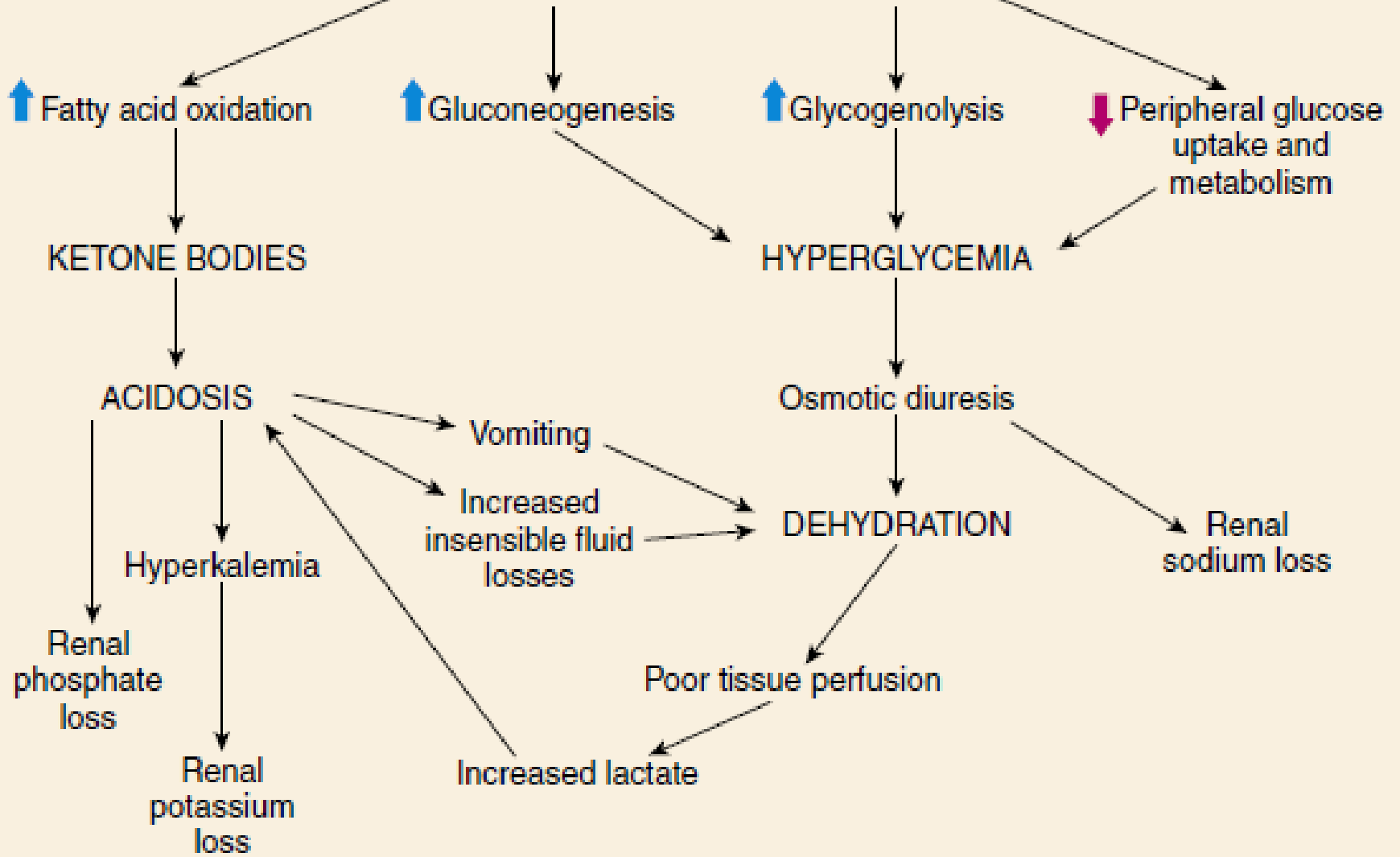
- Accumulation of these keto acids results in metabolic acidosis (diabetic ketoacidosis [DKA]) and compensatory rapid deep breathing in an attempt to excrete excess CO₂ (Kussmaul respiration)

CLINICAL MANIFESTATIONS

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.

