Endocrine system

Pediatric

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Diabetes Mellitus

Introduction and Classification

Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature.

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

- Type I diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

Immune mediated, Idiopathic

- Type 2 diabetes (may range from predominantly insulin resistance with relative

insulin deficiency to a predominantly secretory defect with insulin resistance) Dominant, type 2 due to sulfonylurea receptor 1 mutation.

- Other specific types

Genetic defects of β-cell function Chromosome 20, HNF-4α (MODY1) Chromosome 7, glucokinase (MODY2) Chromosome 12, HNF-1α (MODY3) Insulin promotor factor–1 (MODY4) HNF-1β (MODY5) NEUROD1 (MODY6)

Genetic defects in insulin action

Type A insulin resistance, Lipoatrophic diabetes

Gestational diabetes mellitus Neonatal diabetes mellitus Transient—without recurrence Transient—recurrence 7–20 yr later Permanent from onset

Diseases of the exocrine pancreas

Pancreatitis, Trauma, pancreatectomy, Neoplasia, Cystic fibrosis , Hemochromatosis

Endocrinopathies

Acromegaly, Cushing disease, Pheochromocytoma, Hyperthyroidism

Drug-or chemical-induced

Pentamidine, Nicotinic acid, Glucocorticoids, Thyroid hormone, Diazoxide, β-Adrenergic

agonists, Thiazides, β-Interferon, cyclosporine

Infections

Congenital rubella, Cytomegalovirus

Other genetic syndromes sometimes associated with diabetes

Down syndrome, Klinefelter syndrome, Turner syndrome,, Friedreich ataxia

Huntington chorea, Laurence-Moon-Biedl syndrome,, and Prader-Willi syndrome

Type 1 DM

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,"

(4) Established diabetes associated with acute and chronic complications and decreased life expectancy.

Epidemiology

sex & socioeconomic status :

Girls and boys are almost equally affected; there is no apparent correlation with socioeconomic status.

Age at onset : Peaks of presentation occur in 2 age groups:

The 1st peak (at 5–7 years of age) may correspond to the time of increased exposure to infectious agents coincident with the beginning of school;

the 2nd peak (at the time of puberty) may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal

A growing number of cases are presenting between 1 and 2 years of age.??

cow's milk & initial exposure of infants to cereals before 4 months of age has been suggested to increase the risk of islet cell autoimmunity

Inheritance of HLA-DR3 or -DR4 antigens appears to confer a 2- to 3-fold increased risk for the development of T1DM.

When both DR3 and DR4 are inherited, the relative risk for the development of diabetes is increased by 7- to 10-fold.

Inheritance of HLA-DR2 appear to be protective against diabetes.

Autoimmune Injury:

• T1DM is a chronic, T cell–mediated autoimmune disease that results in the destruction of the pancreatic islets.

• Genetic predisposition and environmental factors lead to initiation of an autoimmune process against the pancreatic islets which leads to a gradual and progressive destruction of β cells, with loss of insulin secretion.

• at the onset of clinical diabetes, 80–90% of the pancreatic islets are destroyed.

• Regeneration of new islets has been detected at onset of T1DM, and it is thought to be responsible for the honeymoon phase (a transient decrease in insulin requirement associated with improved β-cell function).

• In young diabetic children, especially those of DR3/DR4 haplotypes, the destruction of β cells is almost complete during the 1st 3yr after the onset of hyperglycemia, whereas in older patients complete β- cell destruction may take up to 10 yr.

• most individuals progressing to overt diabetes express multiple anti– islet cell antibodies (GAD65, ICA512/IA-2, and IAA) before the onset of diabetes.

• 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.

These hormones, in turn, contribute to the metabolic decompensation:

by further impairing insulin secretion (epinephrine),

by antagonizing insulin action (epinephrine, cortisol, GH),

by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol)

by decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

• 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.

• With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

Clinical presentations:

1. Classical presentation: (60-80%) polyuria, polydipsia, polyphagia and Wt. loss.
2. Diabetic ketoacidosis (DKA): (20–40%)

abdominal discomfort, nausea, vomiting, sever dehydration with persistent polyuria (the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume).

Ketoacidosis exacerbates prior symptoms & leads to Kussmaul respirations (deep, heavy, rapid breathing), fruity breath odor (acetone), diminished neurocognitive function, and possible coma.

Others : candidal vaginitis, secondary enuresis.

DIABETES MELLITUS (DM) diagnosis :

Symptoms of DM plus

Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L)

Symptoms of DM plus

random plasma glucose ≥200 mg/dL (11.1 mmol/L) Or

2 hr plasma glucose during the OGTT ≥200 mg/dL

A baseline hemoglobin A1C (HbA1c) allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy.

Other autoimmunities associated with type 1 diabetes should be checked for including:

celiac disease (by tissue transglutaminase IgA and total IgA) autoimmune thyroiditis (by antithyroid peroxidase and antithyroglobulin antibodies).

Because significant physiologic distress can disrupt the pituitary-thyroid axis, free thyroxine (T4) and TSH levels should be checked after the child is stable for a few weeks.

DKA may be classified as mild, moderate, or severe and the range of symptoms depends on the depth of ketoacidosis.

