Pathophysiology-Endocrine system

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Thyroid gland

produce by ← thyroid gland into circulation.

- The thyroid is a butterfly-shaped gland located in the front of the neck just above the trachea.
- **The thyroid produces and releases into the circulation at least two potent hormones, thyroxine (T_4) and triiodothyronine (T_3),** which influence basal metabolic processes and/or enhance oxygen consumption in nearly all body tissues.
- Thyroid hormones also influence linear growth, and brain function including intelligence and memory, neural development, dentition, and bone development.

brain development ←

1 2 3 4 5 6 7

استهلاك — النمو الطولي — نمو الأسنان

- **The thyroid gland produces hormones by utilizing iodide** (100 µg daily requirement) obtained either from dietary sources or from the metabolism of thyroid hormones and other iodinated compounds.

- **The iodide trapped by the thyroid gland** is subsequently oxidized to iodine by the enzyme thyroid peroxidase, which is **then utilized to produce T_4 and T_3.**

- **T_3 is also produced in other tissues such as the pituitary, liver, and kidney** by the removal of an iodine molecule from T_4 and is the most potent thyroid hormone produced (**3-5 times more potent than T_4**).

- **T_4 and T_3 are both stored in the thyroglobulin protein of the thyroid gland and released into the circulation through the action of pituitary derived thyrotropin (thyroid-stimulating hormone (TSH)).**

→ T_3 and T_4 after produces stored in thyroglobulin protien in thyroid gland ⇒ when the body need these hormone ⇒ pituitary gland released TSH ⇒ this hormone stimulate thyroid gland to release T_3 and T_4 in circulation.

- TSH, secreted by thyrotroph cells located in the **anterior pituitary gland**, regulates thyroid gland function and hormone synthesis and release. **TSH secretion is induced by thyrotropin-releasing hormone (TRH) produced in the hypothalamus**

Note: TRH ينتج في hypothalamus يحفز إفراز (TSH) الذي ينتج من anterior pituitary gland الذي يحفز إفراز (T_3, T_4) اللذان ينتجان في thyroid

- **The secretion of both TSH and TRH is regulated by negative feedback from thyroid hormone, predominantly T_3, from the circulation and/or T_3 that is produced locally from the intracellular conversion of T_4 to T_3.**