- Female patients may develop monilial vaginitis from the chronic glycosuria. 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

INADEQUATE INSULIN SECRETION



Diagnosis

IMPAIRED GLUCOSE TOLERANCE

Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)

2-hr plasma glucose during the OGTT ≥ 140 mg/dL, but < 200 mg/dL (11.1 mmol/L)

DIABETES MELLITUS

Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

or

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} $\geq 6.5\%$ [†]

Diabetic Ketoacidosis (DKA)

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. DKA may be arbitrarily classified as mild, moderate, or severe

the range of symptoms depends on the depth of ketoacidosis. There is a large amount of ketonuria, an increased ion gap, a decreased serum bicarbonate (or total CO₂) and pH, and an elevated effective serum osmolality, indicating hypertonic dehydration.

Severity of DKA can be classified as following:

	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

TREATMENT

Treatment can be divided according to type of presentation , whether present with classical signs and symptoms of T1D (polyuria,polydipsia.weight loss and others) which requires starting insulin only, or present with DKA which need to start a special protocol for treatment.Insulin starting dose can be divided also according to this classification:

	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

The optimal insulin dose can only be determined empirically, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team.

The insulin can be given in different regimens, which include Multiple Daily Injection (MDI) Regimens, Insulin Pump Therapy and NPH-Based Treatment Regimens (split-mixed regimen). Bolus-basal treatment with multiple injections is better adapted to the physiologic profiles of insulin and glucose and can therefore provide better glycemic control than the conventional 2-3 dose regimen.

Insulin can be classified according to the source of production into 3 types:

a. insulin extracted from animal pancreases, specifically beef, beef–pork, and pork insulin (discontinued).

b. human insulin produced by recombinant DNA technology.