Excellent diabetes control involves many goals:

1. to maintain a balance between tight glucose control and avoiding hypoglycemia,
2. to eliminate polyuria and nocturia,
3. to prevent ketoacidosis,
4. to permit normal growth and development with minimal effect on lifestyle. Insulin Therapy

Insulin Preparations

Type of Insulin	Onset	Peak Action	Duration
	VERY SHORT-ACTING		
Lispro, aspart	10-20 min	30-90 min	3 hr
	SHORT-ACTING		
Regular	30 min-hr	2-4 hr	6-10 hr
	INTERMEDIATE-ACTING		
NPH	1-4 hr	4-12 hr	16-24 hr
Lente	1-4 hr	4-12 hr	12-24 hr
	LONG-ACTING		
Protamine ziZinc	4-6 hr	8-20 hr	24-30 hr
Ultralente	4-6 hr	8-20 hr	24-36 hr
Glargine	1-2 hr	No peak	24-30 hr

 Types of insulin and their regimens used are: Actrapid (soluble) , monotard (lente), & mixtard.

1. Two doses regimen (actrapid 1/3 and monotard 2/3) or mixtard only with 2/3 of the daily dose in the morning and 1/3 in the evening, (sometimes we personalize the dose and the % of the combination).

 However, such a schedule would provide poor coverage for lunch and early morning, and would increase the risk of hypoglycemia at midmorning and early night.

2. Basal bolus regimen

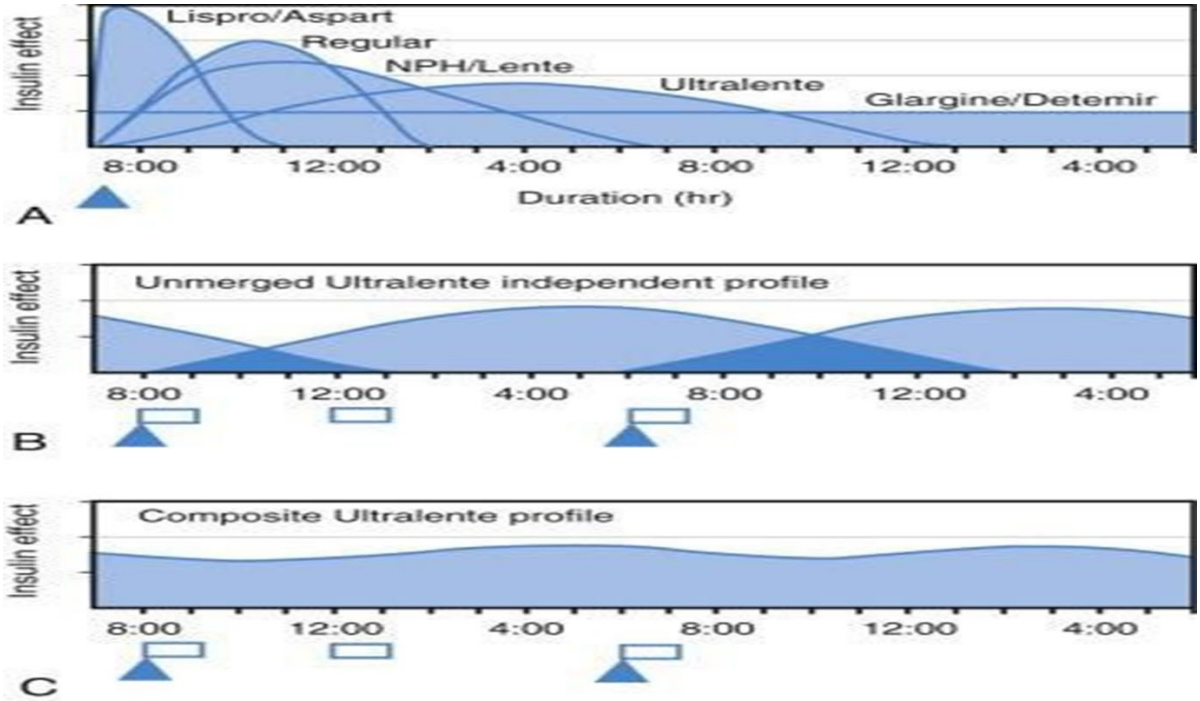
 insulin analogs (Lispro (L) and aspart) which are absorbed much quicker because they do not form hexamers. their action started within 10 minutes with duration of action of 2 hours without peak.

 The long-acting analog glargine (G) creates a much flatter 24-hr profile, making it easier to predict the combined effect of a rapid bolus (L or A) on top of the basal insulin, producing a more physiologic pattern of insulin effect.

 The basal insulin glargine should be 25–30% of the total dose in toddlers

and 40–50% in older children. The remaining portion of the total daily dose is divided evenly as bolus injections for the 3 meals .

 Postprandial glucose elevations are better controlled, and between-meal and night time hypoglycemia are reduced.



- Insulin Pump Therapy : increased use now aday ,and it needs dialy calibration and determination of the insulin dose according to the diet and exersice…….etc
- Inhaled Insulin:

Pre prandial inhaled insulin is being evaluated in adults with T1DM and T2DM (no more use because of pulmonary fibrosis)

- Pre-meal oral insulin (Oralin) has been evaluated in comparison with oral

hypoglycemic agents, mostly in patients with T2DM.

The clinical data appear promising, but further evaluation of efficacy in T1DM is needed

New recommendation regarding starting dose of insulin (unit /kg/ day) as in the table below:

Starting Doses of Insulin (units/kg/day)

NO DIABETIC KETOACIDOSIS

0.25 0.50 U/kg/day prepubertal

0.50 0.75 U/kg/day at puberty

0.25 0.50 U/kg/day post puberty

DIABETIC KETOACIDOSIS (previous attack)

0.8 1.0 U/kg/day prepubertal

1.0 1.2 U/kg/day at puberty may reach 2U kg /day WHY ??

