ENDOCRINOLOGY

Definition:

- It is the science dealing with endocrine glands and their disorders.
- Terminology
  - Endo: f. Greek. edo= within
  - Crine: f. Greek. krino= to separate within
  - Endocrine= to separate or secrete within or internally.

Hormones:

- The wor hormone is from (hormao) from Greek that means to set in motion.
- They are chemical messengers, directly released from endocrine cells into the circulation and acting at a distant site. This is the traditional understanding of hormones.
- Recently other functions for hormones were discovered:
  1. Local action on adjacent cells (=paracrine action).
  2. Direct action on the cells of origin (=autocrine action).
  3. Neurotransmitter.

How hormones act?

- It acts by binding to specific receptors on the surface or within the target cell.
- It then leads to a cascade of intracellular reaction within the target cell leading to certain response.
- The site of their action is different:
  i. Growth H. and thyroxine H.- act on most tissues of the body
  ii. Thyroid stimulating H. (TSH) and adrenocorticotrophic H. (ACTH)- secreted from the pituitary and act on one tissue only.

THE HYPOTHALAMIC AND PITUITARY CONTROL

The hypothalamus:

- Hypo means: under
  Thalamus is from Greek word meaning: thalamos= a bed.
- Functions:
  1. Hypothalamus plays a role in circadian rhythm.
  2. It regulates menstrual cycle.
  3. It functions in stress situation.
  4. Mood regulation
  5. Through a portal system which runs down the pituitary stalk it controls the pituitary gland function by releasing factors that stimulate or inhibit production of hormones from pituitary cells.

The pituitary:

- Anterior pituitary Hs. are stimulated or inhibited by the hypothalamus.
- Posterior pituitary: stores the antidiuretic H (ADH or vasopressin) and oxytocin, that are synthesized by the supraoptic and paraventricular parts of the brain and pass to the posterior pituitary along axons of the producing cells.

Control and feedback:

- Feedback is the mechanism of control of most of hormones.
- The Hs. secreted from the target glands feedback on the hormones that have stimulated its secretion.
- Feedback can be negative (i.e inhibitory) e.g. excess circulating thyroid H.(T3) feeds back on the pituitary and possibly the hypothalamus to suppress the production of TSH & TRH.
- Feedback can also be positive e.g. a fall in thyroid H. after thyroidectomy leads to increased secretion of TSH & TRH.
- Hormone producing tumors do not respond to feedback (this is useful in diagnosis) e.g. in dexamethasone suppression test where giving dexamethasone to patients with high cortisol level from adrenal tumor does not suppress its serum levels.

Regulators	Estrogen Progesterone Androgen Prolactin		IGF-1	Somato -statin		T3	Estrogen Stress	Circadian rhythm Stress Cortisol	Osmolality Intra-vascular volume	
Hypothalamic Hs. and factors	*GnRH*		*GHRH*			*TRH*	*Dopamine*	*CRH*	*Vaso-pressin (ADH)*	*Oxytocin*
Effect on pituitary gland	+		+	-	-	+	-	+	↓	↓
Pituitary Hs. that are secreted or inhibited	*LH*	*FSH*	*GH*		*TSH*		*PRO-LACTIN*	*ACTH*	*Only stored in the pituitary*	*Only stored in the pituitary*
The target glands affected by the pit. H.	*Ovaries & testes*		*Many tissues*		*Breasts & gonads*		*Thyroid*	*Adrenals*	*Distal convoluted tubule*	*+ Breast & uterus*
The ultimate hormone and function	*Ovulation & estrogen*	*Spermatogenesis & testosterone*	*Many Functions Growth*		*Thyroxin metabolism*		*Lactation*	*Steroids Stress*	*Water balance*	*Delivery & Lactation*

Endocrine disorders (dysfunction):

Endocrine dysfunction takes many forms as follows:

1- Hormone excess that can be primary or secondary to excess trophic hormone.
2- Hormone deficiency, can be primary gland failure or secondary to deficient trophic hormone
3- Hormone hypersensitivity, may be due to failure of inactivation of hormone or target organ over activity
4- Hormone resistance, may be due to failure of activation of hormone or target organ resistance
5- Non-functioning tumors.

Endocrine pathology:

Many sorts of diseases affect the endocrine glands, but autoimmune diseases and endocrine neoplasia are the most common ones.

