



- **Short stature:**

- It is defined as height 2 SD below the mean. It is normal when there is normal growth velocity (2 inches/year = 5 cm/year) and pathologic when there is decreased growth velocity.

- **Determining Mid-Parental Height (MPH):**

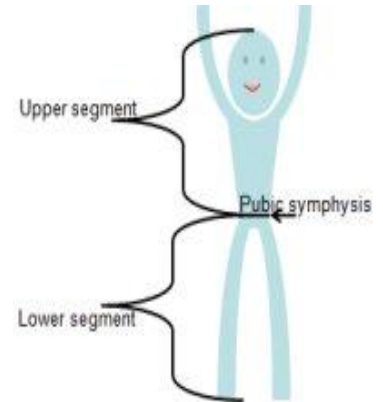
- ✓ Males = $\frac{\text{Father's height} + (\text{mother's height} + 5 \text{ inches})}{2}$
- ✓ Females = $\frac{\text{Mother's height} + (\text{father's height} - 5 \text{ inches})}{2}$

Notice that most children are ± 2 SD around their MPH.

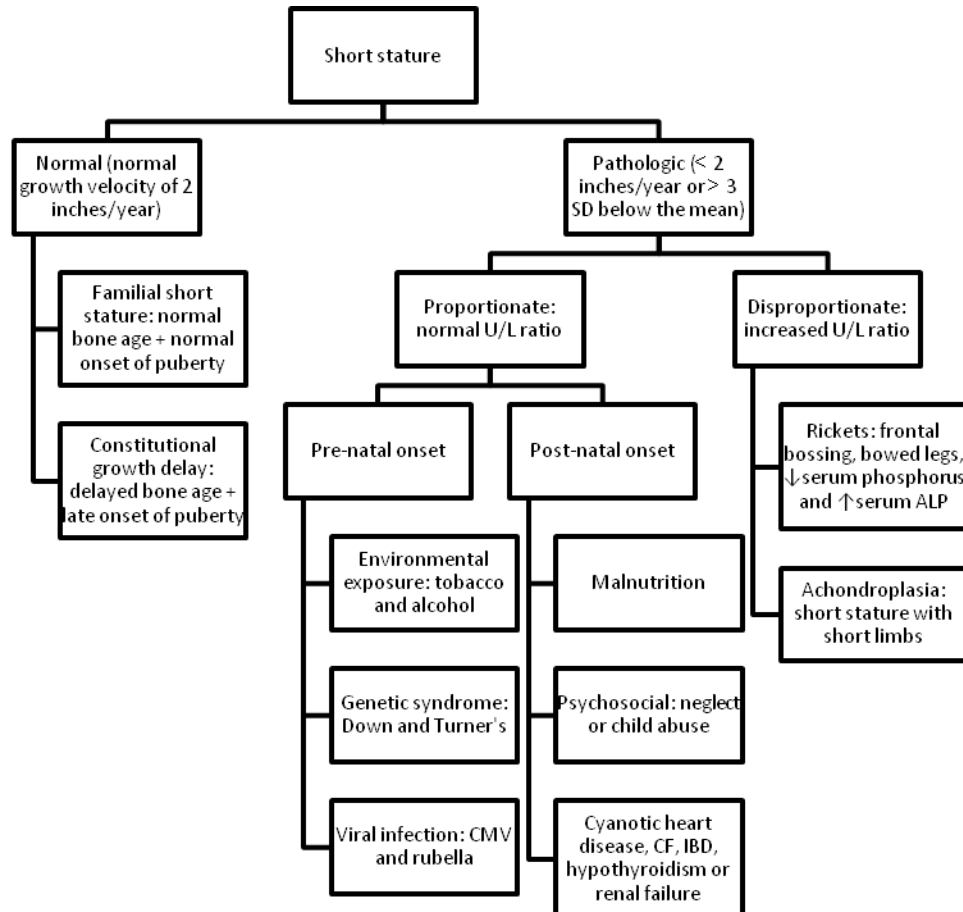
- **How to measure upper-to-lower (U/L) body segment ratio?**

- ✓ Lower segment = from pubic symphysis to the heel.
- ✓ Upper segment = total height – lower segment.
- ✓ Normal ratios:

At birth	1.7
3 years	1.3
> 7 years	1.0



- **Categorization of short stature:**

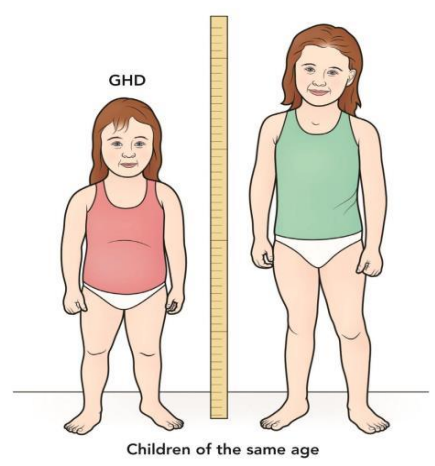


- **Endocrinopathies causing short stature:**

- ✓ Growth Hormone (GH) deficiency:
 - ❖ GH is secreted by the anterior pituitary gland.
 - ❖ *Clinical features:* pathologic short stature (with decreased growth velocity).
 - ❖ *Causes:* trauma, CNS irradiation, CNC vascular malformation or brain tumors.



