CHAPTER 19

Endocrine Disorders

GROWTH HORMONE DEFICIENCY

CASE

Growth hormone deficiency due to brain tumor: A 4-year-old boy presents with a history of ***headache*** and ***vomiting*** for last one month. His ***growth*** has been ***slowed*** for the last one year. On examination, he is below the 3rd centile for height, on the 10th for weight. There is ***papilledema*** on fundoscopy.

- Growth Hormone (GH) is an anabolic hormone that stimulates growth of all tissues. It is secreted in a pulsatile fashion, more during sleep and exercise.
- Its most important effect is on the growth of long bones. Its action on long bone growth is mediated through another hormone IGF-I (insulin like growth factor-1), which is generated in the liver and other tissues.
- Growth hormone is released from the pituitary gland when stimulated by the hypothalamic hormone, Growth Hormone Releasing Factor (GRF). GH promotes linear growth, bone thickness, protein synthesis, insulin resistance and increases blood glucose.

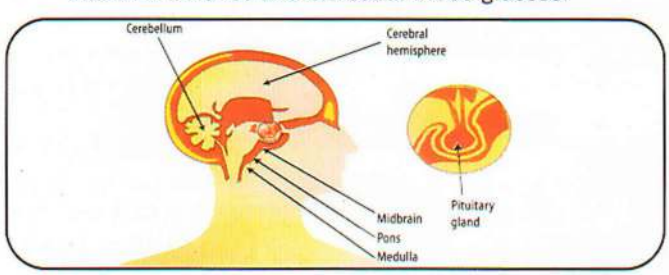


Figure 19.1 : Anatomy of pituitary gland

- Growth hormone deficiency is associated with a variety of clinical conditions and syndromes. In Laron syndrome, there is end organ resistance to GH.

Idiopathic growth hormone deficiency

- It is the most common cause of growth hormone deficiency.
- Usually, the defect is in the hypothalamus, resulting in deficient Growth Hormone Releasing Factor (GRF) stimulation of pituitary gland.
- Growth hormone is not necessary for fetal growth. So, the affected newborns are of normal size. Growth velocity slows after 6–12 months of age.
- Male infants have microphallus secondary to intrauterine gonadotropin deficiency.
- There may be symptomatic hypoglycemia in newborn.
- Older children with idiopathic growth hormone deficiency have very short stature (growth velocities of less than 5 cm/year). There is mild truncal adiposity, frontal bossing, a flat nasal bridge, and a high-pitched voice.

Secondary growth hormone deficiency

- Secondary to CNS tumors
- Trauma
- Surgery involving the hypothalamus or pituitary gland
- Irradiation
- Infectious infiltration

Differential diagnosis

- Constitutional growth delay
- Hypothyroidism
- Syndrome associated—Down, Turner, Prader-Willi, Russel-Silver dwarfism, skeletal dysplasia syndromes, many others
- Psychosocial short stature—emotional deprivation
- Chronic systemic disease—inflammatory bowel and liver disease, celiac disease, glycogen storage disease, cardiac and renal insufficiency.
- Malnutrition.

Diagnosis

- Growth hormone provocative tests:
  - Diagnosis by noting ↓ GH response to insulin, arginine, levodopa, clonidine, or glucagon.
  - Growth hormone levels greater than 10 ng/ml after exercise or insulin induced hypoglycemia are considered evidence of normal growth hormone capacity.
  - Peak levels of 7–10 ng/ml are intermediate and indicate partial growth hormone deficiency or a neuro-secretary defect.
  - Levels less than 7 ng/ml on two provocative tests indicate classic growth hormone deficiency.
- Serum insulin-like growth factor (IGF-1) and IGF binding protein are reduced in GH deficiency.

Management

- Human recombinant Growth Hormone (GH) is given by subcutaneous injection daily or every other day.
- Exogenous GH is approved for GH deficiency, Turner syndrome, renal insufficiency prior to transplant, Prader-Willi syndrome, Small for Gestational Age (SGA) babies with failure of catch-up growth.
- Exogenous GH for constitutional growth delay is also approved.
- Rare side effects of GH therapy are intracranial hypertension, slipped capital femoral epiphysis.

SHORT STATURE

CASE

Growth Hormone (GH) deficiency: An 8-year-old boy

presents with short stature. There is ***no significant medical history***. He is ***developmentally normal***. On examination, he has ***short stature***. Otherwise, his physical examination is normal. His upper and lower body segment measurements (***US/LS***) demonstrate ***normal body proportion***.

Definition

- Short stature is defined as subnormal height relative to other children of the same age, sex, ethnic background, and for family heights.
- The 3rd or 5th percentile of the growth curve is selected for demarcation, but pathologic short stature is usually 3.5 standard deviation below the mean.

Types

Children of short stature can be divided into two main groups:

1. Those who are small but are growing at an appropriate rate
2. Those who are small but are growing slowly

Etiology

1. Normal growth velocity

- Constitutional delay in growth and puberty
- Familial (genetic) short stature
- Low birth weight and intrauterine growth retardation

2. Low growth velocity

- Under-nutrition
- Psychosocial deprivation
- Chronic illness, e.g. renal (chronic renal failure, renal tubular acidosis), cardiovascular (congenital cyanotic heart disease, congestive cardiac failure), respiratory (severe asthma, cystic fibrosis)
- Malabsorption, e.g. Crohn's disease, celiac disease
- Syndromes, e.g. Turner's, Down, Prader-Willi
- Endocrine disease, e.g. Growth hormone deficiency, hypothyroidism, panhypopituitarism, Cushing syndrome (usually iatrogenic), poorly controlled diabetes mellitus
- Inborn errors of metabolism, rickets, mucopolysaccharidosis
- Constitutional (intrinsic) diseases of bone, e.g. achondroplasia, skeletal and spinal dysplasias, osteogenesisimperfecta

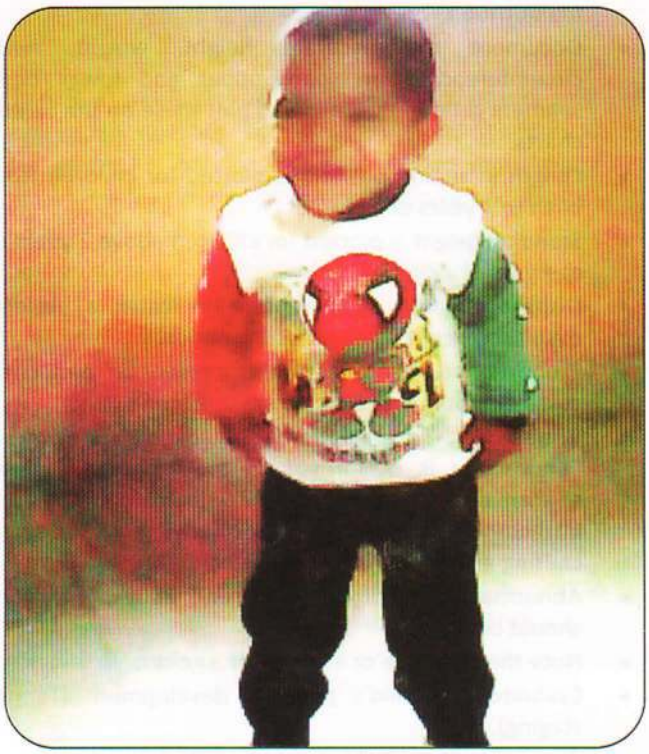
Assessment of a child with short stature