- **Autoimmune Polyglandular Failure (or syndromes):**
  - Auto immune disease may involve isolated endocrine glands.
  - It some times affects many glands at the same time producing what is called autoimmune polyglandular failure or syndromes. There are two main types:

    - **Poly glandular failure type 1.** This syndrome includes:
      i. Addison's disease **without** vitilligo
      ii. Hypoparathyroidism
      iii. Chronic mucocutaneous candidiasis.
      iv. Nail dystrophy

    - **Poly glandular failure type 2.** This syndrome incudes:
      i. Addison's disease **with** vitilligo
      ii. Hypothyroidism
      iii. Hypogonadism (ovarian or testicular)
      iv. Diabetes mellitus type 1
      v. Pernicious anemia

- **Multiple Endocrine Neoplasia (MEN):**
  - It is rare genetic disorder.
  - There are hyperplasia, adenomas or malignant tumors in multiple glands.
  - It should be considered in all patient with more than one endocrine disorder e.g hypercalcemia and pituitary tumor, or patient having solitary endocrine tumor with positive family history of other endocrine disease.
  - It is classified into 2 classes: MEN type I **(Werner's syndrome)** and MEN type II **(Sipple's syndrome):**
    - **MEN type I (due to mutation in the gene menin):**
      - Pituitary tumor
      - Parathyroid tumor
      - Pancreatic tumors (e.g insulinoma, gastrinoma)

    - **MEN type II A- (autosomal dominant due to inheritance of gene with mutations)**
      - Parathyroid tumor
      - Medullary thyroid carcinoma
      - Pheochomocytoma
    - **MEN type II B-**
      - Medullar thyroid carcinoma
      - Pheochromocytoma
      - Mucosal neuroma

- Management-because MEN type II has two fatal conditions, medullary thyroid carcinoma (MTC) and pheochromocytoma, patients positive on genetic testing are advised to have prophylactic thyroidectomy befor the age of 10 years and follow up by regular measurement of urinary catecholamine secretion (yearly) and imaging in case of positive screen.

PITUITARY GLAND DISORDERS

BENIGN TUMORS (ADENOMAS):

- Tumors are the most common forms of pituitary disease.
- Symptoms of pituitary tumors arise as a result of:
  - Underproduction of Hs.
  - Overproduction of Hs.
  - Local pressure or infiltration effects of the tumor.

- **Underproduction of pituitary Hs.:**
  - It is due to hypothalamic or pituitary disease.
  - It results in the following features of hypopituitarism:
    - Unexplained fatigue.
    - Short stature if it starts in childhood.
    - Sexual dysfunction and or infertility.
    - Primary or secondary amenorrhea.

- **Overproduction of pituitary Hs.:**
  - Growth h. (GH) excess
    - GH secreting adenoma is usually from acidophilic cells.
    - It leads to acromegaly if starts in adulthood, or to gigantism if starts in youth before arrest of linear growth of bones.
  - Prolactin excess
    - It is usually from chromophobe adenoma
    - It leads to hyperprolactinemia (with galactorrhea).
  - ACTH excess
    - It is usually from basophil adenoma or hyperplasia.
    - It produces Cushing disease.
  - Lutenizing H. (LH) & follicular stimulating H (FSH)
    - It is very rare.
  - TSH excess
    - Very rare.
    - It produces hyperthyroidism

- **Local effects (infiltration and pressure):**
  1. Pressure on optic chiasma gives rise to visual field defects, usually bitemporal hemianopia.
  2. Pressure on meninges and bony structures causes headache.
  3. Pressure on hypothalamus alters appetite and thirst, leading to obesity or early puberty (precocious puberty) in children.
  4. Interruption of CSF flow leading to hydrocephalus.
  5. Infiltration of cavernous sinus and pressing or damaging the cranial nerves causing III, IV and VI cranial nerve palsy.

- **Management of pituitary adenomas:**
  - Non-functioning pituitary macroadenomas are treated by surgery as a first line and by radiotherapy secondly, followed by repeated imaging for follow up.
  - Functioning tumor causing hyperprolactinemia, acromegaly, Cushing's disease or craniopharyngioma are treated accordingly.
  - Tumors causing visual field defects require urgent therapy.