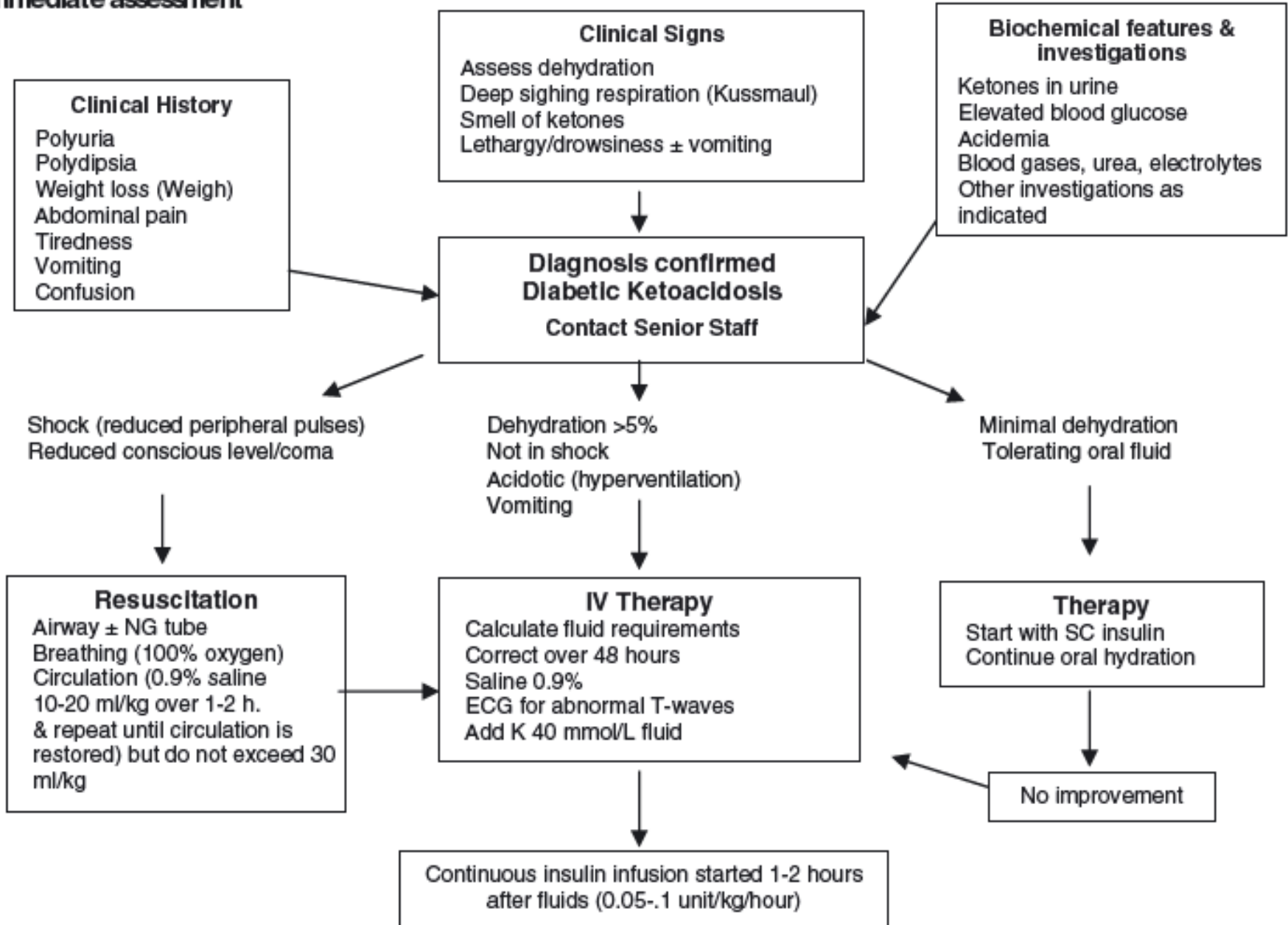
c. insulin analogs, also produced by recombinant DNA technology with the introduction of molecule modifications that change the pharmacokinetic profile.

Currently available insulin types are classified based on their duration of action as rapid, short, intermediate, and long acting.

Table 171-2 Representative Profiles of Insulin			
INSULIN	ONSET	PEAK ACTION	DURATION
Very Short Acting Lispro, aspart, glulisine	5–15 minutes	30–90 minutes	3–5 hours
Short Acting Regular	30–60 minutes	2–3 hours	5–8 hours
Intermediate Acting Neutral protamine Hagedorn (NPH) (isophane)	2–4 hours	4–10 hours	10–16 hours
Long Acting Glargine	2–4 hours	None	20–24 hours
Detemir	2–4 hours	6–14 hours	16–20 hours

DKA treatment

Immediate assessment



Dawn Phenomenon and Somogyi Phenomenon

Elevated morning fasting glucose mainly caused by these conditions.

The dawn phenomenon is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance and therefore morning hyperglycemia and require increase insulin dose.

Somogyi phenomenon: a theoretical rebound from late-night or early-morning hypoglycemia, thought to be from an exaggerated counter regulatory response and require decrease insulin dose.

Mid night measurement of blood sugar can distinguish between these Two phenomenon.

Honeymoon Period

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. This is a period of stable blood glucose control, often with nearly normal glucose concentrations. This phase of the disease, known as the honeymoon period, usually starts in the first weeks of therapy, often continues for 3 to 6 months, and can last 2 years.

Complications

Patients with DM1 for more than 3 to 5 years should receive an annual ophthalmologic examination for retinopathy. Urine should be collected annually for assessment of microalbuminuria, which suggests early renal dysfunction and indicates a high risk of progression to nephropathy. Treatment with ACE I may halt the progression of microalbuminuria. In children with DM1, annual cholesterol measurements and periodic assessment of blood pressure are recommended. Early detection of hypertension and high cholesterol with appropriate intervention can help limit future risk of coronary disease.