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B.PHARM SEMESTER II | BP203T

HUMAN ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY II

(THEORY)

UNIT IV

Endocrine System: Structure, Function and Disorders

Short Notes as per PCI B.Pharm Syllabus

What is covered in this unit

UNIT IV TOPICS

Part A – Hormones and major glands: classification and mechanism of hormone action, hypothalamus and pituitary, thyroid and parathyroid glands.

Part B – Other glands: adrenal gland, endocrine pancreas, pineal gland and thymus.

Part C – Pathophysiology: diabetes mellitus, hypothyroidism, hyperthyroidism, goitre and polycystic ovary syndrome.

Part D – Clinical correlation: endocrine function tests.

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PART A: HORMONES, HYPOTHALAMUS, PITUITARY, THYROID AND PARATHYROID

1. Introduction, Classification and Mechanism of Hormone Action

The **endocrine system** is a group of **ductless glands** that release chemical messengers called **hormones** directly into the **blood**.

Endocrine, paracrine and autocrine action

Type	Meaning	Example
Endocrine	Hormone travels through the blood to distant targets	Insulin, thyroxine
Paracrine	Acts on neighbouring cells by diffusion	Somatostatin in the islets, histamine
Autocrine	Acts on the same cell that released it	Interleukin-2 on T cells
Neuroendocrine	A nerve cell releases the hormone into blood	ADH, oxytocin, adrenaline

Classification of hormones (by chemical nature)

Class	Examples	Solubility and transport	Receptor
Peptide and protein hormones	Insulin, glucagon, GH, ACTH, TSH, FSH, LH, prolactin, ADH, oxytocin, PTH, calcitonin, hypothalamic releasing hormones.	**Water-soluble**; travel free in blood; short half-life; stored in vesicles	**Cell surface** membrane receptors
Amines (catecholamines)	Adrenaline, noradrenaline, dopamine	Water-soluble; short half-life	Cell surface (adrenergic receptors)
Amines (thyroid hormones)	Thyroxine (T4), triiodothyronine (T3)	**Lipid-soluble**; carried on **binding proteins (TBG)**; long half-life	**Nuclear receptor**
Steroid hormones (derived from cholesterol)	Cortisol, aldosterone, oestrogen, progesterone, testosterone, calcitriol (vitamin D)	**Lipid-soluble**; carried bound to proteins; not stored (made on demand)	**Intracellular** (cytoplasmic or nuclear)
Eicosanoids (fatty acid derived)	Prostaglandins, leukotrienes, thromboxanes	Local action (paracrine and autocrine)	Cell surface

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Mechanism of hormone action

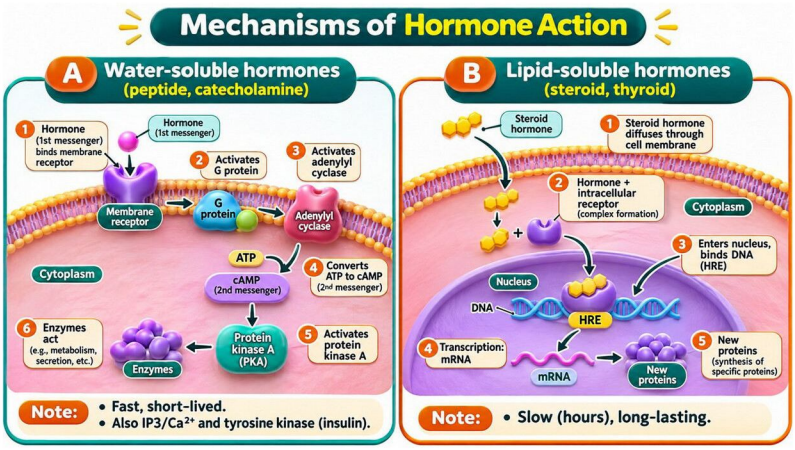

Figure 1: Mechanisms of hormone action

A. Water-soluble hormones (cell surface receptors, second messengers)

- The hormone (**first messenger**) binds to a **receptor on the cell membrane**.
- **cAMP system:** adenylyl cyclase makes **cAMP** from ATP, which activates **protein kinase A.**
- **Phospholipase C system (IP_3 and DAG):** raises intracellular **Ca^{2+}** and activates protein kinase C (e.g. oxytocin, ADH at V1, adrenaline at α1, TRH).
- **Tyrosine kinase receptors:** the receptor itself is an enzyme (**insulin, IGF-1**, growth factors).

B. Lipid-soluble hormones (intracellular receptors)

- The hormone **passes through the cell membrane** and binds to a receptor in the **cytoplasm or nucleus**.
- The effect is **slow (hours to days) but long-lasting**. Examples: cortisol, sex steroids, aldosterone, **thyroid hormones**, vitamin D.

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Regulation of hormone secretion

- **Negative feedback (most common):** the effect of the hormone reduces its own release (e.g. high blood glucose → insulin → glucose falls → insulin falls).
- **Positive feedback (rare):** the effect increases the release (e.g. oxytocin in childbirth; the LH surge before ovulation).
- **Nervous control** (adrenal medulla, posterior pituitary) and **chronotropic (rhythm) control** (cortisol is highest in the morning; melatonin at night).
- Hormone levels are also changed by **receptor up-regulation and down-regulation** (e.g. insulin resistance).

2. Hypothalamus and Pituitary Gland (Hypophysis)

The **pituitary gland** is a pea-sized gland (about 0.5 g) lying in the **sella turcica** of the sphenoid bone, attached to the **hypothalamus** by the pituitary stalk (**infundibulum**).