CRANIOPHARYNGIOMA:

- A bening tumor that originates from the remnant cells the Rathke's pouch that passes between the pharynx and hypothalamus.
- Often cystic and or calcified.
- It occurs more in young people.
- Usually located in the suprasellar or the sella region.
- It presses the optic chiasm from above and causes bitemporal hemianopia that stars as bitemporal inferior quadrantanopia.
- It frequently causes hypothalamic damage and diabetes insipidus.
- It may presents like other pituitary tumors and infrequently causes hypopituitarism.
- Treatment is usually surgical through craniotomy.
- It often recurs and requires further surgery which increases morbidity.
- They are radio-insensitive.

HYPOPITUITARISM:

- **Definition**:
  It is selective or multiple pituitary H. deficiency due to hypothalamic or pituitary disease.

- **Etiology:**
  1. Neoplasia: Tumors, secondaries, craniopharyngioma.
  2. Infective: meningitis, encephalitis syphilis
  3. Vascular: pituitary apoplexy, Sheehan's, empty sella
  4. Immunological congenital: pituitary antibodies
  5. Traumatic: skull fracture, surgery
  6. Infiltration: sarcoidosis, hemochromatosis
  7. Others: radiation, chemotherapy
  8. Functional: anorexia, starvation, emotional deprivation

- **Pathophysiology:**
- Growth hormone then LH, & FSH are the firs Hs. to be affected.
- Hyperprolactinemia rather than prolactin deficiency occurs early due to loss of inhibitory effect of dopamine.
- TSH & ACTH are the last to be affected.
- Panhypopituitarism: is deficiency of all anterior pituitary Hs
- Vasopressin and oxytocin secretion will not be affected if the hypothalamus is involved by hypothalamic tumor or tumor extension from the pituitary.

- **Clinical features:**
- Clinical features in hypopit. depend on the extent of hormone deficiency.
- Gonadotrophin deficiency produces:
  - Loss of libido
  - Amenorrhea
  - Impotence
- GH deficiency:
  - In adults clinically silent but may impair well being and mood.
  - In children it leads to growth retardation.
- TSH deficiency:
  - Produces secondary hypothyroidism: tiredness, slowness of thought and action, and mild hypotension.
- ACTH deficiency
  - Produces secondary adrenal failure that shows the same features of TSH deficiency.
- Hyperprolactinemia (due to loss of the inhibitory dopamine function) produce:
  - Galactorrhea
  - Hypogonadism
- Long standing hypopituitarism produces classic picture of pallor with hairless (alabaster) skin.

- **Specific hypopituitary syndromes**

Specific syndromes may result from hypopituitarism as follows:

- **Kallmann's syndrome:**
  - A form of limited hypopituitarism
  - There is Isolated gonadotrophin deficiency
  - Anosmia
  - Color blindness
  - Midline facial deformities
  - Renal abnormalities
- **Sheehan's syndrome:**
  - It is due to pituitary infarction after severe postpartal hemorrhage.
  - It leads to pan-hypopituitarism
  - First manifested as failure to breast feed a baby.
  - Other features of hypopituitarism appear progressively.

- **Pituitary apoplexy:**
  - Infarction or hemorrhage into a pituitary tumor.
  - May result in life threatening hypopituitarusm
  - There may be severe headache, visual loss and cranial nerve palsy.
- **Empty sella syndrome:**
  - In this syndrome the sella turcica appears radiologically devoid of pituitary tissue.
  - The pituitary is actually present but it is placed eccentrically.
  - The pituitary usually function normally, but sometimes there is hypofunction.

• Investigations of hypopituitarism:

- When hypopituitarism is suspected each of the hypothalamic pituitary axes requires a separate investigation.
- The presence of normal gonadal function (i.e. normal ovulation, menstruation, libido, and erection) suggests that multiple defects of the anterior pituitary are unlikely.
- To investigate pituitary Hs. the following tests are conducted:
  - 1st- Tests of basal hormone levels
  - 2nd- Stimulatory tests of the pituitary
  - 3rd- Feed-back tests of the hypothalamus

• Management of hypopituitarism:

- **Replacement therapy:**

1- Steroids and thyroxin are essential for life.
   - both are replaced orally
   - steroids replaced as hydrocortisone (=cortisol): 15-40 mg/ day (in divided dose)
   - thyroxin: 100-150 microgram/ day
   - it is dangerous to replace thyroid H. without first giving steroids as this may precipitate adrenal crisis i.e. acute sever adrenal insufficiency.