0.8 1.0 U/kg/day post puberty

Management of diabetic Ketoacidosis

DKA is the end result of T 1 DM characterized by:

1.Hyperglycemia serum glucose concentrations ranging from 200 mg/dL to greater than 1000 mg/dL

2.The arterial pH 7 25

3.The serum bicarbonate level 15 mEq/L

4.ketones are elevated in serum or urine

- Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema.so any protocol must be used with caution and close monitoring of the patient

Hyperglycemia and Dehydration:

Insulin (0.1 unit/ kg/ hour) IV must be given at the beginning of therapy to accelerate movement of glucose into cells, to stop hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver.

Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion.

- Repair of hyperglycemia occurs well before correction of acidosis. Therefore, insulin is still needed to control fatty acid release after normal glucose levels are reached.
- To continue the insulin infusion without causing hypoglycemia, glucose must be added to the infusion, usually as a 5% solution.

Glucose should be added when the serum glucose has decreased to about 250 mg/dL (14 mmol/L)

The insulin infusion can also be lowered (0.02–0.05 units/kg/h) from the initial maximal rate once hyperglycemia has resolved.

During repair of fluid deficits we must take in consideration the potential risk of cerebral edema.

Potassium can be added to the IV fluid infusion after ensuring urine output in a dose ranging from 20 – 40 meq / L and sometimes may reach 60 meq / L.

Mildly elevated creatinine or BUN is not a reason to withhold potassium therapy if good urinary output is present.

Bicarbonate therapy is rarely necessary and may even increase the risk of hypokalemia and cerebral edema.

(only indicated in case of sever acidosis , ie :when the blood PH < 7.1)

Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis.

Urine ketones may be positive long after ketoacidosis has resolved…

Manegmant of cerebral edema

- cerebral odema :checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, and seizures.

-Mannitol 10% (10gm /100ml) 10 cc /kg

-dexamethasone 0.3 mg/kg

-hyperventilation

Management of DKA

1. Admission to the emergency unit.
2. ABC if the patient is comatosed and O2 to be delivered via mask.
3. IV LINE and Aspiration of blood for RBS, B.urea, S.Cr, S.K, S.Na, S.Cl,,CBP, B.C/S ,ASTRUP
4. Urine for ketone, sugar, pus cell.
5. Calculation of the deficit and maintenance of the fluids ; to be replaced over 36- 48 hours (hyperosmotic dehydration)

Oral fluid is stopped and only sucking of chips of ice is allowed .

IV fluid (0.9%N/S or RL bolus 10 - 20ml / kg /1st hour) and then rate of fluid replacement from the 2nd hour till resolution of DKA calculated according to the following formula :

(85× Bwt + maintenance – bolus / 23 hours= rate / hour).

Change the type of the fluid from N/S to 5% GW or G/S (,1/3,1/5) when RBS is less than 250 mg/dl.

6 KCl: the patient is hypokalemic even if S.K was normal .WHY? 20 - 40 meq/L (1 ml = 2 meq) and sometimes increased to 60 meq/L .

7. INSULIN : either IV continuous infusion via a separate IV line started at time zero OR interrupted IM or IV dose started after one hour (the dose in both ways is 0.1 unit /kg/h)

Changed to SC insulin and start oral fluid when there are no emesis, or acidosis with normal electrolytes.

8. Sod. Bicarbonate : only used in sever acidosis (PH less than 7.1) in a dose of 20-40 meq (1 ml = 1 meq) with the fluid. WHY? (Cerebral odema)

9. Mannitol :10% if signs of cerebral oedema appear in a dose of 1gm / kg IV infusion.
10. Antibiotic : if infection is present.
11. checking for the initiating events should be done and treated & avoid to be repeated

Preperation of insulin infusion

- put 50 unit of soluble (actrapid) insulin in one pint (500 cc) NS = 0.1 u/cc & use EVAC to control the rate of infusion OR

use micro-drip (burette) & put 10 unit of soluble insulin for every 100 cc NS.

- In either ways you must flush 1cc/ Kg rapidly to saturate the insulin receptors & then the rate will be:

1CC /Kg /hour= 60 micro drops /kg /60 min. = one micro drop /kg/min.

The rate should be reduced to 1/2 if RBS is below 150 mg/dl

NEVER FORGET THE FLOW SHEET FOR DIABETIC KETOACIDOSIS

(name, age, date, time, BWt & SA, PR, BP,PH, RBS , S.electrolyte, Fluid

input, output, insulin dose, signs of cerebral oedema, and notes).

Nutritional Management

- Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate dietary intake is required to meet the needs for energy, growth, and pubertal development.

- The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein.

- Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited.

- Carbohydrate counting has become a mainstay in the nutrition education and management of patients with DM.

Each carbohydrate exchange unit (need one unit of insulin) is variable and must be calculated for each patient but roughly it is about 15 g of CHO.

The total daily caloric intake is divided to provide 20% at breakfast, 20% at lunch, and 30% at dinner, leaving 10% for each of the midmorning, midafternoon, and evening snacks.

Monitoring

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, and records the results and other notes in special notebook to be reviewed with doctor during follow up visit.

(Ideally, the blood glucose concentration should range from approximately 80 mg/dL in the fasting state to 140 mg/dL after meals)

HbA1C represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream.