خصوصًا

↑ T_3 or T_4 ⇒ ↓ TSH, TRH or ↓ T_3, T_4 ⇒ ↑ TSH, TRH

T_3 has two source

- from circulation
- locally from intracellular conversion T_4 to T_3

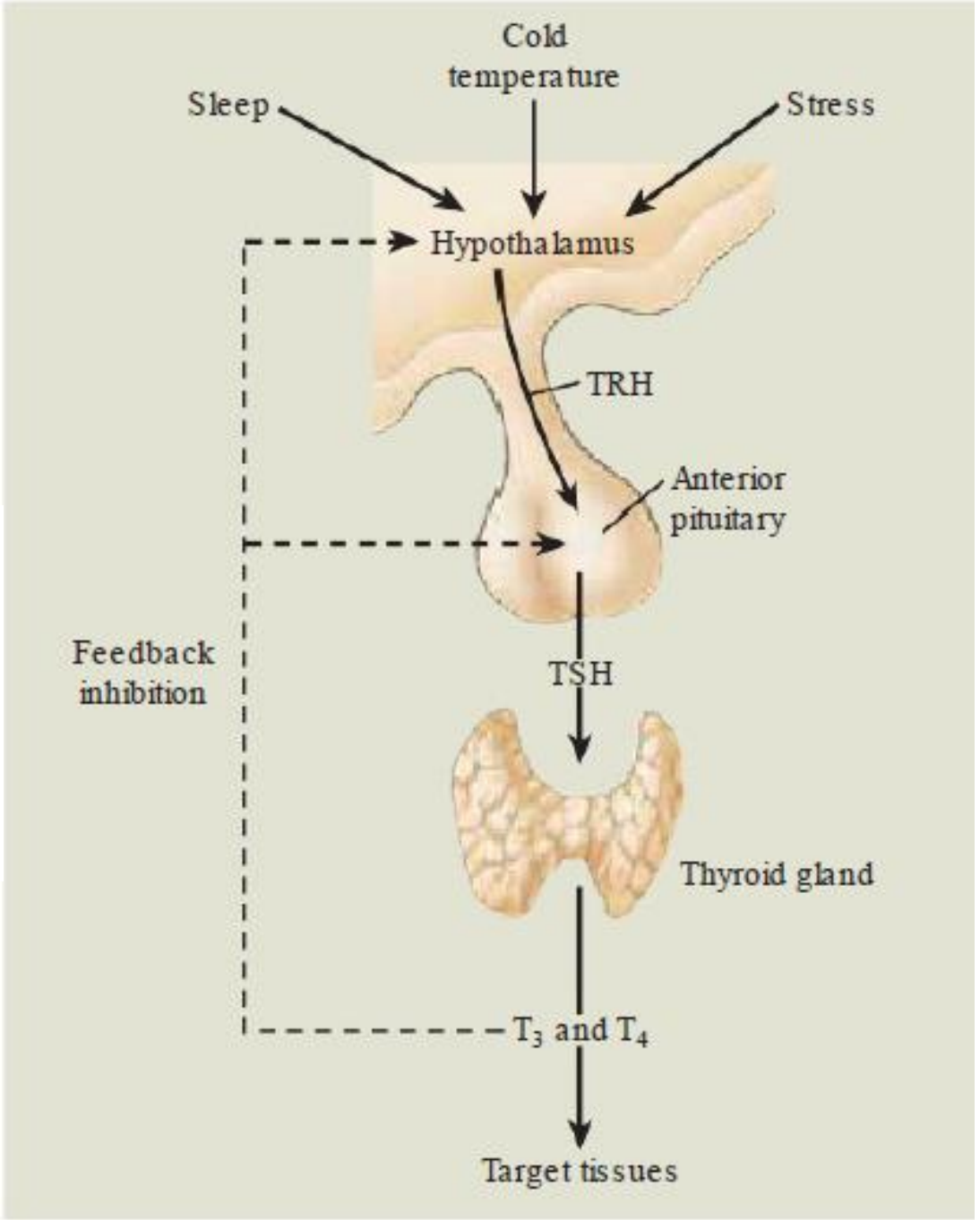


FIGURE 32-6. The hypothalamic-pituitary-thyroid feedback system, which regulates the body levels of thyroid hormone. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

- **T_4 and T_3 circulate bound primarily to carrier proteins.** → thyroxine binding globulin, albumin and prealbumin → in blood
- **T_4** binds strongly to **thyroxine-binding globulin** (75%) and weakly to **prealbumin** (transthyretin, 20%) and **albumin** (5%).
- **T_3** binds tightly to **TBG** and weakly to **albumin**, with little binding to **prealbumin**. ↳ little binding with T_4
- Only a small amount of free T_4 (approximately 2 ng/dl) and T_3 (approximately 0.3 ng/dl) circulates in a free state, and it is this **free concentration that is considered responsible for the biological effects of the thyroid hormones.** ↳ اللي بتكون مرتبطة ببروتينات ناقلة ما بتتفاعل مباشرة مع الجسم بينما الحرة تتفاعل مع خلايا الجسم مباشرة لذلك هي الأكثر أهمية من الناحية البيولوجية
- Any physiologic situations associated with a change in the serum concentration of these thyroid-binding proteins-such **as pregnancy, non-thyroidal illness, or ingestion of drugs that** affect the level and/or affinity of these binding proteins, will lead to changes in the concentrations of total T_4 and T_3. → (T_3, T_4 level) ↳ غالبًا ما بالأعلى → T_3, T_4 with proteins carriers
- The serum concentration of free T_4 and free T_3 are raised in hyperthyroidism and decreased in hypothyroidism.

Actions of thyroid hormone

لبيعمل زيادة بشكل عام
هاعد الوزن بنقصه
(hyperthyroidism)

- **Cardiorespiratory function:** the increase in metabolism will increase the O_2 consumption and metabolic end product which will cause vasodilation.

  ↳ increase blood flow and increase tension

- **Gastrointestinal function:** It increases motility and GI secretions leading to diarrhea. Increase in appetite and food intake due to an increase in metabolic rate and weight loss.

- **Neuromuscular effects:** an increase in the hormone increases the muscle function and tone leading to tremors. It is also important in the brain development in infants and an increase in the hormone leads to sweating, nervousness, anxiety, and difficulty in sleep. These match the activation of the sympathetic nervous system and sympathetic antagonist were found to be of great benefits.

THYROID FUNCTION TESTING

اختبارات وظائف الغدة الدرقية

المصلية (في الدم) — المناعية

Serum-based tests available by immunoassay include:

- Total thyroxine (TT_4 and TT_3) and free (FT_4 and FT_3) hormone.

  تتأثر بأشياء لا علاقة لها بنشاط الغدة مثل بعض الأدوية والحمل — له علاقة بنشاط الغدة

- Direct measurements of thyroid hormone binding plasma proteins, thyroxine-binding globulin (TBG), prealbumin, and albumin are also available.

  تؤثر على (TT_3, TT_4) وليس على (FT)

- Thyroid-stimulating hormone (TSH, thyrotropin) assay.