- Ask about the height of parents and siblings (familial short stature).
- Also ask whether the mother had a history of delayed menarche or father a delayed adolescence growth spurt (constitutional short stature).
- Obtain a detailed nutritional and psychosocial history.
- Identify predisposing conditions such as congenital infections, small for gestational age at birth (primordial short stature), congenital syndromes, chronic illness involving any organ system (especially the gastrointestinal, cardiac, pulmonary, and renal), and malnutrition.
- Document the accurate height, weight, head circumference, arm span, upper and lower body segment ratio of the child and plot these on the centile charts.
- Length in supine position is plotted for children from birth to 2 years of age.
- Standing height is plotted for children above 2 years of age.
- Disproportionate short stature indicates a skeletal dysplasia except osteogenesisimperfecta.
- Proportionate short stature is present in endocrine cases except in hypothyroidism.
- Visual field examination should be performed. Fundoscopy is performed to look for optic nerve abnormalities, which might indicate increased intracranial pressure or an underlying CNS disease causing growth hormone deficiency.
- Abnormalities of digits, joints, and body proportions should be noted.
- Note the presence or absence of a goiter.
- Evaluate the child's pubertal development (Tanner staging).
- Anomalies of genitalia should be noted.
- Assess the child's dentition and status of nutrition.
- Parental heights are also noted and mid-parental height and target height should be determined.
- Document the child's growth rate (growth velocity) from 1 year of age through pre-adolescence. The lower limit of normal growth is approximately 5 cm per year. A short child with a normal growth rate is unlikely to have significant illness or endocrinopathy.
- Rule out thyroid or growth hormone deficiency in children with a significant delayed bone age that are growing less than 4–5 cm a year.
- Consider Turner syndrome (XO genotype) in any short girl even those without typical Turner phenotype. Early diagnosis is important for appropriate therapy. GH therapy should be started at a young age and estrogen and progesterone at the time of puberty.

Investigations

- Choice of investigations depends upon the cause of short stature assessed by a detailed history, physical examination, and accurate measurements.
- Extensive investigations are often unnecessary if history and examination are normal and familial or constitutional causes are suspected.
- Initial investigations include complete blood counts, ESR, complete urine examination, blood urea and creatinine, thyroid function tests, and X-rays for bone age assessment.
- Other investigations include karyotyping (Turner syndrome); jejunal biopsy (celiac disease); serum

calcium, phosphate, and alkaline phosphate (rickets, hypoparathyroidism).



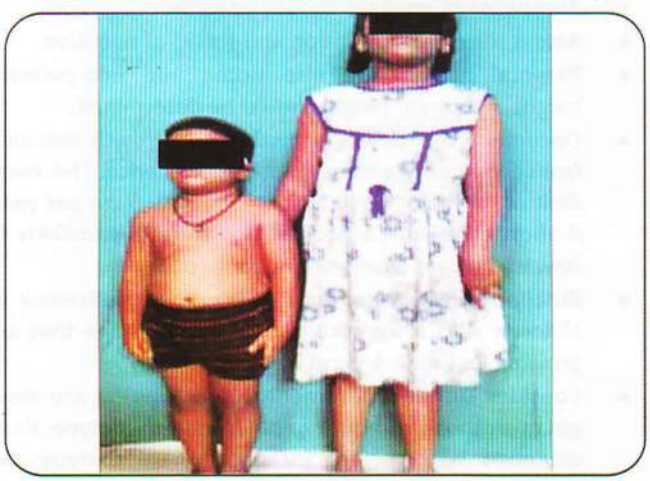


Figure 19.2: Short stature with hypothyroidism

Common causes of short stature

Constitutional delay of growth

CASE

A 14-year-old boy presents with ***short stature***. He is developmentally normal. He has a ***normal past medical history***. He is the shortest boy in his class. His ***father began puberty at age 16*** and completed his growth at age 19 years; he is now ***6 feet tall***.

- Constitutional delay of growth means a delayed growth pattern with delayed maturity and normal final height.
- The condition occurs much more commonly in males than females.
- The child's rate of physical maturation is delayed compared with that of other children of the same age.
- The bone age is usually equal to the height age but is less relative to chronological age.
- Pubertal maturation is correspondingly delayed.
- The ultimate height of these children is usually normal for their families, since the pubertal growth spurt often occurs between 15 and 17 years, and growth continues until 18 to 20 years of age.
- Family members usually are of average height, but there often is a family history of short stature in childhood and delayed puberty in other family members.
- Reassurance that no significant endocrine disease exists and that normal growth and puberty with reasonable adult stature are expected is all that is required.
- Treatment with low doses of testosterone over a 3–6 month period in boys may be useful in hastening the timing of puberty and accelerating growth, but final adult height is not enhanced.
- Growth hormone does not have a place in treating these normal children.

Familial (genetic) short stature

- These children establish growth curves at or below the 5th percentile by 2–3 years of age.
- They are otherwise completely healthy, with a normal physical examination.
- They have growth rate greater than 4 cm per year, and have a bone age appropriate for chronological age.
- Puberty occurs at the usual age.
- Short stature usually is found in at least one parent.
- However, because the inheritance of height is complex, occasionally short stature may be present only in more distant relatives.
- Because puberty occurs at the expected time, these children seem to be less disturbed socially and emotionally as compared with constitutional delay.

Growth hormone deficiency

- Children with classic growth hormone deficiency grow at subnormal growth velocities (<5 cm/year) and have a significant delay of skeletal maturation.
- After establishing that current growth velocity is less than 5 cm/year and that thyroid function is normal and other systemic disease is unlikely, growth hormone testing should be carried out.
- Classic growth hormone deficient patient do not show an increase in serum growth hormone level after

stimulation by various secretagogues (insulin, clonidine).
- For growth hormone deficiency, recombinant human growth hormone is given.
- Acceleration of the height velocity from a baseline of less than 5 cm/year to at least 7–8 cm/year on replacement of growth hormone is confirmation of genuine deficiency.
- A poor response requires review of the diagnosis or compliance.

Hypothyroidism
- Hypothyroidism causes marked growth failure, with growth velocity less than 5 cm/year, and marked retardation of skeletal maturation.
- Because hypothyroidism is easily treatable, almost all children with short stature should have T_4, and TSH levels measured, even in the absence of obvious symptoms, to rule out any degree of hypothyroidism.
- Treatment is with thyroxine.

Chronic systemic disease
- The impact of chronic systemic disease on growth is well known.
- Cyanotic congenital heart disease, poorly controlled diabetes mellitus, gastrointestinal diseases (celiac disease, inflammatory bowel disease), chronic renal failure, and asthma have a deleterious effect on growth, related to a combination of nutritional deficits and increased metabolic demands created by the disease process.
- These children need treatment of primary disease with high caloric balanced diet.

Undernutrition
- On a global basis, malnutrition is the commonest cause of poor growth and short stature.
- Inadequate caloric intake may occur when a child is not offered enough to eat because of inadequate parenting or poverty.
- Adequate dietary advice is needed in such a case.

Psychosocial deprivation
- In some children, a hostile, abusive, or neglected environment appears to result in functional growth hormone deficiency.
- Children with psychosocial deprivation characteristically show bizarre behavior, disturbed sleep, and immature speech.
- Clinically, they may resemble children with growth hormone deficiency, with marked retardation of bone age and delayed puberty.
- Opinion of a child psychiatrist is needed.

Disproportionate short stature
- Skeletal dysplasias cause disproportionate short stature.
- Measurements of arm span and upper-to-lower body segment ratio are helpful in determining whether a child has normal body proportions.
- If disproportionate short stature is found, a skeletal survey may be useful because specific radiographic features characterize certain disorders.

PRECOCIOUS PUBERTY

CASE

A ***5-year-old girl*** presents with ***breast and pubic hair development*** for the last 4 months. On physical examination, she has height and weight above the 95th percentile (***tall stature***) oily skin, and ***facial acne***.

Definition
- Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.
- Depending on the primary source of the hormonal production, precocious puberty may be classified as:
  1. Central (also known as gonadotropin dependent or true).
  2. Peripheral (also known as gonadotropin independent or precocious pseudopuberty).