HbA1C measurement reflects the average blood glucose concentration from the preceding 2–3 mo. It is recommended that HbA1C measurements be obtained 3 to 4 times per year to obtain a profile of long-term glycemic control. the HbA1C fraction:

in nondiabetic individuals, is usually less than 6%.

in diabetics:

values of 6–7.9% represent good metabolic control, values of 8.0–9.9%, fair control,

values of 10.0% or higher, poor control.

Exercise:

- No form of exercise, including competitive sports, should be forbidden to the diabetic child.
- A major complication of exercise in diabetic patients is the presence of a hypoglycemic reaction during or within hours after exercise.

glucoregulation is likely to be improved through the increased utilization of glucose by muscles.

The major contributing factor to hypoglycemia with exercise is an increased rate of absorption of insulin from its injection site and increasing insulin receptor number.

In anticipation of vigorous exercise, one additional carbohydrate exchange may be taken before exercise, or the total dose of insulin may be reduced by about 10–15% on the day of the scheduled exercise.

Management During Infections:

Frequent blood glucose monitoring and adjustment of insulin doses are essential elements of sick day guidelines.

One regimen is to add 10 -20% of the total daily dose as actrapid before each meal in addition to the usual daily dose if hyperglycemia developed (two doses daily regimen).

*Hypoglycemic Reactions:

Hypoglycemia is the major limitation to tight control of glucose levels.

These episodes are usually not predictable, although exercise, delayed meals or snacks, wrong dose and wide swings in glucose levels increase the risk.

Hypoglycemia can occur at any time of day or night.

- Early symptoms and signs :The child may show pallor, sweating, apprehension , hunger, tremor, and tachycardia, all due to the surge in catecholamines as the body attempts to counter the excessive insulin effect. Also, irritability, and aggression are more prevalent in children.

THEN cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia),

progressing to inability to seek help and seizures or coma (severe hypoglycemia).

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Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia.

In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy.

Management

- It is important not to give too much glucose; 5–10 g should be given as juice or a sugar-containing carbonated beverage or candy and the blood glucose checked 15–20 minutes later.

- Patients, parents, and teachers should also be instructed in the administration of glucagon when the child cannot take glucose orally.

An injection kit should be kept at home and school.

The intramuscular dose is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg.

Somogyi Phenomenon, Dawn Phenomenon, and Brittle Diabetes:

In both dawn and somogyi phenomena , there is increase in blood glucose levels with ketosis in the early morning hours before breakfast.

 The **dawn phenomeno**n is thought to be due mainly to overnight growth hormone secretion and increased insulin clearance.

It is a normal physiologic process seen in most non diabetic adolescents, who compensate with more insulin output.

A child with T1DM cannot compensate so we need to increase the evening lente insulin.

 the **Somogyi phenomenon**, a theoretical rebound from late night or early morning hypoglycemia, thought to be due to an exaggerated counter-regulatory response.

so we need to decrease the evening insulin dose.

Continuous glucose monitoring systems may help clarify the cause of the elevated morning glucose levels.

 The term **brittle diabetes** has been used to describe the child, usually an adolescent female, with unexplained wide fluctuations in blood glucose, often with recurrent DKA, who is taking large doses of insulin (no physiological abnormality but usually psychological cause)

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;

(3) neuropathies

Maturity-Onset Diabetes of Youth (MODY)

❖ **Background (AD)**

· MODY is the most common form of monogenic diabetes

· The genes involved control the pancreatic beta cell development, function, and regulation, hence leading to defects in glucose sensing and insulin secretion

· Onset is usually before 25 years of age

❖ **Types**

· MODY 1‑MODY 6 are the most common identified gene mutations, with MODY 3 (hepatocyte nuclear factor-1 alpha = *HNF1A*) being the most common, representing about 50% of monogenic diabetes cases

❖ **Diagnosis**

· Suspect in individuals with the following characteristics:

· Diagnosis before 25 years of age

· AD pattern of inheritance of diabetes (> 2 generations affected)

· Non-obese (usually)

· Negative islet antibodies (markers of type 1 DM)

· Genetic testing is readily available

❖ **Treatment :** · MODY 4‑6 is treated with insulin , · MODY 1 and MODY 3 are treated with sulfonylureas, · MODY 2 is treated with diet and exercise but may require insulin during illness or pregnancy

Hypothyroidism

results from deficient production of thyroid hormone or a defect in thyroid hormone receptor activity . The disorder may be congenital or acquired.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism result from thyroid dysgenesis. Some cases may be familial, usually caused by one of the inborn errors of thyroid hormone synthesis, and may be associated with a goiter.

EPIDEMIOLOGY.

The prevalence of congenital hypothyroidism based on neonatal screening is 1/4,000 infants . male : female = 1:2

AETIOLOGY

Thyroid Dysgenesis. (aplasia, hypoplasia, or an ectopic gland) is the most common cause of congenital hypothyroidism, accounting for 85% of cases;

10% are caused by an inborn error of thyroxine synthesis, and 5% are the result of transplacental maternal thyrotropin-receptor blocking antibody (TRBAb).

CLINICAL MANIFESTATIONS.

asymptomatic at birth due to the transplacental passage of moderate amounts of maternal T4, which provides fetal levels that are approximately 33% of normal at birth.

These low serum levels of T4 and concomitantly elevated levels of TSH make it possible to screen and detect hypothyroid neonates.

The clinician is dependent on neonatal screening tests for the diagnosis of congenital hypothyroidism. Laboratory errors occur, however, and awareness of early symptoms and signs must be maintained.

Birthweight and length are normal, but head size may be slightly increased because of myxedema of the brain.