  يؤثر على عملية إطلاق T_4, T_3 لذا هو يؤثر على نشاط الغدة

- Other methods in thyroid testing include the measurement of thyroid gland autoantibodies, including antithyroid peroxidase, antithyroglobulin, and antibodies against the TSH receptor.

  protein carrier

  الإنزيم اللي يحول iodide إلى iodine الذي يستخدم في T_4, T_3

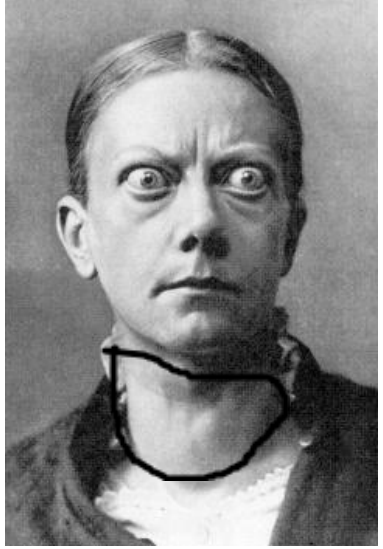
Hypothyroidism

- Hypothyroidism is a **hypometabolic state result from a deficiency in T_4 and T_3.**
- Its major **clinical manifestations** are fatigue, lethargy, cold intolerance, slowed speech, and intellectual function, slowed reflexes, hair loss, dry skin, weight gain, and constipation. It is more prevalent in women than men.
- The most common cause of hypothyroidism is a **disease of the thyroid itself, primary hypothyroidism**. The most common cause of primary hypothyroidism is **chronic autoimmune thyroiditis (Hashimoto's disease),** in which the thyroid is destroyed by antibodies or lymphocytes that attack the gland.
- Other causes are **radioactive iodine and surgical therapy for hyperthyroidism or thyroid cancer, thyroid inflammatory disease, iodine deficiency.**

Hashimoto's Disease

Diagnosis of Hypothyroidism

- **Secondary or central hypothyroidism** may also occur rarely (<1% of cases) as a result of deficiency of TRH or impaired TSH secretion due to hypothalamic or pituitary disease, respectively, because of the negative feedback relationship between serum T_4 and T_3 levels and TSH secretion.
- If an individual has **a high serum TSH concentration and a low free T_4 level, it confirms the diagnosis of primary hypothyroidism.**
- **The diagnosis of secondary hypothyroidism is based on the findings of a low serum free T_4 level and a serum TSH level is low.**



Hyperthyroidism

- Hyperthyroidism is **a hypermetabolic state, that results from excess production of T_4 and T_3**.
- Its major **clinical manifestations** are nervousness, anxiety, heart palpitations, rapid pulse, fatigability, tremor, muscle weakness, weight loss with increased appetite, heat intolerance, frequent bowel movements, increased perspiration (sweating), and often thyroid gland enlargement (goiter). Most individuals with hyperthyroidism are women.
- The most common cause of hyperthyroidism is **Graves' disease**, an autoimmune disease characterized by the production of antibodies that activate the TSH receptor, resulting in stimulation of T_4 and T_3 production and enlargement of the thyroid.

Diagnosis of Hyperthyroidism

- Other causes of hyperthyroidism are a **multinodular goiter, solitary thyroid adenoma, thyroiditis, iodide- or drug-induced hyperthyroidism, and, very rarely, a TSH secreting pituitary tumor.**

- The diagnosis of hyperthyroidism is based on the findings of a **high serum free T_4 level and a low serum TSH concentration**.

Effect of Medications on Thyroid Test Results

- **High doses of glucocorticoids (adrenal hormones)** can lower the serum T_3 concentration by inhibiting the peripheral conversion of T_4 to T_3 and lower serum T_4 (and T_3) by **inhibiting TSH secretion**.

- **Iodide,** contained in solutions used to sterilize the skin and in radiopaque contrast media used in coronary angiography and many other radiological procedures, can cause **either hyper- or hypothyroidism**, depending on whether the individual has a nodular goiter or some unsuspected thyroid injury.