Part	Origin	Connection to the hypothalamus	Hormones
Anterior lobe (adenohypophysis)	Rathke's pouch (epithelial)	**Blood vessels** (hypophyseal portal system) carry **releasing and inhibiting hormones**	GH, PRL, TSH, ACTH, FSH, LH (made here)

Part	Origin	Connection to the hypothalamus	Hormones
Posterior lobe (neurohypophysis)	Nervous tissue	**Nerve fibres** (hypothalamo-hypophyseal tract) from the supraoptic and paraventricular nuclei	ADH and oxytocin (made in the hypothalamus, **stored and released here**)

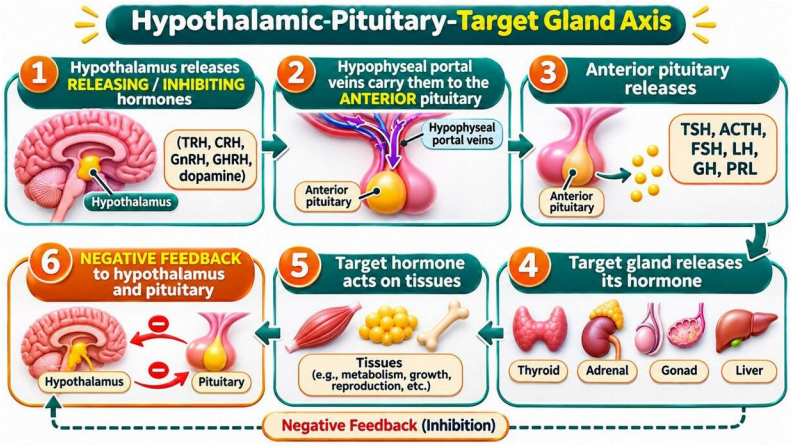

Figure 2: Hypothalamic-pituitary-target gland axis

Hypothalamic hormones

Hormone	Action on the pituitary
TRH (thyrotropin-releasing hormone)	Releases TSH and prolactin
CRH (corticotropin-releasing hormone)	Releases ACTH
GnRH (gonadotropin-releasing hormone)	Releases FSH and LH (pulsatile release is needed)
GHRH and somatostatin (GHIH)	Increase and decrease GH release
Dopamine (PIH)	**Inhibits prolactin** (so dopamine blockers like antipsychotics raise prolactin)

Anterior pituitary hormones

Hormone	Target	Main actions	Disorder
Growth hormone (GH, somatotropin)	Liver, bone, muscle, fat	Stimulates **IGF-1 (somatomedin)** from the liver → growth of bone and tissues.	Excess: **gigantism** (child), **acromegaly** (adult). Lack: **dwarfism**
Prolactin (PRL)	Breast	**Milk production** (lactation); inhibited by dopamine; suckling increases it	Excess (prolactinoma): galactorrhoea, amenorrhoea, infertility
TSH (thyroid-stimulating hormone)	Thyroid	Stimulates T3 and T4 synthesis and release, and thyroid growth	See thyroid disorders
ACTH (adrenocorticotropic hormone)	Adrenal cortex	Stimulates **cortisol** (and androgens) release and adrenal growth	Excess: Cushing's disease

Hormone	Target	Main actions	Disorder
FSH (follicle-stimulating hormone)	Ovary, testis	Female: growth of ovarian follicles, oestrogen. Male: **spermatogenesis**	-
LH (luteinising hormone)	Ovary, testis	Female: **ovulation**, corpus luteum, progesterone. Male: **testosterone** from Leydig cells	High LH in PCOS

Mnemonic: 'FLAT PEG' = **F**SH, **L**H, **A**CTH, **T**SH, **P**rolactin, **E**ndorphins, **G**H. The first four are tropic hormones (act on other glands). **GH and prolactin act directly.**

Posterior pituitary hormones

Hormone	Stimulus	Actions	Disorder
ADH (antidiuretic hormone, vasopressin)	High plasma osmolarity, low blood volume or pressure, pain, nicotine	Acts on the collecting duct (**V2 receptor, aquaporin-2**) to **reabsorb water**; vasoconstriction (V1)	**Diabetes insipidus** (lack of ADH or no response): large volumes of dilute urine, thirst.
Oxytocin	Stretching of the cervix, suckling	**Uterine contraction in labour** (positive feedback); **milk ejection (let-down)**; bonding	Used to induce labour and prevent postpartum haemorrhage

HYPOPITUITARISM AND HYPERPITUITARISM

Causes of hypopituitarism: tumour, surgery or radiation, postpartum necrosis (**Sheehan's syndrome**: bleeding in childbirth, no lactation), trauma. **Panhypopituitarism** affects all hormones.

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3. Thyroid Gland

Structure

The thyroid is a **butterfly-shaped gland** (15 to 25 g) in the front of the neck below the larynx, with **two lobes joined by an isthmus**. It is highly vascular.

Synthesis of thyroid hormones

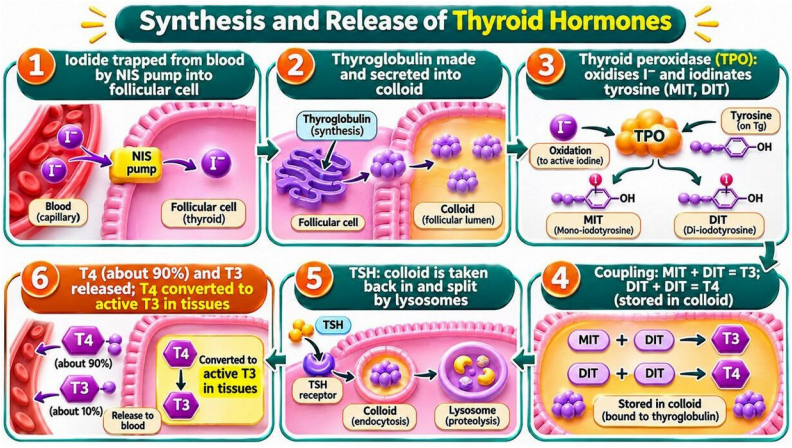

Figure 3: Synthesis and release of thyroid hormones

- **Iodine needed:** about **150 µg/day** (iodised salt, sea food, milk). The thyroid concentrates it by the **sodium-iodide symporter (NIS)**.