Prolongation of physiologic jaundice.

Feeding difficulties, especially sluggishness, lack of interest, and choking spells during feeding, are often present during the 1st month of life.

Respiratory difficulties, due in part to the large tongue, include apneic episodes, noisy respirations, and nasal obstruction.

Affected infants cry little, sleep much, have poor appetites, and are generally sluggish.

constipation

umbilical hernia.

temperature is subnormal, often less than 35°C (95°F), and the skin, particularly that of the extremities, may be cold and mottled.

Edema of the genitals and extremities may be present.

The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common.

Macrocytic anemia is often present and is refractory to treatment with hematinics.’’’’’’

Approximately 10% of infants with congenital hypothyroidism had associated congenital anomalies: Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported.

If congenital hypothyroidism goes undetected and untreated, these manifestations progress, Retardation of physical and mental development becomes greater during the following months, and by 3–6 months of age the clinical picture is fully developed.

The child's growth will be stunted, the extremities are short, and the head size is normal or even increased. Disproportional growth

The anterior and posterior fontanels are open widely; observation of this sign at birth may serve as an initial clue to the early recognition of congenital hypothyroidism.

The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition will be delayed.

The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders (buffalo hump).

The skin is dry and scaly, and there is little perspiration. Myxedema is manifested, particularly in the skin of the eyelids, the back of the hands, and the external genitals. The skin shows general pallor.

Carotenemia may cause a yellow discoloration of the skin, but the sclera remain white. The hairline reaches far down on the forehead, which usually appears wrinkled,especially when the infant cries.

Development is usually retarded. Hypothyroid infants appear lethargic and are late in

learning to sit and stand.

The voice is hoarse, and they do not learn to talk.

The degree of physical and mental retardation increases with age. Sexual maturation may be delayed.

LABORATORY FINDINGS.

Most newborn screening programs measure levels of T4, followed by measurement of TSH when T4 is low (USA).

Regardless of the approach used for screening, some infants escape detection because of technical or human errors;

Serum levels of T4 or free T4 are low; serum levels of T3 may be normal and are not helpful in the diagnosis.

If the defect is primarily in the thyroid, levels of TSH are elevated, often to greater than 100 mU/L.

Serum levels of prolactin are elevated, correlating with those of TSH..

Retardation of osseous development can be shown radiographically at birth in about 60% of congenitally hypothyroid infants and indicates some deprivation of thyroid hormone during intrauterine life.

The distal femoral epiphysis, normally present at birth, is often absent(knee xray)

In undetected and untreated patients, the discrepancy between chronological age

and bone age increases.

U/S examination of the thyroid is helpful, but studies show it may miss some ectopic glands shown by thyroid scan.

123I-sodium iodide is superior to 99mTc-sodium pertechnetate for this purpose.

The ECG may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion.

In children older than 2 yr of age, the serum cholesterol level is usually elevated.

Treatment of hypothyroidism by

· Replacement therapy with L-thyroxine to maintain to serum T4 > upper half of normal range:

· **Dose: -**

o 0 to 3 months →10 -15 mcg/kg/d

o 3 to 12 months → 6 - 10 mcg/kg/d

o 1 to 3years → 4 - 6 mcg/kg/d

o 3 to 10 years → 3-5 mcg/ kg/ d

· **Dose is adjusted according to clinical response:**

o **Overdose:** diarrhoea, fever, **tachycardia,** increased appetite

o **Low dose:** constipation, hypothermia., bradycardia, decreased appetite

· **Follow up: -**

o Clinical: monitor activity, milestones & growth.

o Laboratory: monitor T4 and TSH.

o Radiologic: monitor bone age

❖ **Prognosis**

· Early detection and treatment before 3 months → good mentality.

· Delayed detection and treatment at 3-6 months → variable response.

· Delayed detection and treatment after 6 months → permanent mental retardation.

* HYPERTHYROIDISM:

Graves Disease

Most children with hyperthyroidism have Graves disease, the autonomous functioning of the thyroid caused by auto antibodies[thyroid stimulating immunoglobulin's (TSIs)] stimulating the thyroid.

Hashimoto thyroiditis and thyrotoxicosis are on a continuum of autoimmune diseases; there is overlap in their immunologic findings.

Antithyroid peroxidase and antithyroglobulin antibodies may be present in thyrotoxicosis, although the values are usually lower than in Hashimoto thyroiditis.

Exceptionally high titers of antibodies may indicate the thyrotoxic phase of Hashimoto thyroiditis with the subsequent evolution toward permanent hypothyroidism.

In Graves disease, serum free T4 or T3 or both levels are elevated, whereas TSH is suppressed.

Rare causes of hyperthyroidism include McCune-Albright syndrome, thyroid nodule (often an adenoma), TSH hyper secretion, sub acute thyroiditis, and iodine or thyroid hormone ingestion.

Clinical manifestations: Graves disease presents as hyperthyroidism and is about five times more common in girls than in boys, with a peak incidence in adolescence.

Personality changes, mood instability, and poor school performance are common initial problems.

Short stature

Definition: means height ≤ 2 standard deviations below mean height for children of the same age, sex, and ethnicity (below 3rd percentile)

❖ Types and causes of short stature:

1. Proportionate short stature: which is Characterized by the upper segment/lower segment and the height to span is normal for age.