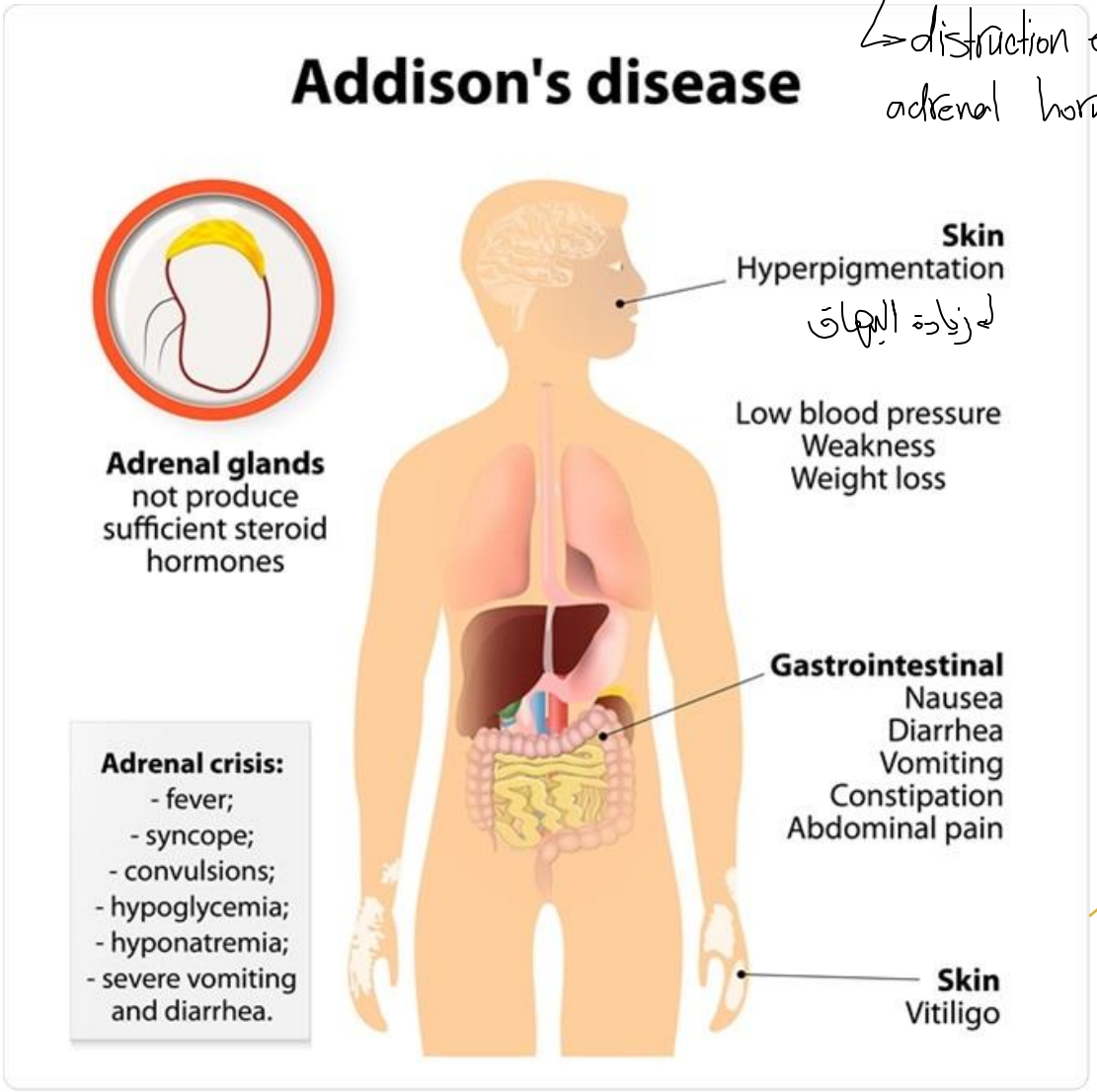
- **The iodide-containing drug amiodarone**, given to patients with cardiac arrhythmias, can also cause either hypothyroidism or hyperthyroidism in appropriately susceptible individuals.