- **Iodination** (organification) by **thyroid peroxidase (TPO)** forms MIT and DIT; coupling forms **T3 (3 iodines) and T4 (4 iodines)**.
- In the blood, **99.9% is bound** to **thyroxine-binding globulin (TBG)**, transthyretin and albumin; only free hormone is active.
- **Drugs:** thiouracils (propylthiouracil) and carbimazole block TPO; perchlorate blocks NIS; high iodide blocks release (**Wolff-Chaikoff effect**).

Control and functions

Hypothalamus (TRH) → anterior pituitary (TSH) → thyroid (T3, T4), with **negative feedback** by T3 and T4 on the pituitary and hypothalamus.

System	Action of thyroid hormones
Metabolism	**Increase basal metabolic rate (BMR)**, oxygen use and heat production (calorigenic effect).
Growth and development	Essential for **brain development and bone growth** in the fetus and child.
Cardiovascular	Increase heart rate and force (more β1 receptors), cardiac output
Nervous system	Alertness, reflexes, mood
GI and muscle	Increase gut movement; muscle tone and strength
Reproduction	Normal menstrual cycle and fertility

Calcitonin

Calcitonin is a peptide from the **parafollicular (C) cells**. It **lowers blood calcium** by **inhibiting osteoclasts** (less bone breakdown) and increasing calcium excretion.

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4. Parathyroid Glands

There are usually **four small glands** (each about 40 mg) on the back of the thyroid. The **chief (principal) cells** secrete **parathyroid hormone (PTH)**, the main hormone for **calcium balance**.

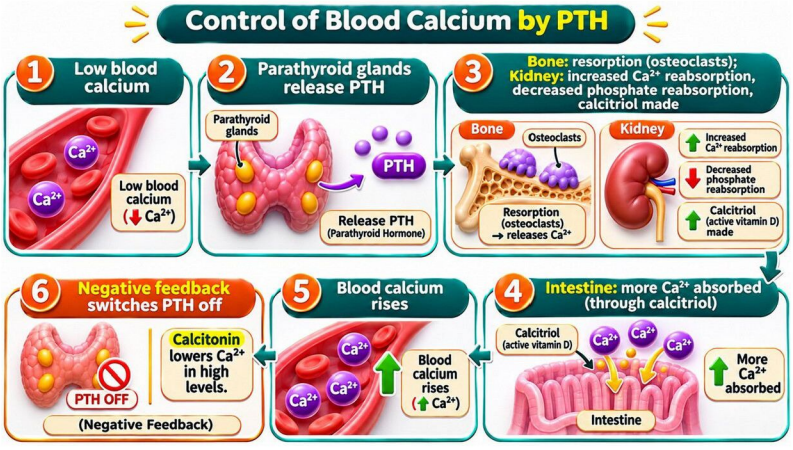

Figure 4: Control of blood calcium by PTH

Target	Action of PTH
Bone	Activates **osteoclasts** (through RANKL on osteoblasts): releases Ca^{2+} and phosphate
Kidney	**Increases Ca^{2+} reabsorption** (DCT), **decreases phosphate reabsorption (phosphaturia)**; activates **1α-hydroxylase** to make **calcitriol**
Intestine	**Indirectly increases Ca^{2+} and phosphate absorption** through calcitriol

PTH **raises blood calcium and lowers phosphate**.

VITAMIN D (CALCITRIOL) IN CALCIUM BALANCE

Skin (UV light) or diet → **vitamin D3** → liver (**25-hydroxylation**) → kidney (**1α-hydroxylation, stimulated by PTH**) → **calcitriol (active)**, which raises intestinal calcium absorption.

PART B: ADRENAL GLAND, PANCREAS, PINEAL GLAND AND THYMUS

5. Adrenal (Suprarenal) Gland

Two small, triangular glands (4 to 5 g each) lie on top of the kidneys.

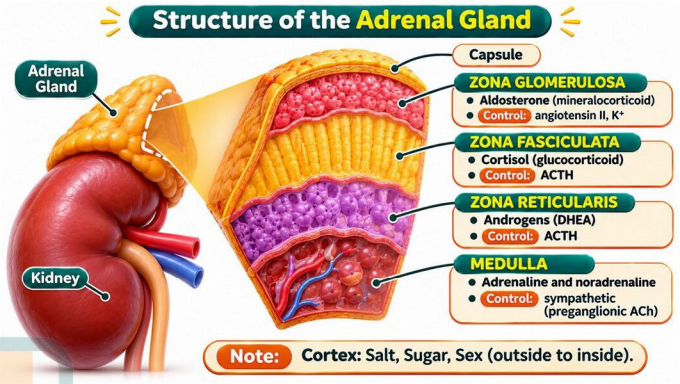

Figure 5: Structure of the adrenal gland

Mnemonic: from outside to inside, **'GFR'** = Glomerulosa, Fasciculata, Reticularis (**salt, sugar, sex**), and the medulla at the centre (**'Fight or flight'**).

Adrenal cortex hormones (all steroids from cholesterol)

Hormone	Action	Control
Aldosterone (mineralocorticoid)	Acts on the late DCT and collecting duct: **↑Na^+ and water reabsorption.**	**Angiotensin II (RAAS), high K^+** (not ACTH)
Cortisol (glucocorticoid)	**Raises blood glucose** (gluconeogenesis), breaks down protein and fat, **anti-inflammatory and immunosuppressive**, supports vascular tone, helps the body to resist stress; permissive for catecholamines	**ACTH** (CRH-ACTH-cortisol axis); highest early morning (circadian); negative feedback
Adrenal androgens (DHEA, androstenedione)	Weak androgens: pubic and axillary hair, libido in women	ACTH

Effects of cortisol

- **Metabolic:** gluconeogenesis, insulin antagonism (hyperglycaemia), protein breakdown (muscle wasting, thin skin), fat redistribution to the face and trunk.
- **Immune:** reduces inflammation (↓prostaglandins, ↓cytokines, ↓lymphocytes and eosinophils); **steroid drugs are used for this action**.
- **Others:** increases blood pressure, bone loss (osteoporosis), mood changes, gastric acid increase, **helps in stress (the 'stress hormone')**.