Classification

Normal variant short stature

• Constitutional delay of growth and puberty (CDGP)

• Familial short stature

• Idiopathic short stature

Pathological short stature

• Chronic disease

o Gastrointestinal (celiac. Crohn disease, cystic fibrosis)

o Cardiac (severe congenital heart defects)

o Pulmonary (cystic fibrosis, asthma on chronic steroids)

o Renal (chronic renal insufficiency. Fanconi syndrome)

• **Endocrine disorders**

o Hypothyroidism

o Cushing syndrome

o Growth hormone deficiency or insensitivity

o Poorly controlled type 1 diabetes mellitus (Mauriac syndrome)

o Pseudohypoparathyroidism (Albright hereditary osteodystrophy)

• Chronic undernutrition

• **Genetic syndromes** (e.g., Turner, Noonan, Russell-Silver, Prader-Willi syndromes)

• Psychosocial growth retardation.

3. Disproportionate short stature:

Characterized by the upper segment/lower segment is abnormal for age and the height is not equal the span.

The ratio of upper body segment divided by lower body segment (U/L ratio) equals approximately 1.7 at birth, 1.3 at 3 years of age, and 1.0 after 7 years of age.

Higher U/L ratios are characteristic of shortlimb dwarfism or bone disorders, such as rickets

• With short limbs e.g. Achondroplasia, Rickets, Osteogenesis imperfecta

• With short trunk e.g. Skeletal dysplasia, Fanconi anaemia

Approach to Diagnosis

1. History

• Perinatal for: -

o Exposures to infections, and maternal drugs

o Birth weight and length (differentiate prenatal and postnatal causes)

o Neonatal problems e. g micro phallus& hypoglycaemia in hypopituitarism.

• Past history suggestive of: - Chronic systemic disease, Endocrinal disorder

• Dietetic history for undernutrition or eating disorders.

• Family history about parent and sibling heights, onset of puberty in parents & siblings

and infant/mother relationship

2. Examination:

1- Plot the height/ length against the growth chart for age

2- follow up the growth after 6 month (normally growth rate= increment of height =5-7cm/ year)

3- calculate the mid-parental height (mother height + father height /2) + 6.5 cm for boys and (– 6.5) for girls and then plot it against the 20 year centile and compare with child.

• May help elucidate cause of short stature or growth failure:

o Goitre for hypothyroidism,

o Midline defect and micro-penis for hypopituitarism,

o Central adiposity and cherubic/pudgy face for classic GH deficiency

• Does child look dysmorphic (which may point to certain syndromes)?

o Turner syndrome: webbed neck, high arched palate, short 4th metacarpal, and shield chest

o Russell-Silver syndrome: triangular face, relative macrocephaly, clinodactyly

• Proportionate short stature versus disproportionate short stature?

• Full systemic examination to exclude chronic systemic disorders

3. Laboratory tests to exclude pathologic causes of short stature

a) Assessment of bone age by x- ray on the wrist

b) Systemic disease investigations:

o Stool analysis for malabsorption

o Urine analysis for glucosuria and UTI

o CBC for anaemia, and ESR for inflammation

o Serum electrolytes (Ca, Po4) & pH, → for renal tubular and metabolic bone disease.

o Urea and creatinine for CRF

o Chest X ray for chronic chest disease

o Echocardiography → for suspected cardiac defect

o Tissue transglutaminase Ig A Ab and total IgA level to identify celiac disease.

c) Hormonal Assay:

o TSH, free T4 or total T4 for hypothyroidism

o Serum IGF1 and IGFBP3 levels to screen for GH deficiency. Growth hormone stimulation test (induce hypoglycemia by clonidine or glucagon , measure GH after 2 hour)

o Morning serum or salivary cortisol for Cushing syndrome

d) Chromosomal karyotyping

o In cases of dysmorphic feature

o Unexplained short stature in girls

4. Treatment

• Depends on underlying etiology

• Adequate nutrition or caloric intake in patients with malnutrition

• If psychosocial distress is present, → psychologic support ± consider short course of IM long-acting testosterone for 4-6 months

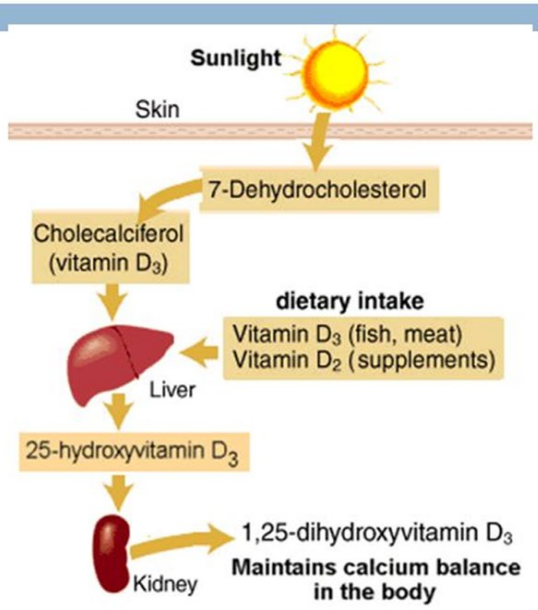
• Daily GH injections in children with GH deficiency.

Cause	Bone Age	Growth Velocity	? Family History	? Proportionate growth
Familial short stature	Normal	Normal	Yes	Yes
Constitutional growth delay	Decreased (often = height age)	Normal	Yes	Yes
Endocrinopathy	Decreased	Decreased	Usually none	Yes (except hypothyroid)
Chronic disease	Decreased	Decreased (esp. decreased weight)	Depends on underlying disease	Yes
Syndromic causes	Normal	Decreased	Depends on underlying disease	Often not (esp. if skeletal dysplasia)

Rickets

Vitamin-D Metabolism

- Is a fat soluble Vitamin.
- It resembles sterols in structure and functions like a hormone.
- During cholesterol synthesis 7-dehydro cholesterol is formed as an intermediate.
- On exposure to sunlight, it is converted to cholecalciferol (vit D3) in the skin.