- ❖ *Investigations:* ↓ IGF-1 which must be followed by head MRI to define the CNS lesion which lead to this condition.
 - ❖ *Management:* daily subcutaneous injections of recombinant GH.
- ✓ Hypothyroidism:
- ❖ The most common being Hashimoto thyroiditis (autoimmune disease).
 - ❖ *Investigations:* ↓ T4, ↑ TSH (due to loss of negative feedback from the product) and antithyroid peroxidase antibodies.



- ✓ Hypercortisolism:
- ❖ Prolonged use of external steroids will result in iatrogenic Cushing's syndrome (with all of its features).



- ✓ Turner's syndrome:
- ❖ GH treatment has been shown to improve the ultimate height of these patients.

- Disorders of puberty:

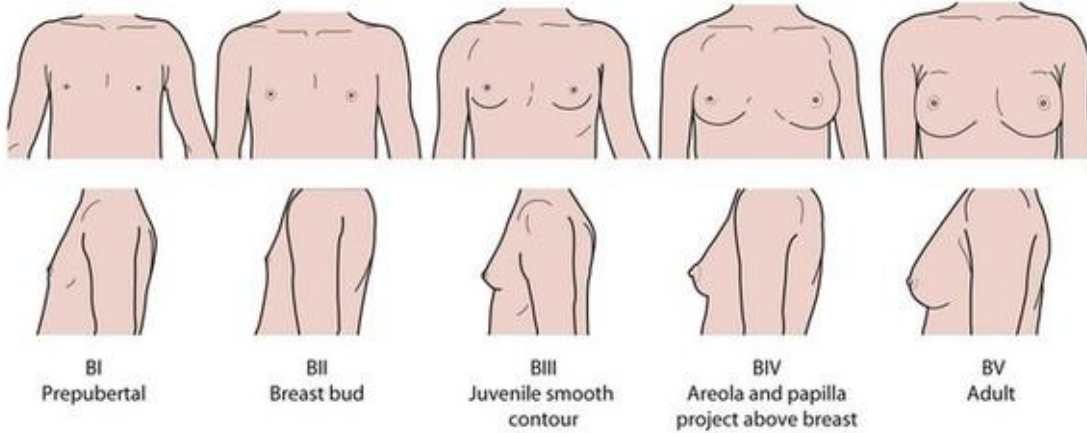
Puberty	
Female puberty	Male puberty
<ul style="list-style-type: none"> • Onset: 7-13 years. • Thelarche (breast development; 1st sign; due to estrogen), adrenarche (pubic/axillary hair development; due to adrenal androgens) and menarche (onset of menstruation). • FSH needed for follicular growth; LH needed for ovulation (usually at day 14). 	<ul style="list-style-type: none"> • Onset: 9-14 years. • Testicular enlargement is usually the 1st sign. • FSH needed for sperm production; LH needed to stimulate Leydig cells for testosterone production



• **Tanner staging:**

Stages of puberty

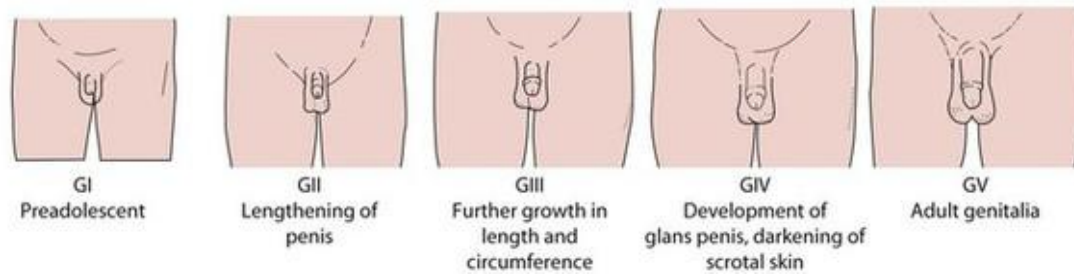
(a) Female breast changes



(b) Pubic hair changes – female and male




(c) Male genital stages




• **Precocious puberty** **البلوغ المبكر**

✓ Is breast development before 7 years of age in females; testicular enlargement before 9 years of age in males.

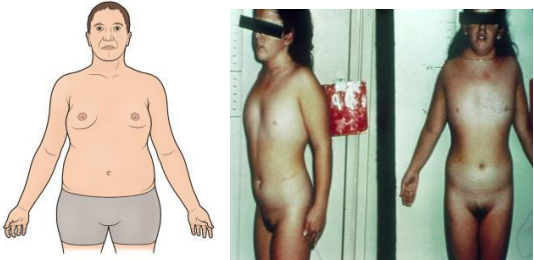
✓ Categories:

<p>Premature thelarche</p>	<ul style="list-style-type: none"> • Breast development in first 2 years of life with no other secondary sexual characteristics. • Due to transient activation of Hypothalamic-Pituitary-Gonadal Axis (HPGA). • No treatment needed 
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<p>Premature adrenarche</p>	<ul style="list-style-type: none"> • Pubic/axillary hair development without breast development or testicular enlargement. • It is common in girls after 5 years of age. • No treatment needed. 
<p>Central precocious puberty</p>	<ul style="list-style-type: none"> • It is premature activation of HPGA which is more common in girls. • Clinical features: <ul style="list-style-type: none"> ✓ Girls (cause is idiopathic): breast development, pubic hair and rapid growth ✓ Boys (cause is always organic and head MRI must be done): testicular enlargement, pubic hair and rapid growth • Investigations: <ul style="list-style-type: none"> ✓ ↑FSH, LH and sex steroids ✓ GnRH stimulation test: by injecting synthetic GnRH and watching for ↑LH (notice that there is flat response in peripheral precocious puberty).
<p>Peripheral precocious puberty</p>	<ul style="list-style-type: none"> • Peripheral production of sex steroids independent of FSH and LH. • Causes: exogenous sex steroids, gonadal tumors or adrenal tumors. • Clinical features: <ul style="list-style-type: none"> ✓ Boys: Feminization (gynecomastia) or premature onset of pubic hair. ✓ Girls: virilization or breast development • Treatment depends on the underlying cause

• **Delayed puberty:**

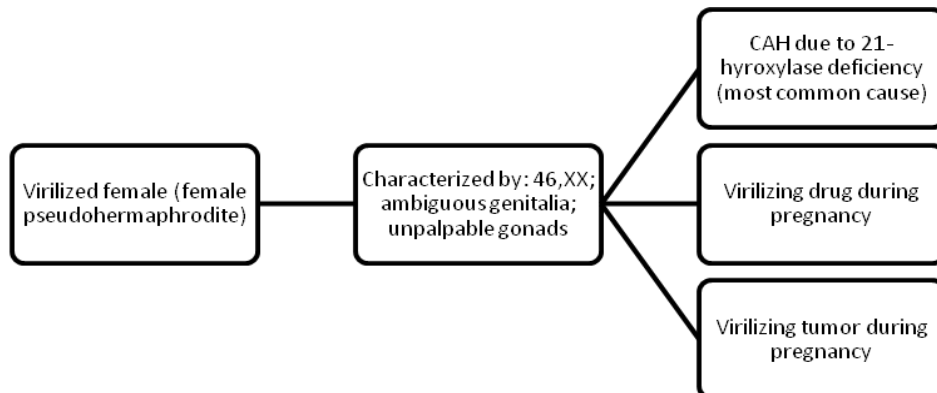
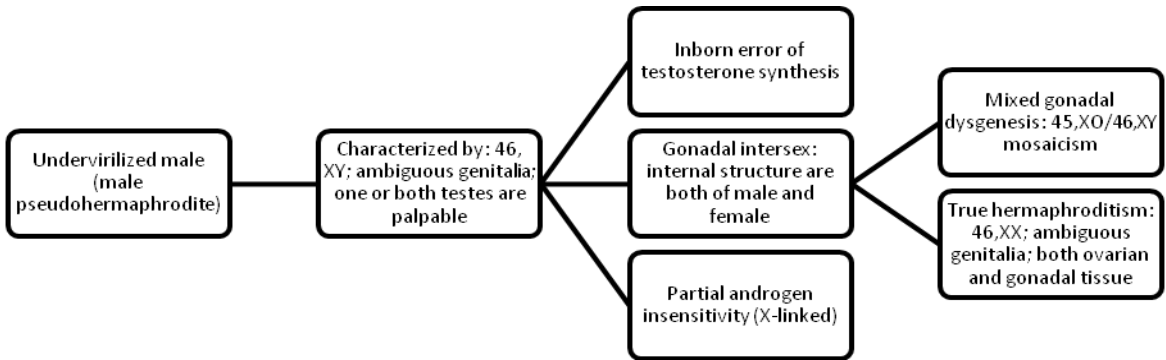
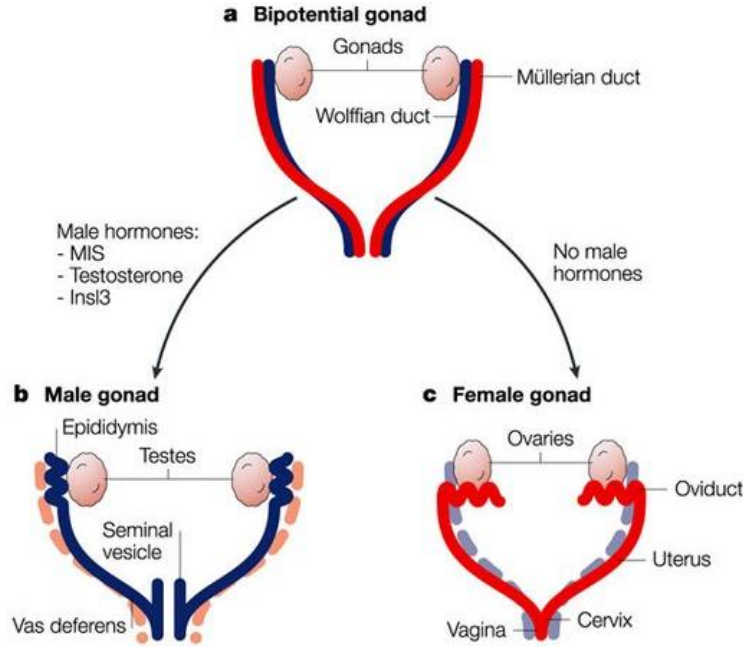
- ✓ It refers to no breast development by 13 years in females; no testicular enlargement by 14 years in males.
- ✓ Classification:

<p>Hypogonadotropic hypogonadism</p>	<ul style="list-style-type: none"> • No activation of HPGA • ↓FSH, ↓LH and ↓sex steroids • Example: Kallman syndrome (isolated gonadotropin deficiency associated with anosmia)
<p>Hypergonadotropic hypogonadism</p>	<ul style="list-style-type: none"> • There is gonadal failure • ↑FSH, ↑LH and ↓sex steroids • Examples: Klinefelter syndrome (in boys); Turner's syndrome (in girls). 



- **Ambiguous genitalia:**

Sexual differentiation	
Male	Female
<ul style="list-style-type: none"> • Y chromosome has the SRY gene which will induce differentiation of gonads to Testes. • Testosterone will be produced by Leydig cells and stimulate formation of internal ducts. • Testosterone will be converted to DHT by 5α-reductase stimulating development of external genitalia. • MIF will be produced by sertoli cells to inhibit the development of Mullerian duct structures. 	<ul style="list-style-type: none"> • Absence of SRY gene will stimulate gonads to differentiate to ovaries. • Mullerian duct structures will develop due to lack of testosterone and MIF. • External genitalia will not virilize due to lack of testosterone and DHT.





- **Disorders of adrenal gland:**

Adrenal insufficiency	
Primary	Secondary
<ul style="list-style-type: none"> • Problem is in adrenal gland itself. • Cortisol deficiency: anorexia/weakness, hyotension and hyponatremia. • Aldosterone deficiency: hyponatremia, hyperkalemia and acidosis. • Investigation: blunted response with ACTH stimulation test • Examples: Addison's disease (autoimmune destruction of adrenal cortex by lymphocytic infiltration), CAH and adrenoleukodystrophy 	<ul style="list-style-type: none"> • Problem is at the level of hypothalamus or pituitary gland resulting in abnormality in secretion CRH or ACTH respectively. • Potassium level will be normal because there is no aldosterone deficiency (it is not dependent on CRH and ACTH axis). • Examples: prolonged use of steroids for more than 2 weeks (most common); pituitary tumors

• **Congenital Adrenal Hyperplasia (CAH):**

- ✓ It is an AR congenital enzyme deficiency in the adrenal cortex.
- ✓ 21-hydroxylase deficiency (90% of cases):

Classic salt-wasting (cortisol + aldosterone deficiency)	Girls present with ambiguous genitalia and electrolyte abnormalities
Simple virilizing (only cortisol deficiency)	<ul style="list-style-type: none"> • Girls: ambiguous genitalia with no electrolyte abnormalities • Boys: late-onset, tall stature, penile enlargement, pubic hair and advanced bone age
Non-classic (late-onset with only cortisol deficiency)	<ul style="list-style-type: none"> • Girls: premature adrenarche, rapid growth, clitoromegaly, acne, hirsutism and infertility • Boys: premature adrenarche, rapid growth and premature acne

- ❖ 21 hydroxylase deficiency is diagnosed by: ↑17-hydroxyprogesterone level.



- ✓ **11β-hydroxylase deficiency:** similar to 21-hydroxylase deficiency but patients are hypertensive and hypokalemic. It is diagnosed by: ↑11-deoxycortisol.
- ✓ **Management:** cortisone and fluorocortisol (if there is mineralocorticoid deficiency).

• **Cushing's syndrome:**

- ✓ **Clinical features:** moon face, nuchal fat pad, central obesity with thin limbs, purplish striae (mostly on abdomen), hypertension, glucose intolerance and poor growth.
- ✓ **Causes:**

Iatrogenic	Most common cause
Cushing's syndrome	Benign or malignant adrenal tumors
Cushing's disease	Excessive ACTH due to pituitary tumors

- ✓ **Investigations:**

- ❖ **Gold standard:** ↑free cortisol in 24-hour urine collection.

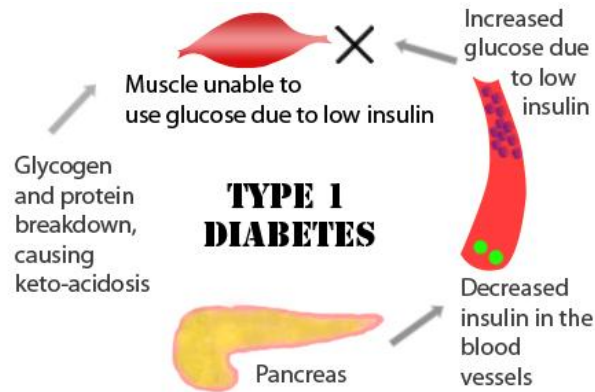


❖ *Dexamethasone suppression test*: absence of expected cortisol suppression.