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Adrenal medulla hormones

The medulla is a modified **sympathetic ganglion**. Its **chromaffin cells** secrete **adrenaline (about 80%)** and **noradrenaline (20%)** when stimulated by **preganglionic sympathetic nerves (acetylcholine)**.

Disorders of the adrenal gland

Disorder	Cause	Features
Cushing's syndrome	Excess cortisol: long-term **steroid drugs (commonest)**, pituitary adenoma (**Cushing's disease**), adrenal tumour, ectopic ACTH	**Moon face, buffalo hump, central obesity, purple striae, thin skin**, muscle wasting, hypertension, **diabetes**, osteoporosis, infections, mood changes.
Addison's disease (primary adrenal insufficiency)	**Autoimmune destruction** (commonest), TB, haemorrhage; low cortisol and aldosterone, **high ACTH**	Fatigue, weight loss, **hyperpigmentation** (ACTH), **hypotension, hyponatraemia, hyperkalaemia**, hypoglycaemia; **Addisonian crisis** is a medical emergency.
Conn's syndrome (primary hyperaldosteronism)	Aldosterone-secreting adenoma	Hypertension, **hypokalaemia**, muscle weakness, metabolic alkalosis; low renin
Phaeochromocytoma	Tumour of the adrenal medulla (catecholamines)	**Episodes of severe hypertension, headache, sweating, palpitation and anxiety**; treat with alpha-blocker (phenoxybenzamine) then beta-blocker, and surgery.
Congenital adrenal hyperplasia	**21-hydroxylase deficiency**: no cortisol → high ACTH → excess androgens	Ambiguous genitalia in girls, early puberty, salt loss

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6. Pancreas (Endocrine Part)

The pancreas is a mixed gland. The **endocrine part (about 1 to 2%)** consists of about **1 million islets of Langerhans**, scattered among the acini and rich in capillaries.

Cell	Share	Hormone	Main action
Alpha (α) cells	20%	**Glucagon**	**Raises blood glucose**
Beta (β) cells	**70%**	**Insulin** (with **C-peptide** and amylin)	**Lowers blood glucose**
Delta (δ) cells	5%	**Somatostatin**	Inhibits insulin, glucagon and growth hormone release (paracrine)
PP (F) cells	Small	Pancreatic polypeptide	Regulates pancreatic and gut secretion

Insulin

- A **51 amino acid peptide** (A chain 21 + B chain 30, joined by 2 disulphide bridges), made as **preproinsulin → proinsulin → insulin + C-peptide**.
- **Stimuli for secretion: high blood glucose (main)**, amino acids, GI hormones (**GLP-1, GIP**), vagal stimulation, sulphonylurea drugs.

- **Mechanism of release:** glucose enters beta cells (**GLUT2**) → ATP rises → **K^+-ATP channels close** → depolarisation → **Ca^{2+} channels open** → insulin vesicles are released (**sulphonylureas act by closing the K^+-ATP channel**).

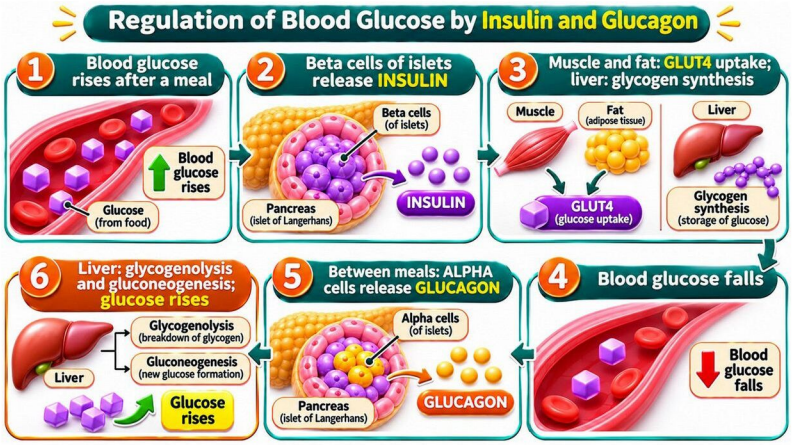

Figure 6: Regulation of blood glucose by insulin and glucagon

Tissue	Action of insulin
Muscle and fat	Insert **GLUT4** transporters → **glucose uptake**; glycogen synthesis (muscle); fat synthesis (**lipogenesis**) and storage.
Liver	Increases **glycogenesis, glycolysis** and fat synthesis; **inhibits glycogenolysis and gluconeogenesis**
General	Pushes K^+ into cells (used in treating hyperkalaemia); promotes growth. **Anabolic hormone**

Glucagon

A **29 amino acid peptide** from alpha cells. Released when **blood glucose is low**, in fasting, exercise and by amino acids (high-protein meal).

> **NORMAL BLOOD GLUCOSE VALUES**
> **Fasting 70 to 99 mg/dL**; 2 hours after a meal below 140 mg/dL. **Hypoglycaemia** is below 70 mg/dL (symptoms: sweating, tremor, palpitation, confusion, coma; treat with glucose or glucagon).

7. Pineal Gland

A small, **pine-cone shaped gland (about 0.1 g)** attached to the roof of the **third ventricle** of the brain.

- **Regulates the sleep-wake (circadian) rhythm** and the biological clock; **helps sleep** (used in insomnia, jet lag and shift work; **ramelteon and agomelatine** are melatonin receptor agonists).
- Inhibits the gonads before puberty (delays puberty) and affects seasonal reproductive rhythms in animals.
- **Antioxidant** and mild immune effects. The pineal gland **calcifies with age** (a landmark on X-ray).

8. Thymus Gland

The thymus is a **bilobed lymphoid organ** behind the sternum in the upper chest (mediastinum).