Conditions causing precocious puberty

Central (GnRH-dependent) precocious puberty
- Idiopathic
- Central nervous system abnormalities
  - Acquired—abscess, chemotherapy, radiation, surgical trauma
  - Congenital—arachnoid cyst, hydrocephalus, hypothalamic hamartoma, septo-optic dysplasia, suprasellar cyst
  - Tumors—astrocytoma, craniopharyngioma, glioma

Peripheral (GnRH-independent) precocious puberty
- Congenital adrenal hyperplasia
- Adrenal tumors
- McCune-Albright syndrome
- Familial male-limited gonadotropin independent precocious puberty
- Gonadal tumors
- Exogenous estrogen—oral (contraceptive pills) or topical
- Ovarian cysts (females)
- HCG-secreting tumors (e.g. hepatoblastomas, choriocarcinomas) (males)

Incomplete (partial) precocious puberty
- Premature thelarche
- Premature adrenarche
- Premature menarche

DELAYED PUBERTY IN BOYS

- Puberty is diagnosed delayed if there is lack of secondary sexual characteristics by age 14 years in boys.

Causes

- Primary testicular failure:
  - Testicular absence or hypoplasia (Klinefelter syndrome is the most common cause)
  - Destruction of testes by irradiation
  - Infection (mumps)
  - Autoimmune inflammation
  - Trauma or tumor
  - Enzyme defects
- Secondary testicular failure:
  - Pituitary or hypothalamic disease
  - Isolated LH or FSH deficiency due to GnRH deficiency (Prader-Willi and Laurence-Moon syndrome)
  - Destructive brain tumors or infections
  - Chronic debility
  - Hypothyroidism

Diagnosis

- Primary testicular failure:
  - Low plasma testosterone with elevated LH and FSH.
- Secondary testicular failure:
  - Testosterone, LH, and FSH are below normal.
- Presence of testes and their ability to respond is measured by plasma testosterone after intramuscular hCG.

Differential diagnosis

- Constitutional growth delay (most common cause of delayed puberty. There is normal growth velocity and delayed bone age).
- Masculinized female (in such a case check karyotype and look for adrenal hyperplasia).
- Cryptorchidism (this may be an isolated finding or associated with hypothalamic-pituitary-gonadal axis, androgen synthesis or receptor defects).
- Abdominal testes (in this case, plasma testosterone after hCG stimulation will be normal).

Management

- Specific therapy depends on cause. Constitutional delay may respond to short course (4–6 months) of low-dose depot testosterone (50–70 mg/month) to stimulate their pubertal appearance and enhance to start their endogenous development.
- Permanent hypogonadism requires regular depot testosterone (50–70 mg up to 150–200 mg/2–3 months) given until their growth is complete.

HYPOTHYROIDISM

- Thyroid hormone is critical for normal postnatal somatic growth and neurologic development in infants and children.
- Deficiency of thyroid hormone in first 2 years of life may result in severe psychomotor retardation.
- Thyroid hormone is also necessary for skeletal growth and maturation in growing children.
- It plays a major role in oxidative metabolism and heat production.
- Hypothyroidism may occur at birth (congenital hypothyroidism) or at any time during childhood or adolescence (juvenile hypothyroidism).

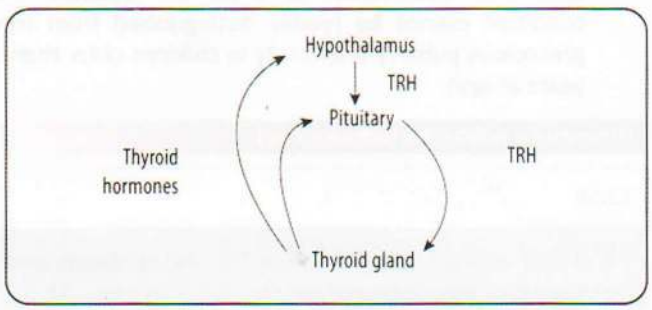


Figure 19.3: Thyroid hormone regulation.

CONGENITAL HYPOTHYROIDISM

CASE

A 2-week-old boy presents with ***constipation*** and ***jaundice***. He is sluggish (hypotonia) and excessive sleepy. On physical examination, he has mild jaundice with a distended abdomen. He has a ***large tongue***, a ***large anterior and posterior fontanel***, an ***umbilical hernia***, and a coarse dry skin. Plasma T_4 is decreased and TSH is raised. No ossification center at knee X-ray. Isotope and ultrasound scanning showed no thyroid tissue.

- Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis.

Definition

- Congenital hypothyroidism is defined as a significant decrease in, or the absence of, thyroid function present at birth.

INCIDENCE

- Congenital hypothyroidism affects boys and girls equally.
- Worldwide 1:4000 infants are affected.
- Goitrous congenital hypothyroidism occurs in about 1:30,000 live births and reflects inborn defect in hormone synthesis or effect, or transplacental passage of anti-thyroid drugs.

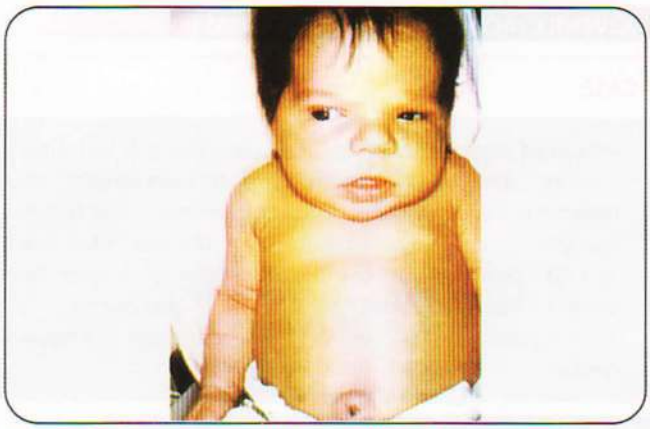


Figure 19.4 (A): Congenital hypothyroidism.

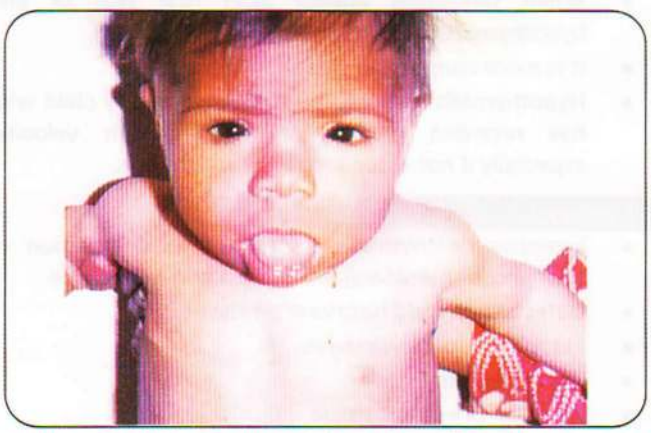


Figure 19.4 (B): Congenital hypothyroidism. Note coarse facies and large tongue.

Etiology

- Dysgenesis or aplasia of thyroid gland (90% of cases)
- Ectopic thyroid gland
- Inborn defect of thyroxine synthesis (may involve defects of iodine transport, organification, thyroglobulin synthesis, or deiodination)
- End organ resistance to thyroxine
- Hypothalamic-pituitary-thyroid axis defect (TRH or TSH deficiency)
- Endemic goiter (iodine deficiency)
- Transplacental suppression of thyroid by drugs, antibodies, etc.
- Idiopathic

Clinical findings

- Because thyroid hormone does not appear to be necessary for fetal growth, infants with congenital hypothyroidism are normal at birth and gain weight normally, even if untreated, for the first 3–4 months of life.
- The severity of symptoms and physical findings correlates with the degree of hypothyroidism.
- At birth, gestation may be >42 weeks (50%), and birth weight >4 kg (25%).
- After birth, there may be:
  - Hypothermia
  - Acrocyanosis
  - Respiratory distress
  - Large posterior fontanel
  - Bradycardia
  - Poor muscle tone
  - Poor feeding
  - Prolonged neonatal jaundice (75%)
- Other symptoms that may be apparent after the first 1–2 months of life are:
  - Feeding problems
  - Lethargy
  - Constipation
  - Noisy breathing
  - Abdominal distension
  - Umbilical hernia
  - Mottled dry skin
  - Coarse facies
  - Large tongue
  - Thick lips
  - Large open fontanels
  - Hypotonia
  - Hoarse cry
  - Scanty dry and brittle scalp hair
  - Lateral thinning of eye brows
  - Non-pitting edema
  - Anemia
  - A slow relaxation component of deep tendon reflexes is present (best appreciated in the ankle)
- Severe congenital hypothyroidism is characterized by:
  - Short stature
  - Epiphyseal dysgenesis
  - Impaired physical growth and development
  - Mental retardation