Results from inadequate sunlight exposure or inadequate intake of dietary vit. D.

Commonest cause developing countries

1- Nutritional rickets:

Lack of vitamin D:

•Lack of exposure to U/ V sun light

–Dark skin: dark-skinned persons require more sunlight exposure than others to produce the same amount of vitamin D because melanin acts as a neutral filter and absorbs solar radiation

–Covered body

–Kept in-door

•Exclusive breast feeding:

Breast milk doesn't contain enough vitamin D to prevent rickets. Babies who are exclusively breast-fed should receive vitamin D drops.

•Mother's vitamin D deficiency during pregnancy:

A baby born to a mother with severe vitamin D deficiency can be born with signs of rickets or develop them within a few months after birth.

Vitamin D dependent rickets

Type 1

•Rare, autosomal recessive disorder.

•Lack of 1 alpha hydroxylase enzyme .

•Clinically and Biochemically similar to nutritional rickets except it appears early at 3-4 months.

• Tetany , convulsions, muscle weakness and growth failure.

Type 2

•Rare autosomal recessive disorder.

•1-a-hydroxylase enzyme is present.

•Lack of Calcitriol receptors.

•Unresponsive to vit.D treatment. + alopecia

• elevated levels of circulating calcitriol differentiate this type from type I.

Vitamin D Resistant Rickets

Also Hereditary Hypophosphatemic Rickets

•X-linked dominant / Autosomal dominant •Males affected more than female

•Phosphate wasting by renal tubules leads to:

–Low serum phosphate

–Normal calcium

Secondary rickets

Renal disease ,Celiac disease , Inflammatory bowel disease, Cystic fibrosis ,Biliary atresia

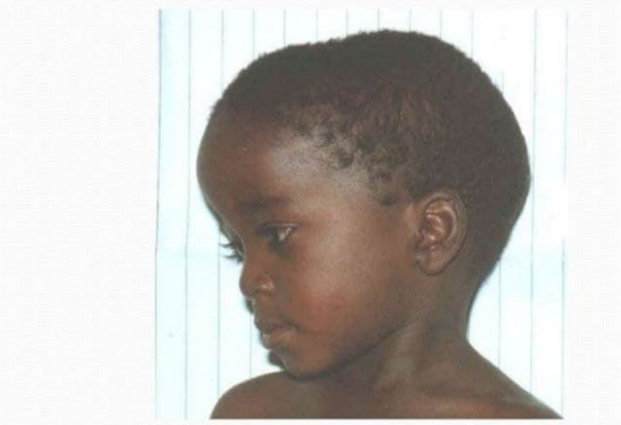
HEAD

• Larger than normal

• Frontal bossing (due to excess osteoid) Craniotabes (ping pong ball sensation) due to thinning of outer table of skull.

• Delayed closure of anterior fontanel

• caput quadratum (square like head) .

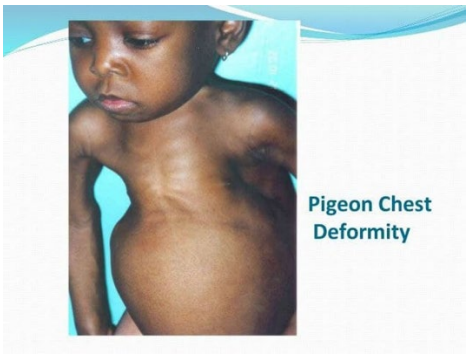


THOREX

• Rachitic Rosery (prominent costochondral junctions)

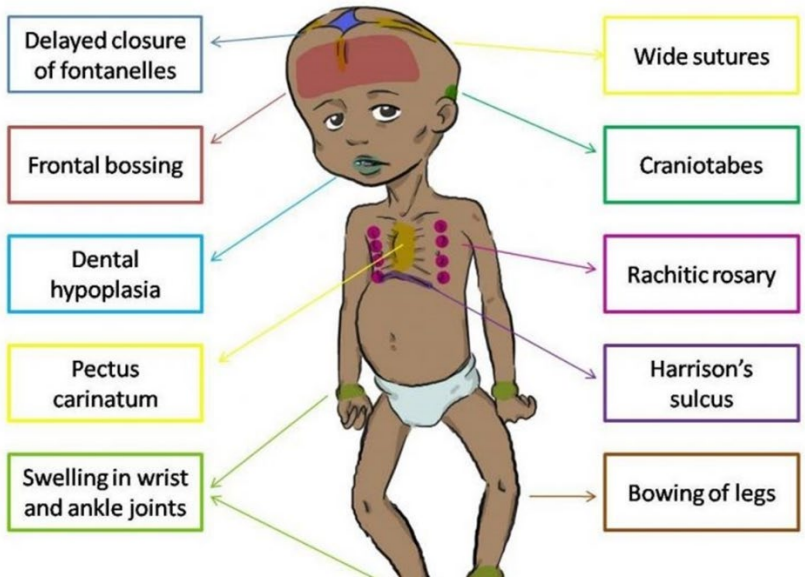
• Harrison's sulcus (depression above the subcostal margin at the site of diaphragm) Pulling of softened ribs by the diaphragm during inspiration.