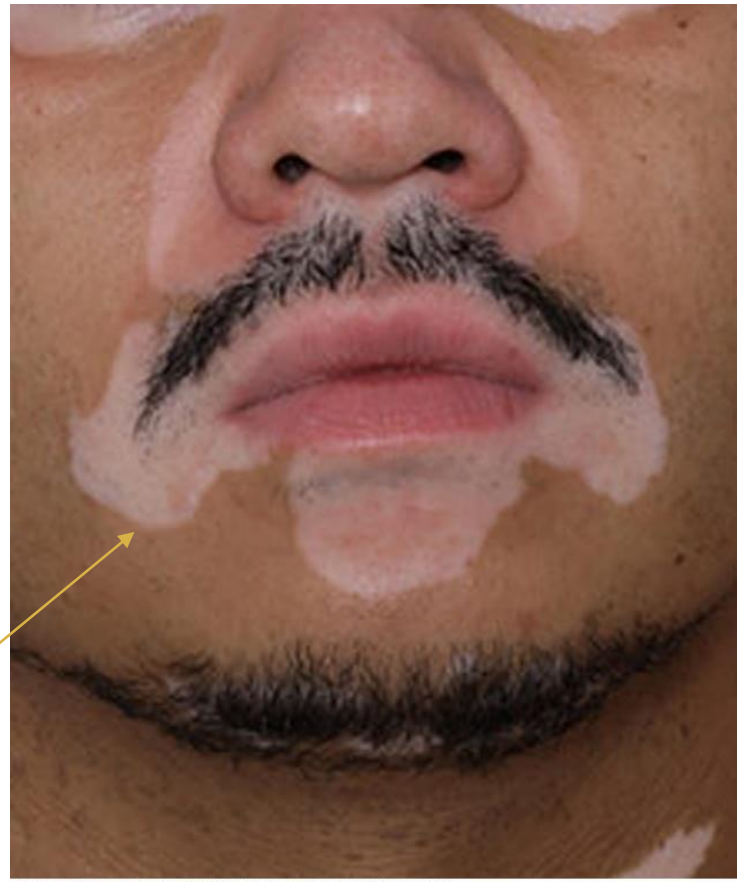
Adrenal gland

- About 5 g size each located over both kidneys.
- The **adrenal medulla** is responsible for the production of adrenaline.
  → epinephrine , norepinephrine
- The **adrenal cortex** is responsible for the production of three hormones:
  - ✓ **Mineralocorticoid (aldosterone)** along with renin-angiotensin system which is responsible for the hemostasis of sodium and potassium.
    → increase reabsorption for Na^+ and water and increase excretion for K^+
    → concentrated urine
  - ✓ **Glucocorticoids** have anti-inflammatory actions and aid in regulating glucose, protein, and fat metabolism during periods of stress.
    → cortisol
    → يثبط استجابة الجهاز المناعي
    → تفكيك الدهون لإنتاج طاقة
    ⇒ increase this hormone lead to ↓ activation to thyroid gland
  - ✓ **Adrenal androgens:** exert little effect on daily control of body function but they probably contribute to the development of body hair in women.
    → يزيد تحطيم البروتين وتحوله إلى جلوكوز

Primary adrenal cortical insufficiency

↳ distruction or dysfunction in adrenal cortex → leading to deficeincy in essential adrenal hormone