Diagnosis

- **Linear growth:**
  - There is short stature
  - Ratio of upper to lower segment is abnormal (infantile)
- **Thyroid function test:**
  - Decreased serum concentration of total T_4
  - Elevated serum concentrations of TSH
- **X-rays:**
  - Retardation of osseous development. At birth, there is no epiphysialcenter visible at knee joint.
  - In older children, the epiphysis often has multiple foci of ossification (epiphyseal dysgenesis).
  - Bone age is delayed.
  - X-ray skull shows large fontanel and wide sutures and intersutural bones (wormian bones).
- **Thyroid scan:**
  - It differentiates between agenesis and ectopic thyroid.

- It includes ultrasound scan, technetium scan, or iodine uptake and perchlorate discharge test.
- A technetium scan shows:
  - Absence of ^{99m}Tc uptake indicates thyroid agenesis.
  - Increased ^{99m}Tc uptake in a normally positioned gland shows an enzymatic defect in thyroid hormone production.
  - An ectopic gland is demonstrated by abnormal localization of ^{99m}Tc uptake.

- **ECG:**
  - Low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion.
- **EEG:**
  - It shows low voltage.

Treatment

- Lifelong treatment with **thyroid hormone replacement**.
- Thyroxin is given as a single daily oral dose.
- Dose is 10–15 mg/kg/day in neonates, and 4 □g/kg/day in children.
- As the child grows, the dosage is adjusted to maintain the serum T_4 in the high-normal range.
- Adequate dose is indicated by alertness and increase in activity, appetite, skin becoming warm and smooth, improvement of constipation and normal linear growth.
- Over dose is indicated by diarrhea, restlessness, excitability, sleeplessness, tachycardia, hyperthermia, and tremors.

Follow up

- Growth and neurologic development are evaluated by regular follow up every 2–3 months in the first 2 years of age, with somewhat less frequent follow up after 2 years of age.
- In follow up visits, weight, height, bone age and developmental assessment is done.

Prognosis

- When diagnosed and treated within the first few weeks of life, there is normal growth and intelligence.
- When the diagnosis of congenital hypothyroidism is delayed beyond 6 months of age, a high proportion of children suffer permanent neurologic impairment.

Neonatal screening

- Congenital hypothyroidism in the next pregnancy should be diagnosed by neonatal screening within 10 days of birth.

JUVENILE (ACQUIRED) HYPOTHYROIDISM

CASE

Acquired hypothyroidism: A 9-year-old girl has ***short stature***, and ***slow growth***. She is ***overweight*** and ***lethargic***. She complains of ***cold intolerance***. She is pale. Her growth curve demonstrates that she has fallen from the 50th percentile to the 5th percentile for height. Her weight has increased to the 90th percentile. On examination, she has ***slow reflexes***. ***Bone age*** is ***delayed*** on X-ray.

Definition

- When symptoms appear after first year of life, hypothyroidism is presumed to be acquired.
- It is more common in girls than in boys.
- Hypothyroidism should be suspected in any child who has retarded growth or slow growth velocity, especially if not associated with weight loss.

Etiology

- Lymphocytic thyroiditis (autoimmune destruction or Hashimoto thyroiditis) is the most common cause.
- Defects in thyroid hormone synthesis
- Ectopic thyroid dysgenesis
- Thyroidectomy
- Removal of ectopic tissue
- Irradiation
- Ingestion of iodide containing medications
- Idiopathic

Clinical features

- Growth retardation
- Skin changes
- Constipation
- Cold intolerance
- Less energy
- Increased sleep
- Delayed bone age
- Some children may present with headache, visual problems, precocious puberty, or galactorrhea.
- These manifestations return to normal with treatment.
- With long standing hypothyroidism, adult height may be impaired.

Diagnosis

- Decreased serum concentrations of total T_4
- Elevated serum concentrations of TSH
- Delayed bone age on X-ray
- Presence of circulating thyroid antibodies shows autoimmune basis of the disease

Treatment

- Thyroid hormone replacement therapy (thyroxine)

Prognosis

- Acquired hypothyroidism is not a cause of permanent developmental delay.
- Unless hypothyroidism develops around the time of puberty when skeletal maturation is nearly complete, the prognosis for catch-up growth is good. Some children may not reach their genetic potential for growth.
- Other signs and symptoms improve completely.
- Children with autoimmune hypothyroidism are at increased risk for other associated autoimmune diseases, such as diabetes mellitus and adrenal insufficiency.

THYROIDITIS

CHRONIC LYMPHOCYTIC THYROIDITIS

- Also called Hashimoto thyroiditis or autoimmune thyroiditis.
- There is firm, freely movable, nontender, diffusely enlarged thyroid gland.
- Thyroid function is usually normal but may be elevated or decreased depending on the stage of the disease.

Clinical findings

- It is the most common cause of goiter and hypothyroidism in children.
- Female/Male ratio is 4:1.
- This is a autoimmune-mediated disorder.
- Usual presentation is as hypothyroid symptoms, goiter, positiveantithyroid peroxidase antibodies. May present with hyperthyroid symptoms
- TSH is generally normal. TSH low during hyperthyroid phase of thyrotoxicosis. TSH is high during hypothyroid phase of thyroiditis.
- This disorder may be associated with autoimmune polyglandular syndrome type 2 (adrenal failure, autoimmune thyroid disease, type 1 diabetes mellitus, vitiligo, celiac disease, atrophic gastritis, gonadal failure).

Differential diagnosis

- Idiopathic goiter
- Graves disease
- Viral thyroiditis
- Iodine deficiency
- Goitrogen ingestion
- Congenital hypothyroidism

Management

- Ideal treatment has not been established.
- Exogenous thyroid hormones are given which decreases goiter size but does not prevent progression of disease
- Regular monitoring for the development of hypothyroidism or Graves disease is needed.

HYPERTHYROIDISM

CASE

A 12-year-old girl presents with a three months history of ***heat intolerance***, ***weight loss*** and poor concentration. On examination, there is symmetrical smooth ***goiter***, ***proptosis*** and ***tachycardia***. Investigations show ***TSH suppression*** with ***high free T_4 and T_3***.

- Hyperthyroidism results from excessive secretion of thyroid hormone.
- During childhood, with few exceptions, it is caused by Graves disease.
- **Graves disease** is an autoimmune disorder.

GRAVES DISEASE

Etiology

- Graves disease (diffuse toxic goiter):
  - It is hyperthyroidism secondary to diffuse thyroid hyperplasia.
  - It is an autoimmune disorder. Enlargement and hyperfunction of the thyroid gland is stimulated by circulating immunoglobulins. Stimulatory immunoglobulins lead to increased levels of free T_4 that suppresses TSH to undetected levels.
- Neonatal Graves disease:
  - It is caused by transplacental passage of thyroid-stimulating immunoglobulins (i.e. IgG).
- Autonomous hyperfunctioning hot thyroid nodule
- Subacute thyroiditis

Clinical findings

- Girls are more commonly affected than boys (ratio 5:1).
- There is often a family history of Graves disease.
- The usual age of manifestation is after 5 years of age.
- The onset of symptoms is insidious.
  - Emotional liability
  - Increased appetite
  - Heat intolerance
  - Weight loss
  - Frequent loose stools
  - Deterioration of behavior and school performance
  - Poor sleeping
- Child appears flushed and warm.
- There is marked tachycardia, fever, diaphoresis, nausea and vomiting (thyroid storm).
- There may be proptosis and widened palpebral fissures.
- Thyroid gland is diffusely enlarged, smooth, firm, but not hard. It is nontender.
- Precordium is hyperactive. There is resting tachycardia and widened pulse pressure.