- **Type-I DM (insulin-dependent):**

• **Etiology**: there is a genetic predisposition (HLA DR3 & DR4) with the trigger of an environmental factor (such as a viral infection) will result in autoimmune destruction of β -cells of pancreas by lymphocytic infiltration. Antibodies which play a role include:

- ✓ Islet cell antibodies (ICA): it is present in 85% of patients.
- ✓ Anti-insulin antibodies.
- ✓ Anti-GAD antibodies (Glutamic Acid Decarboxylase).



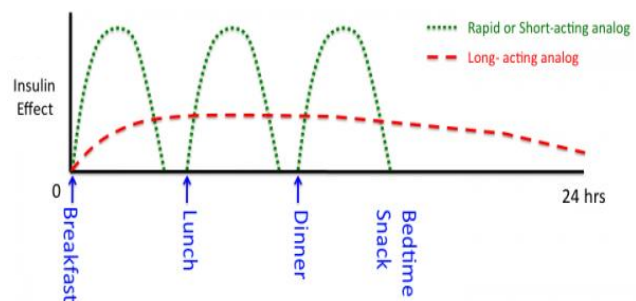
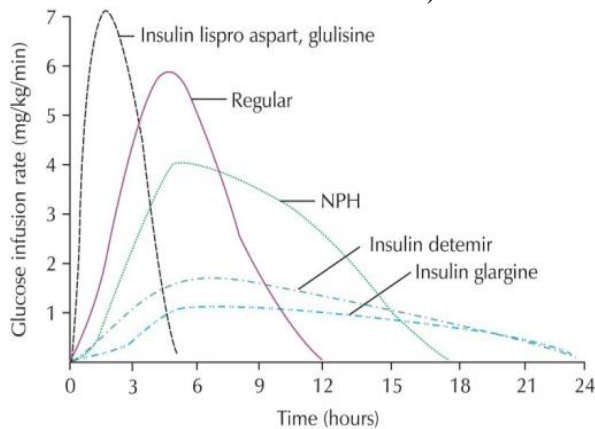
• **Clinical features**: polyuria, polyphagia and polydipsia. Notice that DKA can be the initial presentation in 25% of patients. Adolescents may present with type-I DM during their growth spurt due to insulin antagonizing effects of sex steroids.

• **Diagnosis**: FBS > 7 mmol/L; RBG > 11.1 mmol/L and HbA_{1c} > 6.5%

• **Management**:

✓ Insulin:

- ❖ *These are the types of insulin*: rapid-acting (e.g. lispro and aspart), short-acting (e.g. soluble insulin), intermediate-acting (NPH), long-acting (glargine and detemir).
- ❖ *The most common regimen which is used is*: administration of long-acting insulin at night to provide a 24-hour coverage in addition to rapid or short-acting insulin with each meal (breakfast, lunch and dinner).



✓ Monitoring:

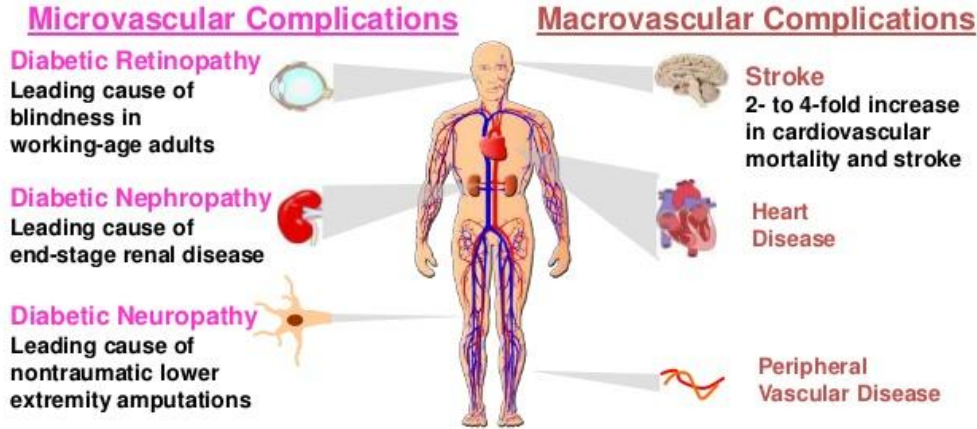
- ❖ Daily blood glucose monitoring using a glucose meter before each meal and at bed time.
- ❖ Checking HbA_{1c} which reflects control for the past 3 months.
- ❖ *Watch for hypoglycemia*: patients must have parenteral glucagon with them or simply a source of glucose.



- ❖ *Watch for honeymoon period:* transient recovery of residual islet cell function resulting in endogenous release of insulin.
- ❖ *Watch for Somogyi phenomenon:* this occurs when evening dose of insulin is too high causing hypoglycemia in early morning which results in release of counter-regulatory hormones that will increase blood glucose and ketones.