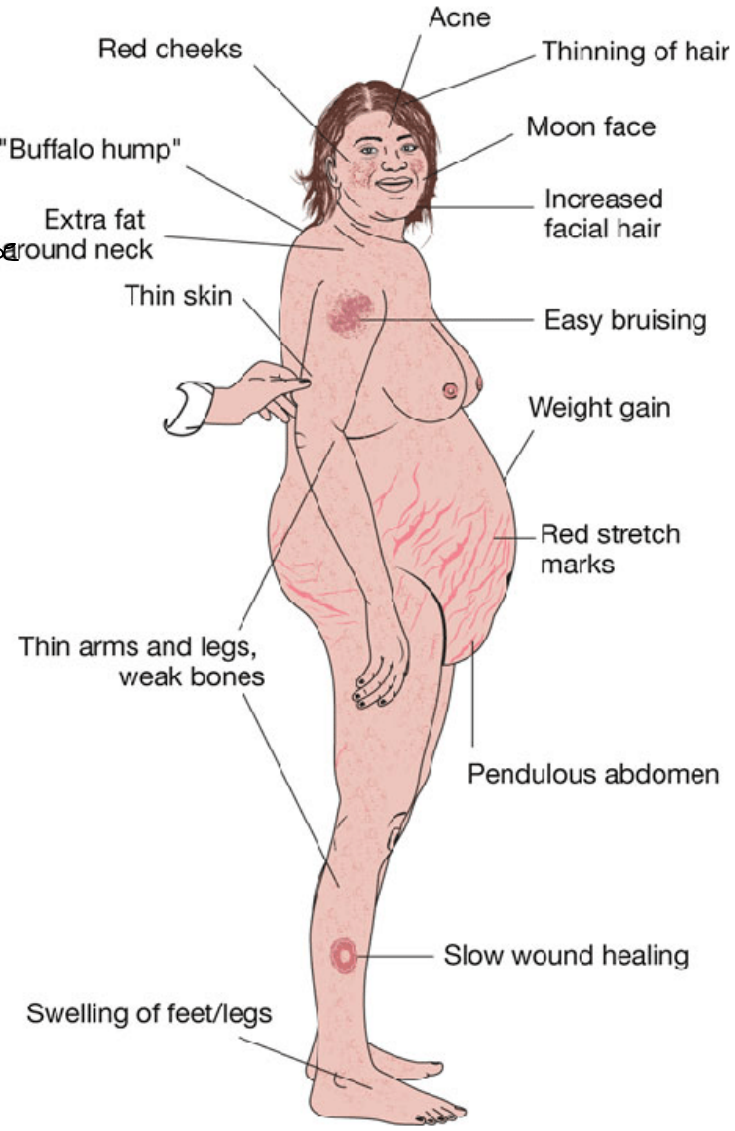




Adrenal corticoid excess

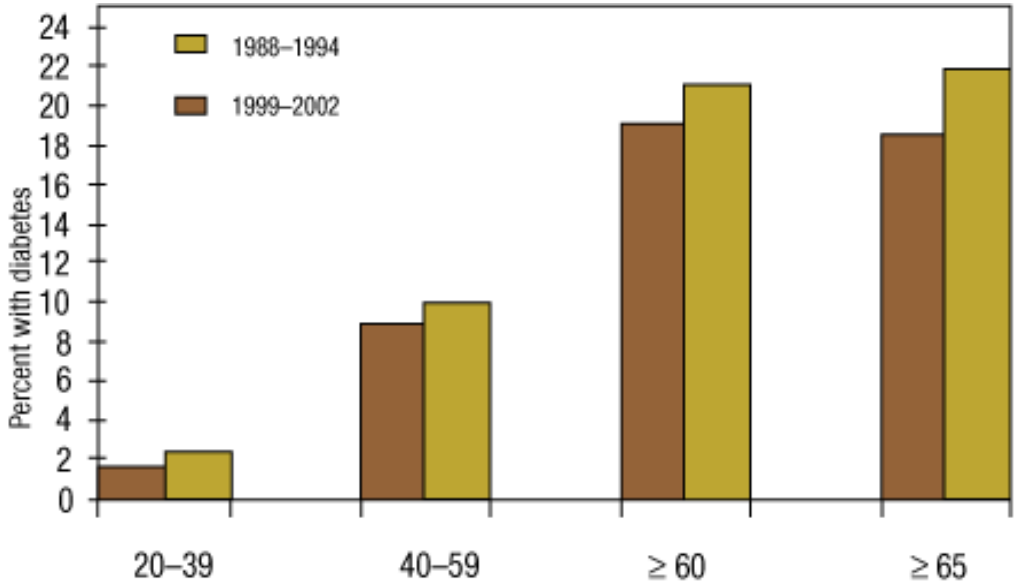
❑ Cushing syndrome results in:

- Glucose metabolism defect (**glucose intolerance**). → increase glucose level in blood.
- Disorders of sodium and potassium regulation **(increase sodium retention and potassium loss)**. → urine concentrated
- Impaired (ضعف) ability to respond to stress because of **inhibition of inflammatory and immune responses.** ← زيادة نمو الشعر في أماكن غير معتادة
- Signs of increased androgen levels such as **hirsutism.**
- The syndrome may result from **pharmacologic doses of glucocorticoid, pituitary, or adrenal tumor, or an ectopic tumor that produces adrenocorticotropic hormone (ACTH).**



Diabetes Mellitus

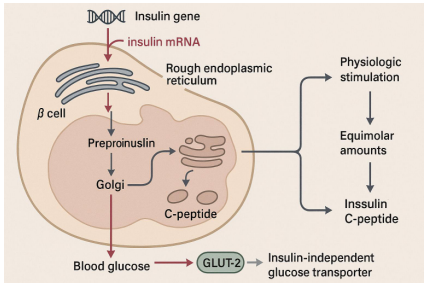
- Diabetes mellitus is a *group of metabolic disorders sharing the common underlying feature of hyperglycemia*. Chronic hyperglycemia and attendant metabolic dysregulation may be associated with secondary damage in multiple organ systems, especially the kidneys, eyes, nerves, and blood vessels.



DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

أول خمس أسطر ونص بيحكي كيف بيتصنع الإنسولين؟
لـ سطر سبعة , ثمانية , تسعة ← تأثير C بيبيد

Insulin



The insulin gene **is expressed in the β cells of the pancreatic islets**. Preproinsulin is synthesized in the rough endoplasmic reticulum from insulin mRNA and delivered to the Golgi apparatus. There, a series of proteolytic cleavage steps generate mature insulin and a cleavage peptide, *C-peptide*. Both insulin and C-peptide are then stored in secretory granules and secreted in equimolar quantities after physiologic stimulation; thus, **C-peptide levels serve as a surrogate** (مؤشر بديل) **for β-cell function, decreasing with loss of β-cell mass in type 1 diabetes, or increasing with insulin resistance–associated hyperinsulinemia.**

The most important stimulus for insulin synthesis and release is glucose itself. **A rise in blood glucose levels results in glucose uptake into pancreatic β cells, facilitated by an insulin-independent glucose-transporter, GLUT-2.**

كيف يصير إفراز للإنسولين

- **B-cells express an ATP-sensitive K+ channel on the membrane**, which comprises two subunits: an inward rectifying K+ channel (kir6.2) and the **sulfonylurea receptor (SUR1), the latter being the binding site for oral hypoglycemic agents (sulfonylureas) used in the treatment of diabetes.** → importance sulfonylurea receptor ?

- **Metabolism of glucose by glycolysis generates ATP, increasing β-cell cytoplasmic ATP/ADP ratios.** This inhibits the activity of the ATP-sensitive K+ channel, leading to membrane depolarization and the influx of extracellular Ca through voltage-dependent Ca channels. **The resultant increase in intracellular Ca stimulates the secretion of insulin,** presumably from stored hormone within the β-cell granules. This is the phase of the *immediate release of insulin*.