- Skin is smooth, warm, flushed, and moist.
- There may be a fine tremor of outstretched fingers, and proximal muscle weakness.

Diagnosis

- Increased serum concentrations of total T_4 (or free T_4) and total T_3
- Low or suppressed levels of TSH
- Increased radioactive iodine uptake

Management

- Antithyroid medications:
  - Propylthiouracil (PTU) 150–600 mg/day
  - Methimazole 15–60 mg/day
- Propranolol 10–20 mg four times daily for 2–4 weeks may give symptomatic relief.
- Subtotal thyroidectomy is indicated if the patient is noncompliant with medical therapy.
- Radioactive iodine is used for ablation of thyroid tissue.

CONGENITAL HYPERTHYROIDISM

CASE

A 5-days old full term 3.2 kg neonate presents with irritability, ***jitteriness***, ***tachycardia***, ***sweating***. He has difficulty to feed and ***diarrhea***. Heart rate is 190 beats/minute (***tachycardia***). Respiratory rate is 80 breaths/minute (***tachypnea***). Liver is 4 cm palpable. He has poor peripheral pulses. His mother is getting treatment for hyperthyroidism.

- Transient congenital hyperthyroidism or neonatal Graves disease occurs in about 1% of infants born to mothers with Graves disease.
- It occurs when maternal TSH receptor antibodies cross the placenta and stimulate excess thyroid hormone production in the fetus and newborn.

Clinical findings

- Irritability, IUGR, poor weight gain, flushing, jaundice, hepatosplenomegaly, and thrombocytopenia.
- Severe cases may result in cardiac failure and death.
- Hyperthyroidism may develop several days after birth, especially if the mother was treated with PTU which crosses the placenta. Symptoms develop as PTU levels decline in the newborn after birth.

Diagnosis

- Thyroid studies are obtained at birth and repeated within the first week.

Management

- Immediate management of cardiac manifestations is needed.
- Temporary treatment may be necessary with iodide, antithyroid agents, -adrenergic antagonists, or corticosteroids.
  - Oral propranolol (1–2 mg/kg/24 hours, orally in 3 divided doses)
  - Methimazole (0.25–1.0 mg/kg/24 hours given every 12 hours)
  - Saturated solution of potassium iodide (1 drop per day) may be added)
- If heart failure occurs, digitalization is indicated.
- Hyperthyroidism gradually resolves over 1–3 months as maternal antibodies decline.

HYPOPARATHYROIDISM

CASE

A 2-year-old male child presents with generalized tonic-clonic afebrile convulsive attack. Cerebrospinal fluid examination and EEG are normal. Serum calcium, Vitamin D_3, and PTH levels are low.

Clinical findings

- Hypocalcemia causes tetany: muscular pain, cramps, numbness, stiffness, tingling of the hands and feet, positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms, convulsions.
- Headache, vomiting, increased ICP, papilledema–may suggest a brain tumor.
- In long standing hypocalcemia–teeth erupt late and irregularly–enamel formation is irregular–skin may be dry and scaly–nails may have horizontal lines.
- Mucocutaneous candidiasis
- Cataracts

Diagnosis

- Serum calcium level is low (Ca 5–7 mg/dL)
- Serum phosphorus elevated (7–12 mg/dL)
- Alkaline phosphatase (normal or low)
- 1, 25 $(OH)_2$ D_3 (usually low)
- Magnesium (normal)
- PTH levels (low)
- Radiographs or CT scans of the skull (calcifications in the basal ganglia)
- ECG (prolongation of the QT interval)
- EEG (shows widespread slow activity)

Differential diagnosis

- Pseudo-hypoparathyroidism
- Transient tetany in newborns is a relative Parathyroid Hormone(PTH) deficiency associated with high phosphate diet (whole cow's milk), infant of diabetic mother, fetal alcohol syndrome.
- Severe vitamin D deficiency

- Gastrointestinal (GI) malabsorption syndromes, chronic renal disease, tumorlysis syndrome, rhabdomyolysis
- DiGeorge syndrome—congenital absence of parathyroid gland
- Autoimmune polyendocrine syndrome type 1
- Autosomal dominant hypocalcemia—gain of function mutation in extracellular calcium receptor which causes low serum PTH despite calcium loss and hypocalcemia
- Postoperative or postradiation for thyroid disease
- Iron or copper overload—hemochromatosis, thalassemia, Wilson's disease
- Hyperandhypomagnesemia

Management

- Treatmentof severe tetany or seizures resulting from hypocalcemia is intravenous calcium gluconate (1 to 2 ml/kg of a 10% solution) given slowly over 10 minutes under cardiac monitoring (ECG for bradycardia, which can be fatal).
- Long-term treatment of hypoparathyroidism involves administering vitamin D, preferably as 1,25-dihydroxyvitamin D and calcium.
- Therapy is adjusted to keep the serum calcium in the lower half of the normal range to avoid episodes of hypercalcemia that might produce nephrocalcinosis and to avoid pancreatitis.
- High calcium diet and dietary calcium supplements
- Vitamin D supplementation with calcitriol
- Treat underlying cause if possible
- PTH is not generally used

PSEUDO-HYPOPARATHYROIDISM

(Albright Hereditary Osteodystrophy)

- PTH elevated even when the patient is hypocalcemic or normocalcemic.
- Biochemical features of pseudo-hypoparathyroidism are similar to those of hypoparathyroidism with the one exception that in pseudo-hypoparathyroidism, PTH levels are elevated.

Clinical findings

- Tetany
- Short stature
- Round face
- Obesity
- Dental hypoplasia
- Brachydactyly (index finger may be longer than middle finger; usually due to shortened fourth or fifth metacarpals or metatarsals)
- Short and wide phalanges, bowing exostoses, and thickening of the calvaria
- Calcium deposits and metaplastic bone formation subcutaneously (subcutaneous calcifications)
- Mental retardation (below normal IQ)
- Calcification of basal ganglia
- Lenticular cataracts
- Other hormone abnormalities (hypothyroidism, hypogonadism)

Diagnosis

- Hypocalcemia
- Hyperphosphatemia
- Elevated PTH levels
- Alkaline phosphatase (increased)

Management

- Same as for hypoparathyroidism
- Specific treatment is needed for ocular, mental, and physical disabilities

HYPERPARATHYROIDISM

CASE

A 6-year-old child presents with complaint of ***numbness and tingling of the hands***. He also has history of tonic clonic***seizures***. Laboratory investigations show ***low PO4*** and ***high Ca^{++}***.

Clinical findings

- Muscular weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, loss of weight, fever
- Nephrocalcinosis
- Progressively diminished renal function (renal calculi–renal colic–hematuria).
- Osseous changes may produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors.

Diagnosis

- Serum calcium level is elevated (>12 mg/dL)
- Serum phosphorus level is reduced (<3 mg/dL)
- Serum magnesium–low
- Urine may have a low and fixed specific gravity
- Serum levels of PTH–elevated
- Radiographic findings–resorption of subperiosteal bone

Differential diagnosis

- Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism:
  - Excessive Calcium or Vitamin D
  - Hypercalcemia of malignancy (Primary bone tumors, Metastatic tumors with osteolysis)
  - Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
  - Acute or Chronic Renal Failure
  - Hypophosphatasia

between midnight and 2 am may be a sensitive indicator of the loss of diurnal variation.