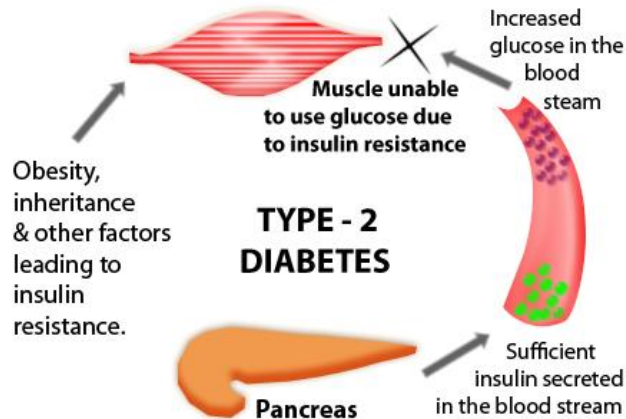
- **Long-term complications:**

- ✓ Microvascular: nephropathy, neuropathy and retinopathy.
- ✓ Macrovascular: stroke, MI and hypertension.



- **Type-II DM (insulin-independent):**

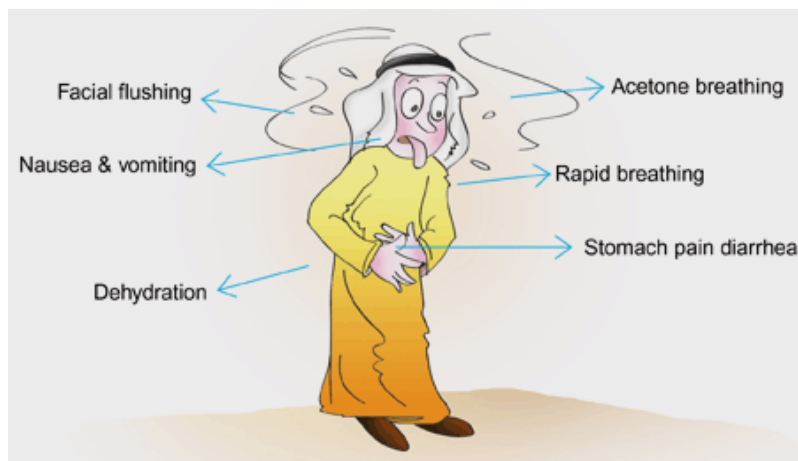
- It is known as the adult-type and occurs due to insulin resistance and progressive decreased insulin production, but nowadays incidence is increased among children due to obesity!



- **Clinical features:** polyuria, polydipsia, polyphagia, obesity and acanthosis nigricans. DKA is uncommon.
- **Management:** oral hypoglycemics (such as metformin). Insulin will be used when there is a failure to control blood sugar with oral hypoglycemics.

- **Diabetic Ketoacidosis (DKA):**

- **It is characterized by the triad of:** hyperglycemia (> 300 mg/dL), ketonuria and anion gap metabolic acidosis (pH < 7.3). The acidosis will result in shifting of potassium outside cells resulting in pseudohyperkalemia.
- **Pathophysiology:**
 - ✓ Due to insulin deficiency there will be diminished glucose at the cellular level resulting in gluconeogenesis.
 - ✓ High glucose will result in osmotic diuresis with polyuria and eventual dehydration.
 - ✓ Glucagon release will stimulate the conversion of free FA to ketone bodies (acetone, acetoacetate and β -hydroxybutyrate).
- **Clinical features:** polyuria, polyphagia, vomiting, dehydration, Kussmaul breathing, abdominal pain and fruity breath odor.



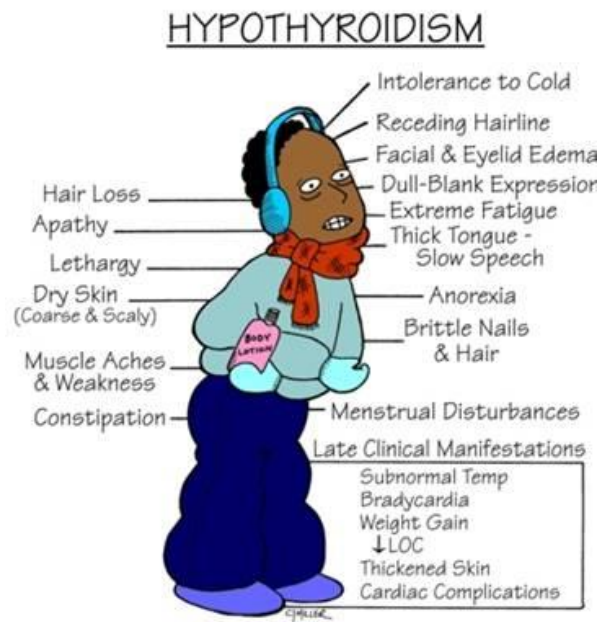
• **Management:**

- ✓ Fluid and electrolyte therapy (isotonic saline). Notice that a gradual decline in osmolality is critical to minimize the risks of cerebral edema which occurs 6-12 hours into therapy and mortality can reach up to 70%.
- ✓ Potassium repletion (once urine output is initiated) using the following:
 - ❖ *Potassium acetate (50%):* managing metabolic acidosis.
 - ❖ *Potassium phosphate (50%):* shifting oxygen dissociation curve to the right.
- ✓ Regular insulin.