• Pigeon chest deformity.(The weakened ribs bend inwards due to the pull of respiratory muscles and ,causing anterior protrusion of sternum).



Extremities : Widening of wrists and ankles , Bending of long bones results in bow legs knock knees,(genu valgum) , Green stick fractures.

Trunk : Kyphosis • Scoliosis

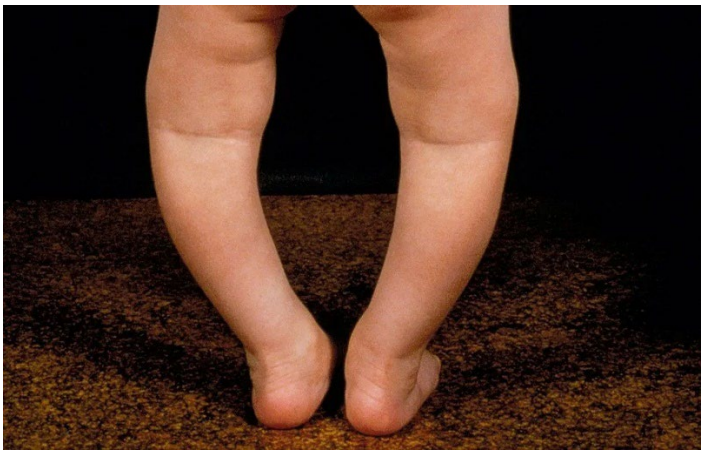


Radiological findings of rickets:

Generalized Osteopenia. •Widening of the unmineralized epiphyseal growth plates.

•Bowing of legs. •Fractures.

Oral or parenteral administration of Vitamin D is preferred.



Active treatment:

In active, massive dose of 600000 IU vitamin-D intramuscularly as a single dose every 2 wks.

once healing is started ,400 IU can be given daily: stoss therapy

In milder case 2000 to 6000 I.U vitamin-D daily for 4-6 wks ,in addition adequate intake of calcium should be ensured by giving milk or oral calcium gluconate or calcium lactate.

For established deformity :

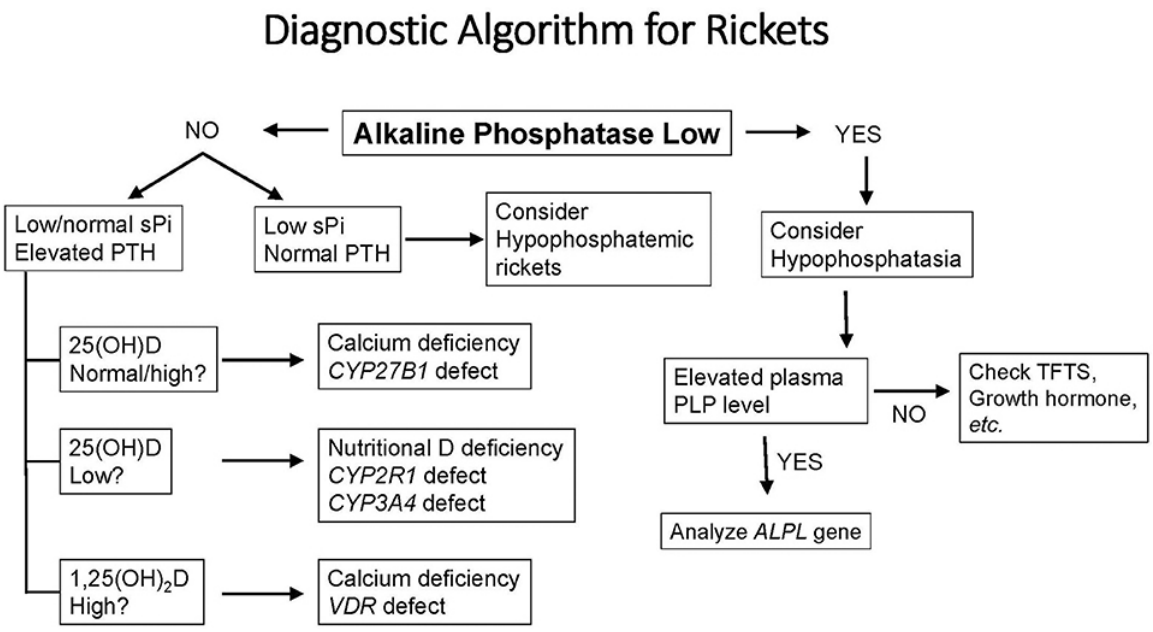
A) Splinting:

• When deformity is slight and disease still active, in younger children below age of 4 years splinting can be helpful Correction by

B) osteotomy:

• This method is used when the deformity is in the vicinity of a joint.

• Osteotomies attempted before this period leads to nonunion.



Condition	Genetics	Ca	Phos.	Alk Phos	PTH	Vit D	1,25 (OH)VitD
Vitamin D Resistant Rickets (Hypophosphatemic)	X linked dominant	–	↓	↑	–	–	
Vitamin D Deficiency Rickets (Nutritional)	Nutritional	–↓	↓	↑	↑	↓	
Type I Vitamin D Dependent	Auto. Recessive	↓	↓	↑	↑		↓↓
Type II Vitamin D Dependent	Auto. Recessive	↓	↓	↑			↑↑
Hypophosphatasia	Auto. Recessive	↑	↑	↓↓	–	–	
Renal Osteodystrophy	Renal Disease	↓	↑	↑	↑		
Hyperparathyroidism	90% adenoma	↑	↓	↑	↑		

Thanks