- **T cell maturation:** immature T cells (thymocytes) from the bone marrow enter the cortex.

- **Hormones: thymosin, thymopoietin and thymulin** help T cell development and function. The **epithelial cells and Hassall's corpuscles** support maturation.
- **Disorders: DiGeorge syndrome** (thymic aplasia, low T cells, low calcium), **myasthenia gravis** (associated with thymic hyperplasia or thymoma; treated by thymectomy), SCID, thymoma.

PART C: PATHOPHYSIOLOGY OF ENDOCRINE DISORDERS

9. Diabetes Mellitus

Definition

Diabetes mellitus (DM) is a group of **metabolic disorders with chronic hyperglycaemia** due to a **defect in insulin secretion, insulin action, or both**. It affects carbohydrate, fat and protein metabolism.

Classification

Type	Features
Type 1 DM (IDDM)	**Autoimmune destruction of beta cells**; absolute insulin deficiency.
Type 2 DM (NIDDM)	**Insulin resistance + relative insulin deficiency**; adults, obesity (90 to 95% of cases); gradual onset; strong family history.
Gestational DM	Glucose intolerance first found in **pregnancy** (hormones such as human placental lactogen cause resistance); raises the risk of later type 2 DM and large babies
Other specific types	MODY (single gene defect), pancreatic disease (pancreatitis), endocrine disease (Cushing's, acromegaly), drugs (steroids, thiazides)

Pathophysiology of type 1 diabetes

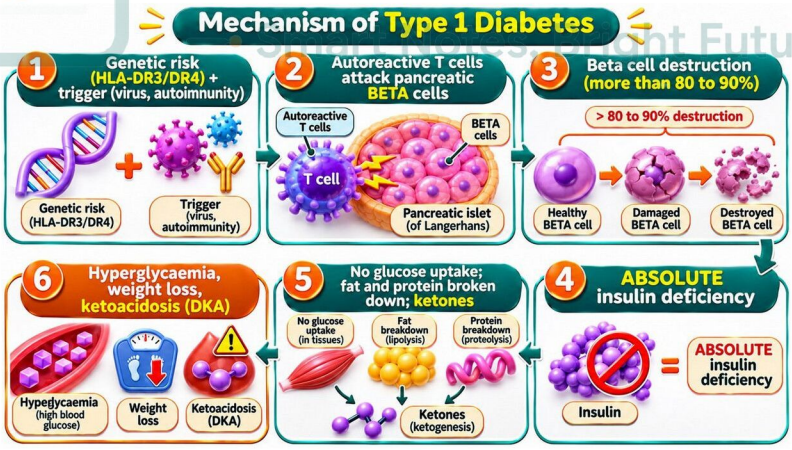

Figure 7: Mechanism of type 1 diabetes

- **Genes:** HLA-DR3 and DR4 (HLA class II); **environment:** viral infection (Coxsackie B, rubella), early cow's milk.
- **CD8⁺ T cell and macrophage attack (insulitis)** destroy more than 80 to 90% of the beta cells, so there is **little or no insulin and no C-peptide**.

Pathophysiology of type 2 diabetes

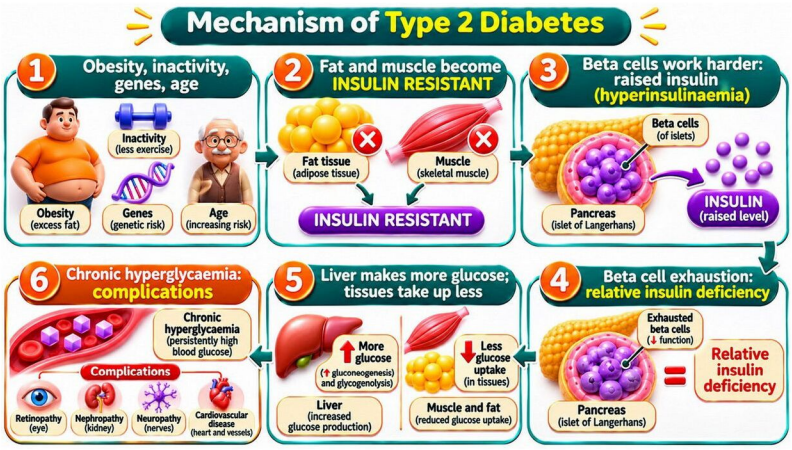

Figure 8: Mechanism of type 2 diabetes

- **Insulin resistance** in muscle, fat and liver: the cells respond poorly to insulin (fewer GLUT4 signals, post-receptor defects.
- At first, **beta cells compensate** by making more insulin (hyperinsulinaemia).
- The liver makes **too much glucose (loss of suppression by insulin)**; **incretin effect** (GLP-1) is reduced; **glucagon is high**.
- Insulin is still present, so **ketoacidosis is rare** (but a **hyperosmolar hyperglycaemic state** can occur).

Metabolic changes and clinical features

- **Lack of insulin effect:** glucose cannot enter cells → **hyperglycaemia** (when above the renal threshold of 180 mg/dL.
- **Classic triad: the 3 Ps: polyuria, polydipsia, polyphagia**; also fatigue, blurred vision, recurrent infections, slow healing, itching (candidiasis).
- **Fat breakdown (lipolysis) → free fatty acids → liver → ketone bodies (acetoacetate, β-hydroxybutyrate.**

Diagnosis (ADA criteria)

Test	Normal	Prediabetes	Diabetes
Fasting plasma glucose (8 hours)	Below 100 mg/dL	100 to 125	**126 mg/dL or more**
2-hour glucose in OGTT (75 g load)	Below 140	140 to 199	**200 or more**
HbA1c (glycated haemoglobin)	Below 5.7%	5.7 to 6.4%	**6.5% or more**
Random glucose with symptoms	-	-	**200 mg/dL or more**

HbA1c reflects the **average glucose over the last 2 to 3 months** (life span of red cells); the **treatment target is usually below 7%**.