- Serum ACTH levels:
  - Slightly increased with adrenal hyperplasia (Cushing disease)
  - Decreased in cases of adrenal tumor
  - Greatly increased with ACTH-producing pituitary or extra-pituitary tumors
- Dexamethasone suppression testing:
  - The suppression of adrenal function by a small dose (0.5 mg) of dexamethasone is reduced in adrenal hyperfunction;
  - Larger doses (4–16 mg/d in four divided doses) of dexamethasone cause suppression of adrenal activity when the disease is due to ACTH hypersecretion, whereas hypercortisolism due to adenomas and adrenal carcinomas is not suppressed.
- Serum chloride and potassium levels are lowered.
- Leukocyte count shows polymorpho-nuclear leukocytosis with lymphopenia. Eosinophil count is low.
- Salivary cortisol obtained at midnight is a highly specific and sensitive test for hypercortisolism.
- CRH stimulation test: It is effective test in distinguishing pituitary and ectopic sources of ACTH excess.
- 24 hours urinary free cortisol excretion: This value is raised.
- Radiologic imaging (MRI) studies are performed to visualize a pituitary, adrenal, or ectopic ACTH-producing tumor. Radionuclide studies of the adrenals are indicated in complex cases.

Management

- Removal of the cause of hypercortisolism is the main treatment.
- In all cases of primary adrenal hyperfunction due to tumor, surgical removal is indicated if possible.
- Pituitary microadenomas may respond to pituitary surgery or irradiation.
- In pituitary Cushing disease, medications (cyproheptadine and bromocriptine) are effective in lowering ACTH levels.
- In adrenal adenoma, adrenalectomy is the treatment of choice. In adrenal hyperplasia, a partial adrenalectomy may be performed.

Prognosis

- Prognosis depends on the underlying cause.
- Patients with adrenal or pituitary adenomas have a good prognosis after surgical resection.
- Patients with adrenal or ectopic ACTH-producing carcinomas have a poor prognosis.

DIABETES MELLITUS

CASE

A 14-year-old girl presents with ***frequent urination***, ***excessive thirst*** and hunger. She has the ***rapid loss of weight*** within few months. ***Serum glucose level 250 mg/dL***. ***Urinalysis*** is positive for ***2+ glucose*** but is otherwise normal.

Definition

- Diabetes mellitus is a chronic metabolic disorder resulting from absolute lack of insulin and results in abnormal metabolism of carbohydrate, protein, and fat.
- It is characterized by:
  - Polyuria, polydipsia, and weight loss
  - Hyperglycemia and glucosuria with or without ketonuria
- Diagnosis of DM is made based on four glucose abnormalities:
  - Fasting serum glucose concentration ≥126 mg/dl
  - A random venous plasma glucose ≥200 mg/dl with symptoms of hyperglycemia
  - An abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dl
  - A HbA1c ≥6.5%

Incidence

- Type I Diabetes Mellitus (DMI) is the most common endocrine disorder in children.
- Peak age of presentation is 5–7 years and at the time of puberty.
- DMI affects approximately 0.7 in 100,000 per year in Karachi.
- Siblings or offspring of a diabetic patient have a 5% risk to develop diabetes.
- Identical twin has a 50% risk.
- Individuals with HLA-DR_3 or HLA-DR_4 or HLA DQ2/8 genotype have 3–4 times increased risk to develop diabetes.
- Individuals with both HLA-DR_3 and–DR_4 alleles have a 10 times increase in risk. There is insulin gene locus IDDM2.

Etiology

- Diabetes mellitus is due to lack of insulin.
- Type I diabetes is characterized by pancreatic islet β-cell destruction mediated by immune mechanisms.
- There is a **genetic predisposition**. HLA antigens DR_3 and DR_4 being generally associated. More than 90% of children with IDDM possess HLA-DR_3, DR_4 alleles, or both.
- **Environmental factors** also play a role in addition to diabetes susceptibility genes to trigger autoimmune

destruction of the islet cells. There is an increased incidence of IDDM in children exposed to cow's milk or cereals (gluten) induce autoimmunity before 2 years of age. There is lower incidence of diabetes among breast fed infants.

- **Viral infections** may be also responsible including coxsackie B virus, cytomegalovirus, mumps, and rubella virus.
- Patients with IDDM have positive glutamic acid decarboxylase antibody (GAD in 80% of patients), insulin autoantibodies (in 100% of cases), and islet cell antibody (ICA in 80–90% of cases).
- **Idiopathic:** Almost 95% of juvenile cases belong to this category. It is believed to be hereditary inborn error of metabolism but exact mode of inheritance is not known. Polygenic (multifactorial) inheritance is suggested.
- **Secondary causes:** Cushing syndrome, hemosiderosis, hyperpituitarism and surgical removal of pancreas.
- Juvenile diabetes is not related to diet or nutritional status of child.

Pathophysiology

- Type 1 diabetes results from immunologic damage to the insulin-producing Beta cells of the pancreatic islets.
- This damage occurs gradually and symptoms do not appear until about 90% of the pancreatic islets have been destroyed.
- Deficiency of insulin results in non-utilization of glucose by the peripheral tissues and hence hyperglycemia.
- The excess glucose causes osmotic diuresis (polyuria) and body tries to compensate that by increasing thirst and large intake of fluids (polydipsia).
- Lack of glucose utilization by the body leads to increased appetite (polyphagia).
- Now body utilizes alternate sources of energy and mobilizes fat from adipose tissue and when rate of free fatty acid exceeds rate of utilization, excess fatty acids are converted to ketone bodies (acetoacetate and beta-hydroxybutyrate) and ketonemia and ketonuria occur.
- Protein synthesis is impaired resulting in loss of weight, muscle wasting, and growth retardation.

Clinical findings

- Diabetes is more acute in onset in children than adults.
- Onset is usually preceded by infection and clinical symptoms include polyuria, polydipsia, polyphagia, and rapid loss of weight.
- Nocturia may be an early symptom in a child who was earlier dry at night.
- Often, diabetic coma is the first manifestation and patient with ketoacidosis presents with:
  - Profound dehydration
  - Hypotension
  - Sunken eyes
  - Dry tongue
  - Kussmaul respiration (rapid and sighing)
  - Lethargy
  - Somnolence
  - Coma
- Recurrent infections and candidiasis may occur.
- On laboratory report, the initial manifestation is postprandial hyperglycemia. Then fasting hyperglycemia develops.

Diagnosis

- Classic symptoms of polyuria, polydipsia, and weight loss are suggestive.
- Diabetes mellitus is also suspected if there are symptoms of diabetes plus random plasma glucose ≥200 mg/dl.
- **Urine examination:**
  - Glycosuria
  - Ketonuria
- **Blood sugar:**
  - Random above 200 mg/dl
  - Fasting above 126 mg/dl
- **Serum electrolytes:**
  - Hyponatremia
  - Hypokalemia
  - Low chloride
- **Acid-base balance:**
  - Bicarbonate base deficit
  - pH is low
- **Blood examination:**
  - Hemoglobin and hematocrit elevated due to dehydration
  - Leukocytosis
- **Glucose tolerance test:** An abnormal Oral Glucose Tolerance Test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dl.

Management

- Primary prevention:
  - Prolong breastfeeding
  - Delay cow's milk introduction
  - Delay cereal introduction
- The goals of chronic management include:
  - Adequate nutrition for normal growth and development and an active life
  - Exogenous insulin sufficient to avoid acute clinical manifestations
  - Metabolic control sufficient to minimize long-term complications

Insulin replacement

- The usual insulin-dependent child requires 0.75–1.0 U/kg of insulin daily subcutaneously when the diabetes is fully developed.

- However, during first few months of the disease, the requirement may be less than 0.5 U/kg/day, especially during the 'honeymoon' or remission phase of IDDM.
- The total daily dose is divided between short-acting regular insulin (1/3rd of total dose) and intermediate acting (NPH) insulin (2/3rd of total daily dose).
- It is conventional to give two-thirds of the daily dose before breakfast and one-third before the evening meal.
- Lispro and aspart insulin analog can give better control.
- Insulin pump can be used to give s/c (subcutaneous) insulin and simultaneously monitoring blood sugar levels. Inhaled insulin is also being developed.
- Further adjustment of the dosage is done on results of blood or urine sugar.
- The goal of treatment is to maintain fasting blood sugar between 80–120 mg/dl and post-prandial blood glucose less than 200 mg/dl.
- Oral hypoglycemic agents can be used in type 2 DM.