- If the secretory stimulus persists, a delayed and protracted response follows that involves the *active synthesis of insulin*. **Other factors, including intestinal hormones and certain amino acids (leucine and arginine), also stimulate insulin release, but not its synthesis.**

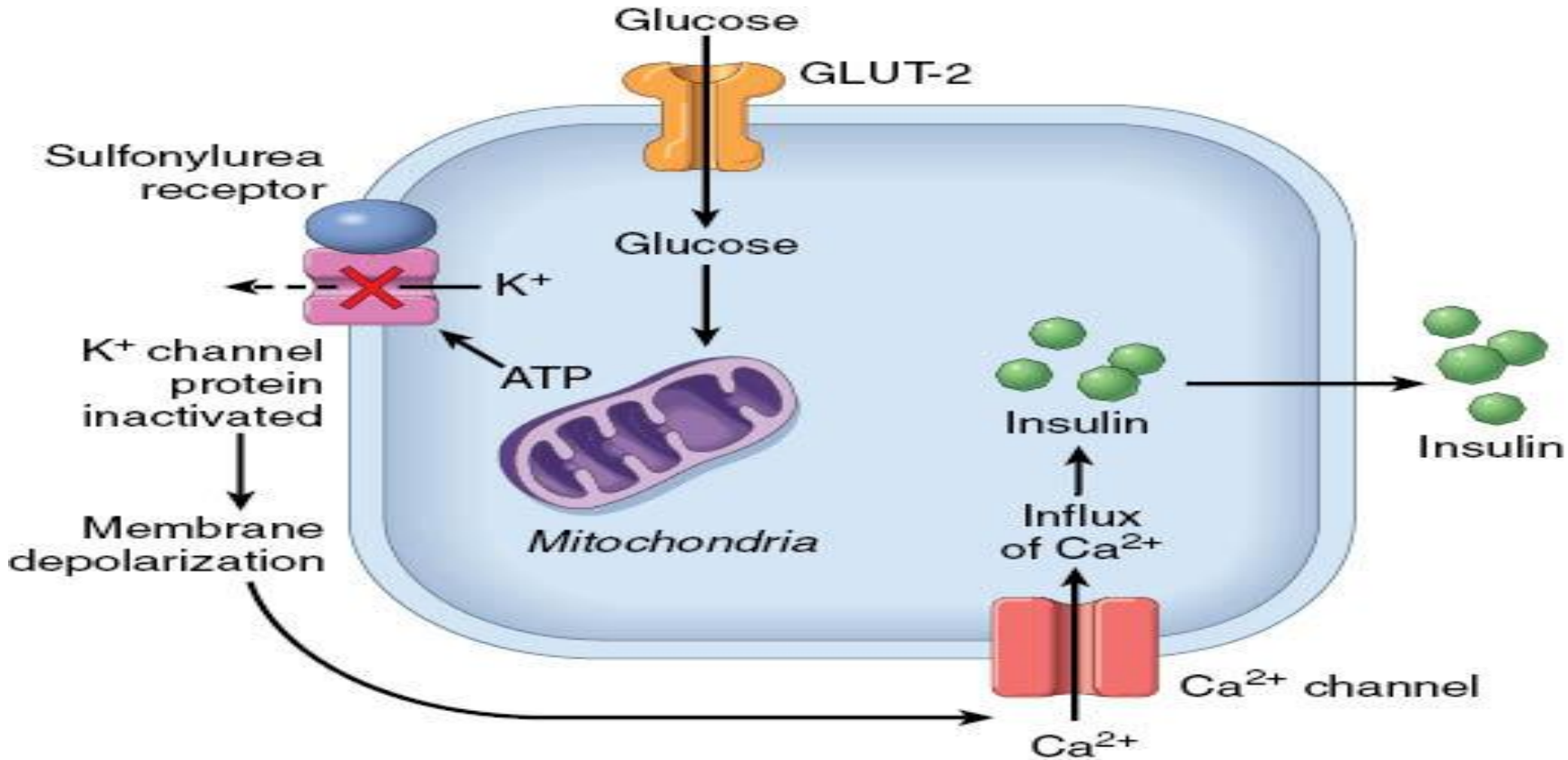


FIGURE 24–27 Insulin synthesis and secretion. Intracellular transport of glucose is mediated by GLUT-2, an insulin-independent glucose transporter in β cells. Glucose undergoes oxidative metabolism in the β cell to yield ATP. ATP inhibits an inward rectifying K^+ channel receptor on the β-cell surface; the receptor itself is a dimeric complex of the sulfonylurea receptor (SUR1) and a K^+-channel protein (Kir6.2). Inhibition of this receptor leads to membrane depolarization, influx of Ca^{2+} ions, and release of stored insulin from β cells. The sulfonylurea class of oral hypoglycemic agents bind to the SUR1 receptor protein.