Complications

Type	Complication	Mechanism and features
Acute	**Diabetic ketoacidosis (DKA)**	Type 1; high glucose, **ketones, metabolic acidosis**; treat with IV fluid, **insulin infusion**, potassium
	Hyperosmolar hyperglycaemic state (HHS)	Type 2, elderly; very high glucose (above 600 mg/dL), severe dehydration, **no significant ketosis**

Type	Complication	Mechanism and features
	Hypoglycaemia	Treatment-related (insulin, sulphonylureas); sweating, tremor, confusion, coma
Chronic microvascular	**Retinopathy**	Capillary damage; leading cause of blindness
	Nephropathy	Glomerular damage (Kimmelstiel-Wilson nodules); albuminuria → kidney failure
	Neuropathy	Numbness, burning pain in feet, autonomic problems, **foot ulcers**

HOW DOES HIGH GLUCOSE CAUSE DAMAGE?

Polyol pathway: excess glucose is converted by **aldose reductase to sorbitol**, which collects in the lens, nerves and retina (cataract, neuropathy).

Basis of treatment

Group	Examples	Mechanism
Insulin	Regular, lispro, aspart (rapid); NPH (intermediate); glargine, detemir, degludec (long-acting)	Replaces insulin; essential in type 1
Biguanide	**Metformin** (first-line in type 2)	↓Hepatic glucose production, ↑insulin sensitivity; no weight gain; risk of lactic acidosis in renal failure.
Sulphonylureas	Glimepiride, glibenclamide, gliclazide	Close the beta cell K^+-ATP channel: ↑insulin release; risk of hypoglycaemia and weight gain
Thiazolidinediones	Pioglitazone	PPAR-γ agonist: ↑insulin sensitivity
α-Glucosidase inhibitors	Acarbose, voglibose	Delay carbohydrate absorption in the gut
DPP-4 inhibitors and GLP-1 agonists	Sitagliptin, vildagliptin; liraglutide, semaglutide	Raise incretin effect: ↑glucose-dependent insulin, ↓glucagon (GLP-1 agonists also cause weight loss)

10. Hypothyroidism

Definition

Hypothyroidism is a condition of **low thyroid hormone (T3 and T4) levels**, which slows the body's metabolism.

Causes

Type	Causes
Primary (thyroid, 95%)	**Hashimoto's thyroiditis (commonest, autoimmune; anti-TPO and anti-thyroglobulin antibodies)**; **iodine deficiency** (commonest cause worldwide).
Secondary	Pituitary failure (low TSH)
Tertiary	Hypothalamic failure (low TRH)

Pathophysiology

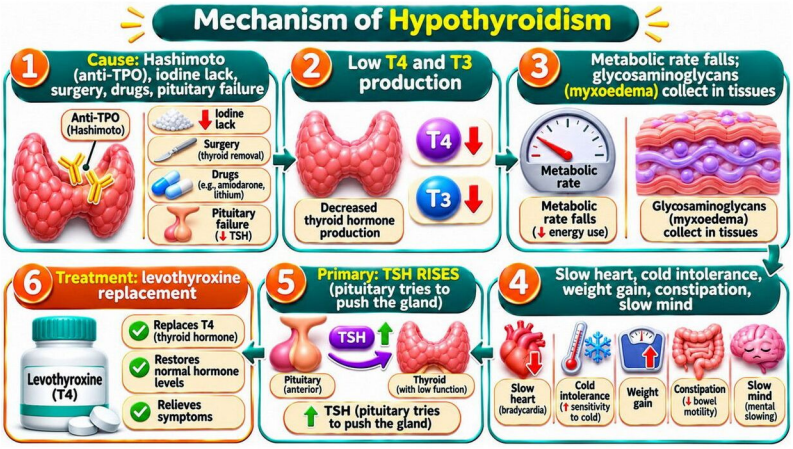

Figure 9: Mechanism of hypothyroidism

- **Hashimoto's: autoreactive T cells and antibodies (type IV hypersensitivity)** destroy the thyroid follicles, with lymphocyte infiltration and fibrosis.
- Low T3 and T4 reduce the **basal metabolic rate**, heat production and protein synthesis.
- **Myxoedema: glycosaminoglycans (hyaluronic acid) collect in the skin and tissues**, binding water: non-pitting swelling, puffy face, thick tongue and hoarse voice.
- LDL cholesterol rises because of less LDL receptor expression (**risk of atherosclerosis**).

Clinical features

System	Features
General	Tiredness, **cold intolerance**, **weight gain** with poor appetite, hoarse voice, puffy face
Skin and hair	Dry, coarse, pale skin; hair loss (outer third of eyebrows); brittle nails
Heart	**Slow heart rate (bradycardia)**, low cardiac output, pericardial effusion, high cholesterol
GI and muscle	**Constipation**, muscle weakness, cramps
Nervous and mental	Slow thinking, poor memory, depression, slow relaxation of reflexes (**delayed ankle jerk**)
Reproductive	Heavy periods (menorrhagia), infertility

Diagnosis and treatment

- **Primary hypothyroidism: high TSH, low free T4** (subclinical: high TSH with normal T4).
- **Treatment: levothyroxine (T4) lifelong**, taken on an **empty stomach** (30 to 60 minutes before breakfast), apart from calcium.

11. Hyperthyroidism (Thyrotoxicosis)

Definition

Hyperthyroidism means **excess synthesis and release of thyroid hormone by the thyroid**.