Diet

- Diet is a cornerstone of diabetes management.
- Children with IDDM require a nutritionally balanced diet with adequate calories and nutrients for normal growth.
- The recommended diet should contain 55% carbohydrate calories, 15% protein, and 30% fat. Mostly carbohydrate calories are complex carbohydrates, and the fat portion should contain low levels of cholesterol and saturated fats.
- Timing of meals and snacks should be to minimize blood glucose variability. Bedtime snacks are important for most children receiving evening NPH doses.
- Diet should be adjusted from the household diet. Avoid refined sugars and give more food with higher fiber content.

Exercise

- Children with IDDM should be encouraged to exercise regularly.
- Regular aerobic exercise at least 25 minutes a day is needed.
- With exercise, insulin requirements are lowered, and metabolic control is improved.
- During exercise, extra calories or lower insulin doses may be needed to prevent hypoglycemia.

Patient/parents education

- Children with IDDM and their families should be taught the principles of home management.
- This training should include:
  - The pathophysiology of diabetes in lay language
  - Insulin types, action, and storage
  - The techniques and timing of insulin injection
  - Home blood glucose monitoring
  - Dietary information
  - The recognition and treatment of hypoglycemia and hyperglycemia
  - Urinary ketone checks
  - Management of diabetes during intercurrent illness
- Education must be appropriate to the child's age and the family's educational background, and it must be ongoing, as the child grows older.

Monitoring

- Blood glucose is monitored:
  - Before meals
  - Before snacks (midmorning, midafternoon, bedtime)
  - In the middle of the night at approximately 3:00 a.m. (the anticipated lowest night-time point), if evening NPH is used
- Two to four recorded readings a day usually provide enough information to assess and achieve control.
- During a period of metabolic instability (during infection or fever, etc), more frequent monitoring is necessary.
- Fasting and pre-prandial blood glucose readings in the 70–150 mg/dl range, post-prandial levels below 180–200 mg/dl, and 3:00 a.m. values above 65 mg/dl indicate good control.
- Doses of regular insulin can be changed using a sliding scale when a specific blood glucose level is outside the target range.

Table 19.1: Sliding Scale of Insulin.

Blood glucose level	*Required insulin*
<60 mg/dl	No insulin needed
60–90 mg/dl	0.1 U/kg/dose
90–180 mg/dl	0.2 U/kg/dose
180–270 mg/dl	0.3 U/kg/dose
270–360 mg/dl	0.4 U/kg/dose
>360 mg/dl	0.5 U/kg/dose

- The **measurement of $HbA1_c$ levels** is also helpful in diabetes monitoring. It represents the fraction of hemoglobin to which glucose has been non-enzymatically attached in the bloodstream. Its measurement reflects the average blood glucose concentration of the preceding 2–3 months.
  - The upper limit of normal is 6.5%.
  - **Intensive control** of diabetes mellitus is indicated by $HbA1_c$ level below 6.5%.
- Urine sugar can be checked by **Benedict's test**. 5 ml of Benedict's reagent is taken in a test tube and 8 drops of urine are added. Boil it for 2 minutes and observe

for the color change. Results on the basis of color changes are given below:

Table 19.2: Benedict's test.

Light green: <0.5 gm% glucose concentration Green precipitate: 0.5–1.0 gm % glucose concentration Yellow precipitate: 1–2 gm % glucose concentration Red precipitate: >2 gm % glucose concentration

- Urinary ketones should also be monitored, particularly when:
  - The blood glucose levels are above 250 mg/dl.
  - There is fever.
  - There is nausea or vomiting.
  - Child is not feeling well.
- This will detect and prevent diabetic ketoacidosis.

Follow-up

- The main steps to be checked in the follow up clinic are:
  - Growth
  - Blood pressure
  - School progress
  - Dietary compliance
  - HbA_{1c} level
  - Joint mobility
  - Fundus examination
  - Thyroid function tests
  - Injection sites

Complications

- **Brittle diabetes:**
  - Marked fluctuation in control of blood glucose, hypoglycemia or hyperglycemia and ketoacidosis despite frequent adjustment of the dose of insulin.
- **Hypoglycemia:**
  - It is a major and common complication of insulin therapy.
  - Hypoglycemia (insulin reaction) is defined as a blood glucose level below 60 mg/dl.
  - It is characterized by behavior changes, weakness, pallor, diplopia, sweating, nausea, vomiting, tachycardia, palpitations, hunger, abdominal discomfort, disorientation, confusion, dizziness, anxiety or tremors and may progress to convulsions and coma.
  - In severe hypoglycemia, give injection glucagon IM (0.3 mg), or 10% glucose IV (1 ml/kg).
- **Hyperosmolar diabetic coma:**
  - This is characterized by severe hyperglycemia (blood glucose greater than 600 mg/dl), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma.
  - There may be neurologic signs (seizures, hemiparesis, etc).
- Diabetic ketoacidosis
- **Peripheral neuritis:** Neuropathy
- **Nephropathy:** Progressive renal failure
- **Retinopathy and blindness**
- **Vasculopathy**
- Hypertension
- Atherosclerosis
- **Infections:** Boils, abscesses, moniliasis, and urinary infection
- **Lipoatrophy**
- **Growth retardation and emotional problems**
- **Somogyi phenomenon:**
  - There is early morning hyperglycemia from mid-night hypoglycemia due to excess insulin, and counter-regulatory hormones effect.
- **Dawn phenomenon:**
  - There is early morning hyperglycemia without hypoglycemia due to growth hormone secretion and increased insulin clearance.

Prognosis

- Long-term complications are retinopathy, nephropathy, neuropathy, and macrovascular disease.
- These problems usually occur after 10–15 years of initiation of disease process.
- Some degree of retinopathy is present in nearly 100% of patients with IDDM.
- Macrovascular disease leads to an increased risk of myocardial infarction and stroke.
- Administration of small doses of insulin to at risk individuals for IDDM may delay or prevent the onset of diabetes.

ACUTE DIABETIC KETOACIDOSIS (DKA)

CASE

A 5-year-old boy presents with ***weight loss*** over the previous 2 weeks and night time ***enuresis***. He is increasingly ***confused*** for the last several hours. His breath smelled fruity. On examination, blood pressure is 90/60 mmHg and heart rate 130 beats per minute. ***Mucous membranes*** are ***dry*** and ***respiration*** is ***rapid*** and ***deep*** (Kussmaul breathing). ***Blood glucose*** is ***550 mg/dL***.

Definition

- DKA can be defined as a:
  - Blood glucose level usually greater than 250 mg/dl
  - pH less than 7.25
  - Plasma bicarbonate level of 15mEq/l or less

- Severe DKA is defined as a pH of 7.1 or less and a bicarbonate level of 10 mEq/l or less.
- DKA is a common and potentially life-threatening, acute complication of IDDM. Mortality rates may be as high as 6–10%.

Precipitating factors

DKA may be precipitated in a known diabetic patient by:

- An acute infection
- Omission of insulin dose

Management

The basic steps in the treatment of DKA are:

1. Fluid and electrolyte replacement (especially potassium)
2. Insulin administration

Fluid replacement

- Dehydration is present in nearly all patients with DKA.
- Water and electrolyte losses are mainly due to polyuria (osmotic diuresis by glucosuria), hyperventilation, vomiting, and diarrhea.
- Most patients with DKA are 5% to 10% dehydrated.
- As soon as the diagnosis of DKA is established, adequate IV fluid replacement is given.
- Normal saline or Ringer's lactate are given initially because they are isotonic solutions and restore the intravascular volume and maintain blood pressure and kidney perfusion. This enhances the glucose loss through the kidney and results in a lower blood glucose level.
- Fluid deficit = 100 ml x W_t (kg)
- Fluid required = Fluid deficit + Maintenance fluid
- Always assume that child is 10% dehydrated (needs 100 ml/kg fluid).
- Give maintenance fluid as given in the table.