- **Thyroid disorders:**

• **Hypothyroidism:**

- ✓ General clinical features: proportionate pathologic short stature, goiter (due to ↑TSH), myxedema (puffy dry skin) and amenorrhea in adolescent girls. Other features include: weight gain, lethargy, constipation and cold-intolerance.



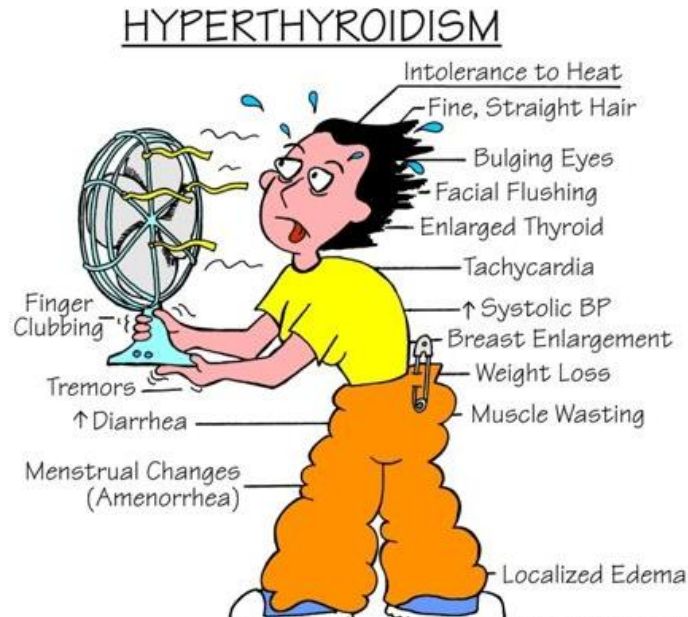
✓ Congenital hypothyroidism:

- ❖ Causes: thyroid dysgenesis (90% of cases), thyroid dysmorphogenesis, maternal use of anti-thyroid drugs during pregnancy such as PTU (which will cause transient hypothyroidism in her baby) or maternal autoimmune thyroid disease.
- ❖ Clinical features: defect in neurologic development (thyroid hormones are important for neurodevelopment in first 2 years of life), large posterior fontanel, protruding tongue, lethargy, constipation, myxedema and prolonged jaundice.
- ❖ Investigations: ↑TSH, ↓T4
- ❖ Management: L-thyroxine.



- ✓ Hashimoto thyroiditis:
 - ❖ It is an autoimmune disease in which there will be autoantibodies directed against thyroid gland causing its destruction and infiltration with lymphocytes. It occurs more in girls.
 - ❖ *Clinical presentation:* can be asymptomatic or resulting in goiter and short stature in addition to other features of hypothyroidism.
 - ❖ *Investigations:* ↑TSH, ↓T4 and thyroid antiperoxidase antibodies.

- Hyperthyroidism:
 - ✓ Clinical features: exophthalmos and lid lag, tachycardia and palpitations, warm and flushed skin, weight loss and diarrhea, tremors and irritability, enlarged thyroid gland, delayed menarche or gynecomastia in boys.

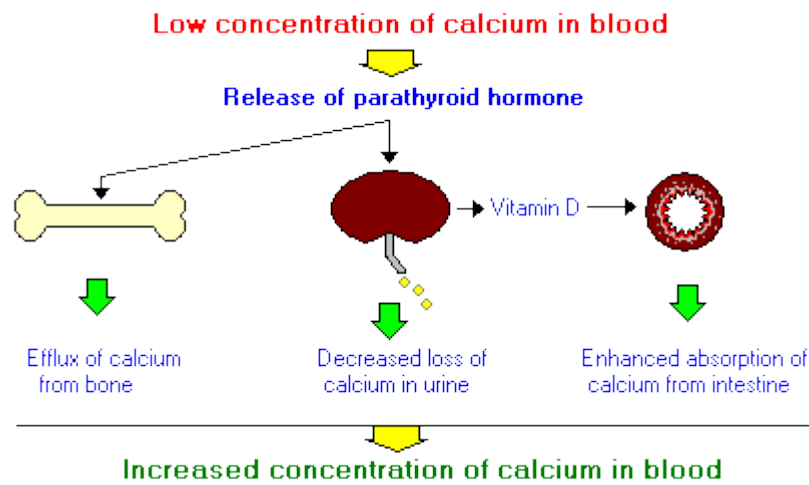


- ✓ Grave's disease:
 - ❖ It is an autoimmune disease which is characterized by the presence of Thyroid Stimulating Immunoglobulin (TSI) that will bind to receptors on the surface of thyroid gland mimicking the action of TSH and producing excessive thyroid hormones. It is considered as the most common cause of hyperthyroidism in childhood and occurs more in females.
 - ❖ *Investigations:* ↓TSH, ↑T3 and T4, (+) TSI
 - ❖ *Management:*

Anti-thyroid medication	PTU or methimazole
Partial thyroidectomy	If anti-thyroid medications fail
Radioactive iodine	Eventually resulting in permanent hypothyroidism

- **Bone mineral disorders:**

- **Actions of PTH which is secreted by parathyroid gland when calcium levels are reduced:**
 - ✓ Release of calcium and phosphorus from bones (bone resorption).
 - ✓ Reabsorption of calcium from DCT of kidneys.
 - ✓ Excretion of phosphorus by PCT of kidneys.
 - ✓ Stimulating the formation of 1,25 (OH) vitamin D (the active form) by kidneys thus increasing absorption of calcium from intestine.