Causes

Cause	Details
Graves' disease (about 70 to 80%)	**Autoimmune: thyroid-stimulating immunoglobulins (TSI, TRAb)** bind to the **TSH receptor** and **stimulate it continuously** (type II hypersensitivity); diffuse goitre; eye disease; more in women (20 to 50 years).
Toxic multinodular goitre	Autonomous nodules (older persons)
Toxic adenoma	Single autonomous nodule
Thyroiditis	Inflammation (subacute, postpartum): stored hormone leaks out for a limited time
Others	Excess iodine or amiodarone, excess thyroxine tablets, TSH-secreting tumour (rare), thyroid storm (a crisis)

Pathophysiology

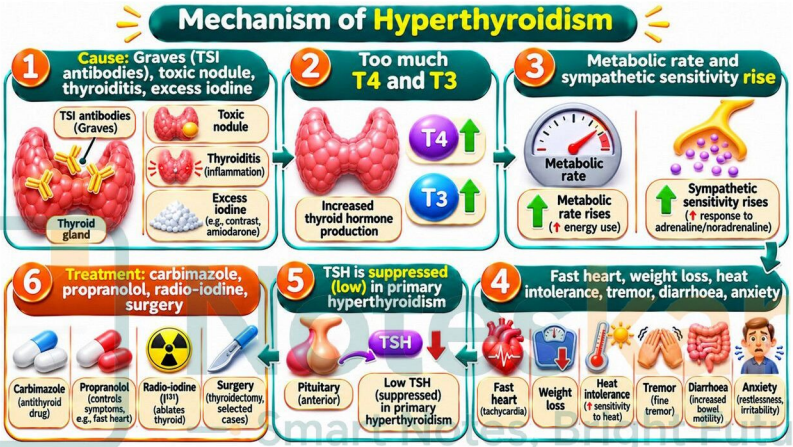

Figure 10: Mechanism of hyperthyroidism

- **In Graves' disease** the antibodies mimic TSH, so the gland makes too much T3 and T4 and **escapes negative feedback**, and **TSH is low**.
- Excess thyroid hormone **raises BMR, oxygen use and heat production**, and **increases the number and sensitivity of β-adrenergic receptors**, which causes many of the 'sympathetic' symptoms.
- **Graves' eye disease (exophthalmos):** antibodies against orbital fibroblasts cause **glycosaminoglycan deposition and inflammation** behind the eye.

Clinical features

System	Features
General	**Heat intolerance, sweating, weight loss despite a good appetite**, fatigue, warm moist skin
Heart	**Tachycardia, palpitations, atrial fibrillation**, high pulse pressure, heart failure
Nervous and mental	**Tremor**, anxiety, irritability, insomnia, brisk reflexes
GI and muscle	**Diarrhoea** (frequent stools), proximal muscle weakness
Reproductive	Scanty periods, infertility
Eye and neck	Lid retraction and lid lag; **exophthalmos** and diplopia (Graves'); **goitre** with a bruit

Diagnosis and treatment

- **Low TSH, high free T4 and T3** (T3 toxicosis: only T3 high); **TSH-receptor antibodies** in Graves'.
- **Antithyroid drugs: carbimazole (methimazole)** and **propylthiouracil (PTU, preferred in the first trimester and thyroid storm; also blocks T4 → T3 conversion)**.
- **Beta-blockers (propranolol)** for quick control of tremor, palpitations and anxiety.
- **Radioactive iodine (I-131)** destroys thyroid tissue (contraindicated in pregnancy); **surgery (thyroidectomy)** for large goitre; lifelong levothyroxine is needed afterwards.

12. Goitre

Definition

Goitre is **enlargement of the thyroid gland** (a swelling at the front of the neck that moves up on swallowing).

Types and causes

Type	Cause and features
Simple (endemic) goitre	**Iodine deficiency** in hilly areas (the Himalayan belt, 'goitre belt' of India).
Sporadic goitre	**Goitrogens**: cabbage, cassava, soy, drugs (**lithium, amiodarone**), enzyme defects in hormone synthesis (dyshormonogenesis)
Diffuse toxic goitre	**Graves' disease**
Multinodular goitre	Long-standing simple goitre with nodules; may become **toxic (Plummer's disease)**
Hashimoto's goitre	Autoimmune thyroiditis; firm rubbery goitre
Thyroid nodule or cancer	Single nodule: adenoma, cyst, **papillary carcinoma (commonest)**, follicular, medullary, anaplastic.

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Pathophysiology of iodine-deficiency goitre

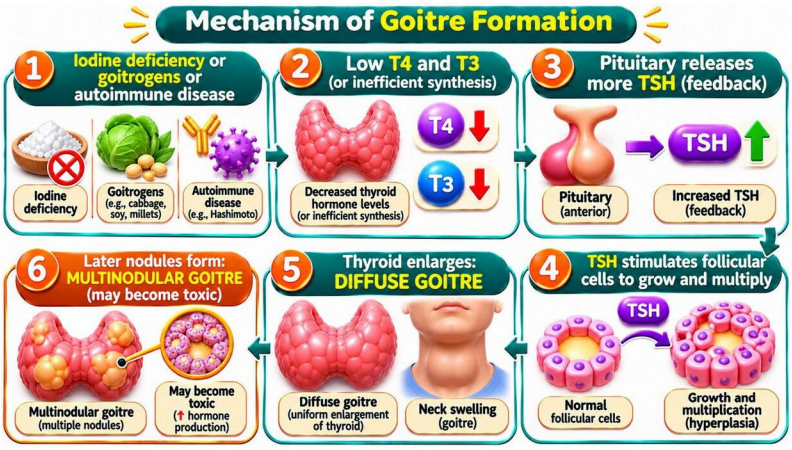

Figure 11: Mechanism of goitre formation

- **Iodine lack → less T3 and T4 → loss of negative feedback → more TSH.** TSH stimulates **growth (hypertrophy and hyperplasia) of follicular cells** to trap more iodine, and the gland enlarges to keep hormone output normal (**compensated goitre, euthyroid**).
- With **long-term stimulation**, some follicles become **autonomous** (nodules) and may later secrete hormone without TSH: **toxic multinodular goitre**.