2- Mineralocorticoid replacement is not necessary

3- Androgens and estrogens
   - replacement is for symptomatic control. Testosterone restores potency and libido but not fertility.
   - if fertility is desired injections of HCG (pregnyl to replace LH)) and FSH analogues are used for around 6 months until semen can be stored.

4- GH therapy
   - Should be given to the growing child under specialist supervision.
   - In adults, it may improve work capacity, psychological well being, mood, lipid profile, muscle strength and bone density.
   - Reduces central obesity and increase lean body weight.
   - Reduces LDL levels.
   - Given by daily subcutaneous self injection and treatment is monitored with IGF-1 levels.

- GH can also be given to patients with renal failure and Turner's syndrome to facilitate growth.

- **Management of the underlying cause of hypopituitarism accordingly.**

HYPERPROLACTINEMIA

- Primary function of prolactin is to enhance breast development and initiate lactation.
- Prolactin testing is usually performed in females in the morning at the beginning of the cycle and again seven days later during the mid-luteal phase to determine if the prolactin levels are normal.
- Normal prolactin level in women is approximately 25 nanograms per milliliter.
- Dopamine coming from the hypothalamus normally inhibits prolactin release.
- Hyperprolactinemia may be physiologic or pathologic.

- **Physiological rise** of prolactin hormone occurs during:
  1- Stress
  2- Pregnancy
  3- Lactation (this is due to stimulation of its secretion by suckling of the nipples).
  4- Chest wall reflex
  5- Wet nursing reflex (e.g. baby crying)

- **Pathologic rise** of prolactin in the following states:
  1. Prolactin secreting pituitary adenoma (prolactinoma). This is the commonest cause.
  2. Non functioning pituitary or hypothalamic tumors pressing on the pituitary stalk that interfere with dopamine inhibition of prolactin release (disconnection hyperprolactinemia).
  3. Primary hypothyroidism- as high TRH stimulates prolactin secretion.
  4. Polycystic ovarian disease, due to excess estrone.
  5. Drugs:
     - Dopamine inhibitors or antagonists e.g. metoclopramide and phenothiazines (frequent) and antidepressants (rare) .
     - Dopamine depleting drugs e.g. reserpine and methyl dopa.
     - Estrogens
- In 30% of hyperprolactinemia the cause is unexplained.

- **Clinical features:**
  - Galactorrhea- is the cardinal feature of hyperprolactinemia.
  - Hypogonadism- is another cardinal feature (due to inhibition of GnRH by high levels of prolactin, it includes the following features:
    1- Oligomenorrhea, amenorrhea, or menorrhagia.
    2- Impotence in males, and decreased libido in females.
    3- anovulation.
    4- subfertility or infertility.

5- lethargy

- Prolactinoma may present with tumor pressure symptoms: headache and visual field defects.

- **Investigations:**
  1. Serum prolactin level increased– at least 3 measurements
     - Physiologic and drug causes of rise should be excluded
  2. Thyroid function to exclude hypothyroidism.
  3. MRI of pituitary.
  4. Pituitary function tests if pituitary tumor is suspected.
  5. Perimetry of visual field.

- **Management:**
  - Treat the cause: drugs, hypothyroidism…etc.
  - Treatment of prolactinoma
    - Definitive treatment is controversial. It depends on:
      - the size of the tumor
      - the patient's wish for fertility
      - the available facilities
    - Asymptomatic small tumor (microadenomas) only need observation.
    - Symptomatic small and large tumors are treated with Dopamine agonist:
      - Bromocriptin: oral 2.5-15 mg/day, 8-12 hourly.
      - Bromocriptin
        - Normalizes plasma prolactin in almost all cases.
        - Returns gonadal function.
        - Produces shrinkage of most of the macroadenomas.
        - It produces ergotamine-like side effects (nausea, headache, postural hypotension and constipation).
      - Cabergoline 0.25-1 mg/week, 2 doses/week (a long acting dopamine agonist)
      - Quinagolide 50-150μg/day (a non-ergot).
    - If there is intolerance to dopamine agonists:
      - Small tumors can be removed by trans-sphenoidal surgery (cure rate 80%).
      - Large tumor: requires surgical removal of the tumor via a trans-sphenoidal approach combined with postoperative radiotherapy.