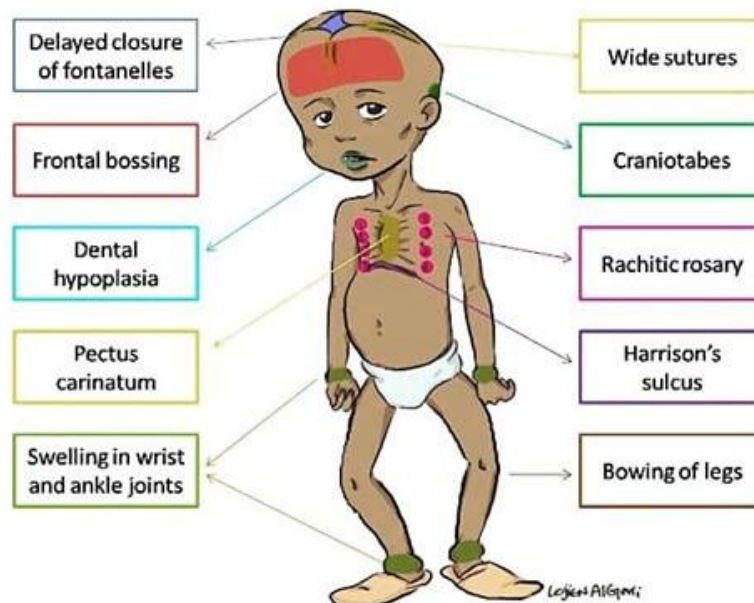


- **Hypocalcemia:**

- ✓ It is defined as ionized calcium < 2.5 mg/dL
- ✓ Clinical features: seizures or coma (in young patients); tetany (neuromuscular hyperexcitability) and parasthesias (in older patients).
- ✓ Causes: hypoparathyroidism (such as in DiGeorge syndrome), hyperphosphatemia and vitamin D deficiency (causing hypocalcemia with low phosphorus level).
- ✓ Management:
 - ❖ *Mild asymptomatic hypocalcemia does not require treatment.*
 - ❖ *Oral calcium*: if there are no seizures or there is moderate tetany.
 - ❖ *IV calcium gluconate*: if patients are more symptomatic.

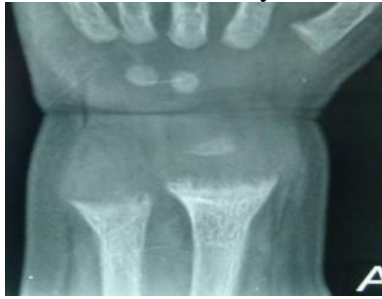
- **Rickets:**

- ✓ It is defined as deficient mineralization of growing bone due to vitamin D deficiency. Vitamin D deficiency occurs due to:
 - ❖ *Less exposure to sunlight.*
 - ❖ *Exclusive breast-feeding (because breast milk is deficient in vitamin D).*
 - ❖ *Liver or renal diseases (as metabolism of vitamin D occurs in these two organs).*
- ✓ It occurs in first 2 years of life and in adolescents when bone growth is most rapid.
- ✓ Clinical features: delayed suture closing and widely-opened anterior fontanel, frontal bossing, craniotabes, rachitis rosary (prominent costochondral junctions), bowed legs and short stature.





- ✓ Radiographic findings:
 - ❖ *Rickets*: distal end of metaphysis of the wrist shows widening, fraying and cupping.
 - ❖ *Healing rickets*: line of provisional calcification.
 - ❖ *Healed rickets*: bone density returns to normal with slight cupping.



- ✓ Laboratory investigations: ↓vitamin D, normal/↓calcium, ↑PTH, ↓phosphorus and ↑ALP (due to increase of osteoblastic activity during formation of excessive osteoids).
- ✓ Management:
 - ❖ Oral vitamin D (1500-5000 IU/day) for 6-8 weeks.
 - ❖ Shock therapy: 600,000 IU IM injection. The dose is repeated after 2-4 weeks if there is no evidence of healing.

- Diabetes Insipidus (DI):

- It is the inability to maximally concentrate urine either due to deficiency in ADH (central DI) or resistance to ADH (nephrogenic DI). Normally, ADH is synthesized by hypothalamus and stored in posterior pituitary gland. It is released when there is increase in serum osmolality to cause reabsorption of water from kidneys.
- **Classification:**

Central DI (deficiency of ADH)	Nephrogenic DI (resistance to ADH)
Etiology: autoimmune, trauma, hypothalamic tumors or inherited as autosomal dominant	Etiology: Inherited as an X-linked recessive disorder
Clinical features: polyuria, polydipsia, nocturia and enuresis	
Investigations: early morning urine sample with specific gravity > 1.018; water deprivation test (if, at the end of the test, the patient does not respond to administered ADH, then the patient has nephrogenic DI)	
Management: DDAVP	-