Complications, diagnosis and treatment

- **Pressure effects of a large goitre:** difficulty in swallowing, breathing and hoarseness (recurrent laryngeal nerve), **retrosternal extension**, cosmetic problem, thyroid dysfunction, and malignancy in a nodule.
- **Diagnosis:** examination, **TSH, T4, T3**, antibodies, ultrasound, FNA, radio-iodine scan, **urinary iodine**.
- **Treatment: iodine supplement** (iodised salt: the national programme), **levothyroxine** to suppress TSH (in some diffuse goitres).
- **Prevention: universal salt iodisation (15 ppm at the consumer level in India)**; the recommended iodine intake is about 150 µg/day (250 µg in pregnancy).

13. Polycystic Ovary Syndrome (PCOS)

Definition

PCOS is the **commonest endocrine disorder in women of reproductive age (about 5 to 15%, and over 20% in some Indian studies)**.

Diagnosis: Rotterdam criteria (any 2 of 3, after excluding other causes)

- **1. Oligo-ovulation or anovulation:** irregular or absent periods (cycle above 35 days or fewer than 8 per year).
- **2. Clinical or biochemical hyperandrogenism:** hirsutism, acne, scalp hair thinning, raised testosterone.
- **3.**

Pathophysiology

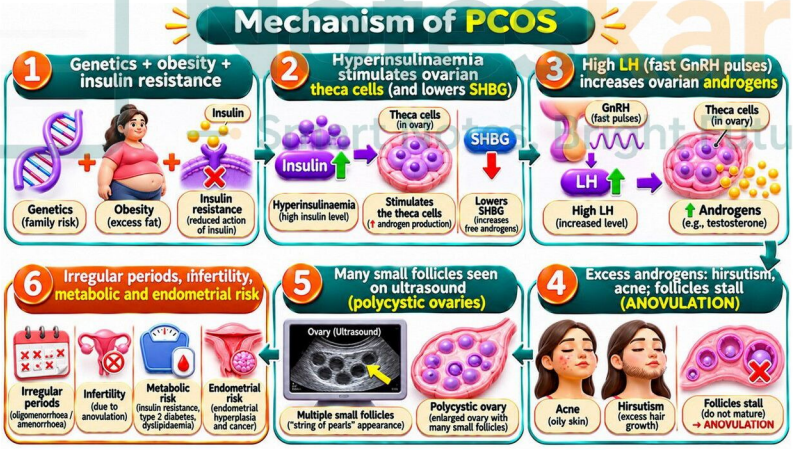

Figure 12: Mechanism of PCOS

- **Insulin resistance and compensatory hyperinsulinaemia** (even in lean women): insulin acts with LH on the ovarian **theca cells** to **increase androgen production**, and **reduces liver production of SHBG** (sex hormone-binding globulin) so that **more free testosterone** is available.
- **High LH and normal or low FSH** (fast GnRH pulses): the **LH:FSH ratio is raised (above 2:1)**.
- **Excess androgens** in turn disrupt feedback and keep the cycle abnormal (a vicious circle).
- **Genes, intra-uterine environment, obesity and inflammation** contribute. Adipose tissue also converts androgens to oestrogen.

Clinical features

Group	Features
Menstrual and reproductive	**Oligomenorrhoea or amenorrhoea**, infertility from anovulation (the commonest cause of anovulatory infertility), miscarriage
Androgen excess	**Hirsutism** (face, chest, abdomen), acne, oily skin, **male-pattern hair loss**, rarely virilisation (should suggest a tumour).
Metabolic	**Obesity (central)**, **insulin resistance, type 2 diabetes, dyslipidaemia, hypertension (metabolic syndrome)**, fatty liver.
Long-term risks	**Endometrial hyperplasia and cancer** (unopposed oestrogen), cardiovascular disease, depression and anxiety, pregnancy complications (gestational diabetes, pre-eclampsia).

Investigations and treatment

- **Tests:** testosterone, **LH and FSH**, prolactin, TSH, **17-hydroxyprogesterone** (to exclude non-classic CAH), fasting glucose or OGTT, lipids, **transvaginal ultrasound**.
- **Lifestyle: weight loss (5 to 10%), diet and exercise** restore ovulation in many women (**first-line treatment**).
- **Menstrual regulation and androgen control: combined oral contraceptives** (lower LH and androgens, protect the endometrium); **progestin** withdrawal; **anti-androgens (spironolactone.**
- **Insulin sensitisers: metformin** (improves insulin resistance and cycle regularity), inositol.
- **Infertility: clomiphene citrate** or **letrozole (first-line ovulation induction)**, gonadotropins, laparoscopic ovarian drilling, IVF.

Drug	Mechanism in PCOS
Metformin	↓Insulin resistance and hepatic glucose production → ↓androgens
Clomiphene (SERM)	Blocks oestrogen receptors in the hypothalamus, so FSH and LH rise and ovulation occurs
Letrozole (aromatase inhibitor)	Lowers oestrogen and increases FSH; higher live birth rate than clomiphene
Combined oral contraceptive	Suppress LH and ovarian androgen, increase SHBG; regulate periods
Spironolactone, finasteride	Anti-androgens for hirsutism

PART D: CLINICAL CORRELATION AND REFERENCE TABLES

14. Endocrine Function Tests

Test	Normal (approx.)	Use
TSH	0.4 to 4.0 mIU/L	Best first test of thyroid function (high in primary hypothyroidism, low in hyperthyroidism)
Free T4 and T3	T4 0.8 to 1.8 ng/dL; T3 80 to 200 ng/dL	Confirm thyroid status
Anti-TPO / TSH-receptor antibodies	Negative	Hashimoto's / Graves' disease

Test	Normal (approx.)	Use
Fasting glucose, OGTT, HbA1c	Below 100 mg/dL; below 140; below 5.7%	Diabetes diagnosis and control
C-peptide, islet autoantibodies	-	Type 1 versus type 2
Serum calcium and PTH	Ca 8.5 to 10.5 mg/dL	Parathyroid disease

GLUCOSE EMERGENCY DRUGS

Hypoglycaemia: oral glucose, IV 25% dextrose, **glucagon IM**. **DKA:** IV saline, **regular insulin infusion**, potassium replacement, treat the cause.

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