Table 19.3: Body weight with its fluid maintenance requirements.

Body weight (kg)	*Fluid maintenance requirements*
Up to 10	100 ml/kg
10–20	1000 ml + 50 ml/kg over 10 kg
>20	1500 ml + 20 ml/kg over 20 kg

For example, a 10 kg child with DKA presents with 10% dehydration.

Fluid deficit = 100 × 10 = 1000 ml

Maintenance fluid = 100 × 10 = 1000 ml

Fluid needed for replacement = 1000 + 1000 = 2000 ml

Insulin therapy

- Insulin should be given as a continuous IV infusion.
- The usual recommended dose is 0.1 U/kg/hour.
- Fluids used for making insulin infusion should be deducted from total fluids for replacement.
- The insulin infusion is given separately from the replacement fluids so the rates can be adjusted independently.

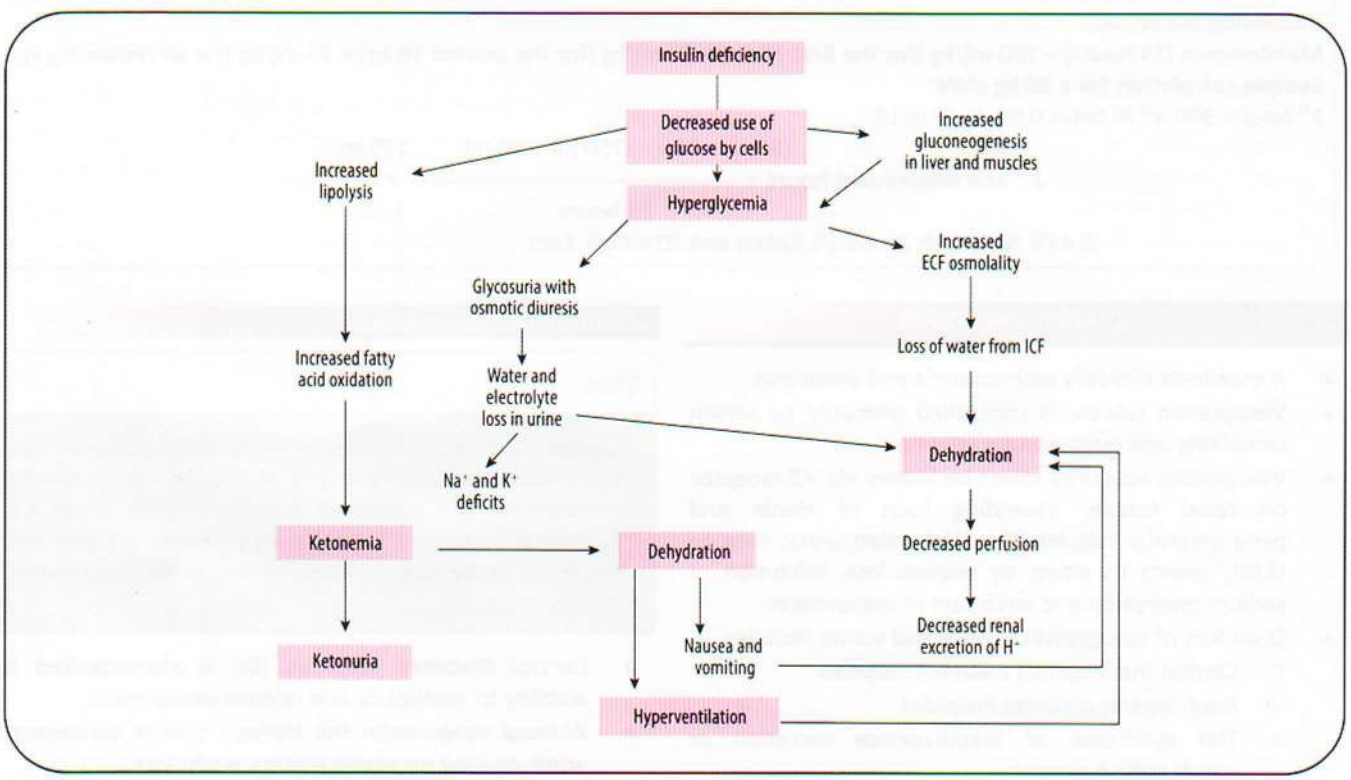


Figure 19.8 Pathogenesis of DKA.

- If the blood glucose level decreases to 250 mg/dl and acidosis persists, glucose is given as 5% dextrose and may be increased to 10% dextrose to keep the blood glucose approx 250 mg/dl.
- Measure glucose every hour; electrolytes and acid-base every 2–4 hours for the first 24 hours.

Bicarbonate

- Bicarbonate is given when there is severe acidosis (pH <7.0–7.1) causing respiratory or cardiac disturbances.
- Bicarbonate is given to raise pH to 7.2 in a dose of 1–2 mEq/kg over 2 hours.

Treatment of infection

- Appropriate antibiotics are given to control any infection.

Converting to subcutaneous insulin

- Change to subcutaneous injection should only be carried out when:
  - Patient is conscious and taking orally.
  - There is no evidence of metabolic acidosis.
  - Blood sugar level is 180–240 mg/dl.
  - Any identified precipitating factor (e.g. infection) should have been treated.
- Dose of subcutaneous insulin may be adjusted by sliding scale method.

Table 19.4: Diabetic ketoacidosis treatment protocol.

Time	Therapy	Comments
1st hr	10.20 ml/kg IV bolus 0.9% NaCl or LR insulin drip at 0.05 to 0.10 units/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral
2nd hours until DKA	0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar >250 mg/dL (14 mmol/L)	$\text{IV rate} = \frac{\text{85 ml/kg+maintenance-bolus infusion}}{\text{23 hour}}$ If K <3 mEq/L, give 0.5–1.0 mEq/kg as oral K solution or increase IV K to 80 mEq/L
Variable	Oral intake with subcutaneous insulin	No emesis; CO_2 ≥16 mEq/L; normal electrolytes

Note that the initial IV bolus is considered part of the total fluid allowed in the first 24 hours and is subtracted before calculating the IV rate.

Maintenance (24 hours) = 100 ml/kg (for the first 10 kg) + 50 ml/kg (for the second 10 kg) + 25 ml/kg (for all remaining kg)

Sample calculation for a 30 kg child:

1st hour = 300 ml IV bolus 0.9% NaCl or LR

$$\text{2nd and subsequent hours} = \frac{(85 \text{ ml} \times 30) + 1750 \text{ ml} - 300 \text{ ml}}{23 \text{ hours}} = \frac{175 \text{ ml}}{\text{hour}}$$

(0.45% NaCl with 20 mEq/L Kphos and 20 mEq/L Kac)

DIABETES INSIPIDUS

- It manifests clinically with polyuria and polydipsia.
- Vasopressin release is controlled primarily by serum osmolality and intravascular volume.
- Vasopressin exerts its effect on kidney via V2 receptor on renal tubule, ascending loop of Henle and periglomerular tubules. The 'Atrial Natriuretic Peptide (ANP)' exerts its effect by sodium loss, inhibition of sodium resorption and inhibition of vasopressin.
- Disorders of vasopressin release and action include:
  - Central (neurogenic) diabetes insipidus
  - Nephrogenic diabetes insipidus
  - The syndrome of inappropriate secretion of antidiuretic hormone

Central diabetes insipidus

CASE

Central diabetes insipidus: A 10-year-old boy presents with ***excessive urination*** and thirst. ***No other family member*** has this complaint. A urine analysis shows no glucose and ketones. ***Urine specific gravity*** is ***1.005***. He improves (***urine concentrates***) when parenteral ***DDAVP*** is administered.

- Central Diabetes Insipidus (DI) is characterized by inability to synthesize and release vasopressin.
- Without vasopressin the kidneys cannot concentrate urine, causing excessive urinary water loss.