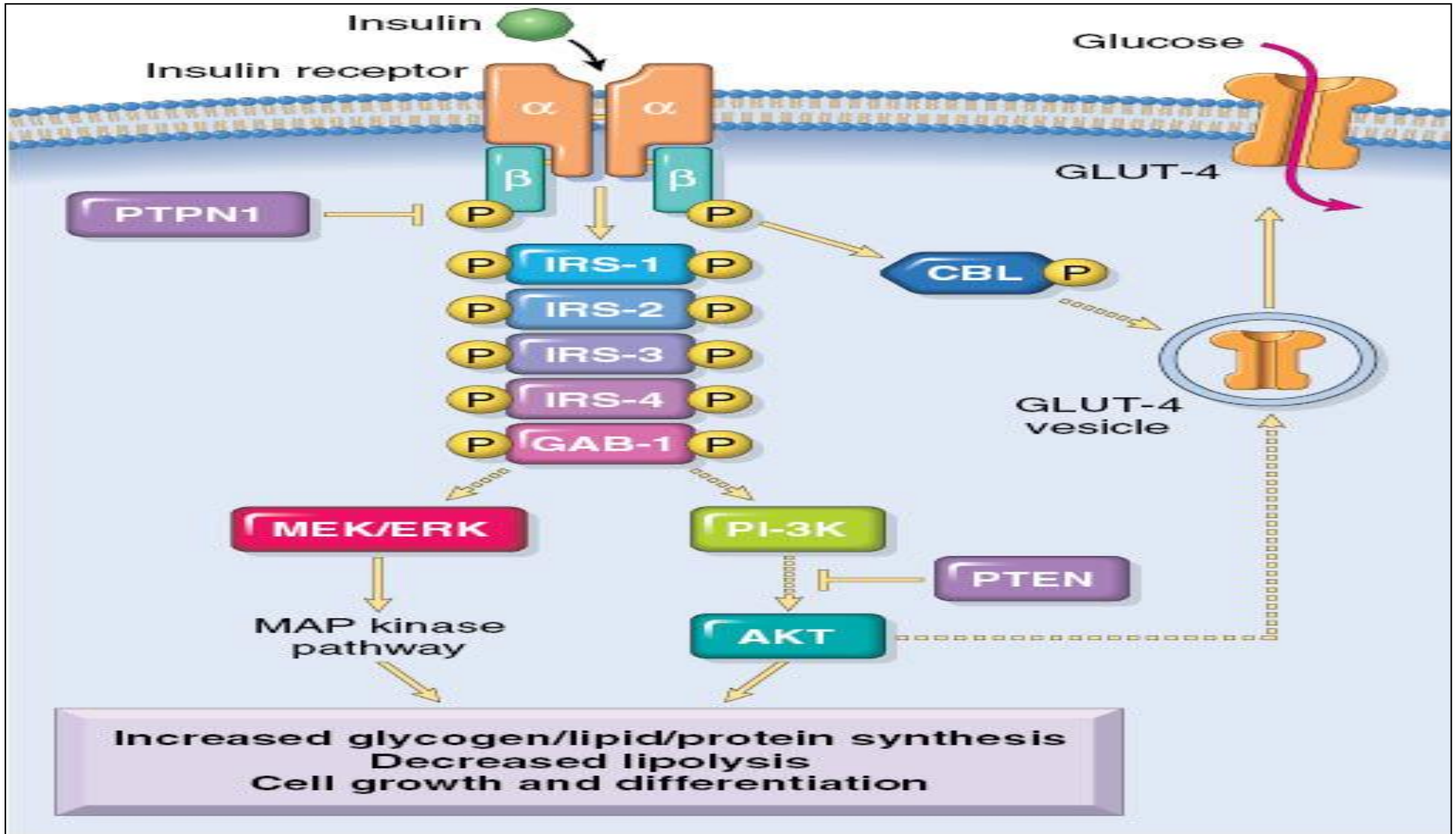


FIGURE 24–29 Insulin action on a target cell. The metabolic actions of insulin include promoting glycogen synthesis by activating glycogen synthase, and enhancing protein synthesis and lipogenesis while inhibiting lipolysis. Dashed arrows represent intermediate proteins and binding partners that are not shown in this overview diagram.

Classification

- **Majority of diabetics are classified into 2 categories:**
  - Type 1: absolute deficiency of insulin.
  - Type 2: the presence of insulin resistance with reduced insulin secretion.
- **Gestational diabetes:**
  - Triggered by the stress of pregnancy.
- **Other specific types:**
  - Infections, drugs, endocrinopathies, pancreatic destruction, genetic defects.

Classification

Type 1 diabetes

An autoimmune disease characterized by pancreatic β-cell destruction and an absolute deficiency of insulin. It accounts for approximately 5% to 10% of all cases and is the most common subtype diagnosed in patients younger than 20 years of age.

Type 1 DM Pathogenesis

1. **Preclinical period:**
   - Immune markers present. ⟵ بدء مهاجمة الجهاز المناعي لخلايا بيتا
   - B-cell destruction.
2. **Hyperglycemia:**
   - 80 to 90% of β-cells destroyed. ⟵ Hyperglycemia
3. **Transient remission:**
   - Honeymoon phase. بتلبش تصير الحالة مستقرة لفترة بعد التشخيص وبدء العلاج
4. **Established disease**

⟵ بصير مرض مزمن مستقر تتطلب العلاج الحقن بالإنسولين

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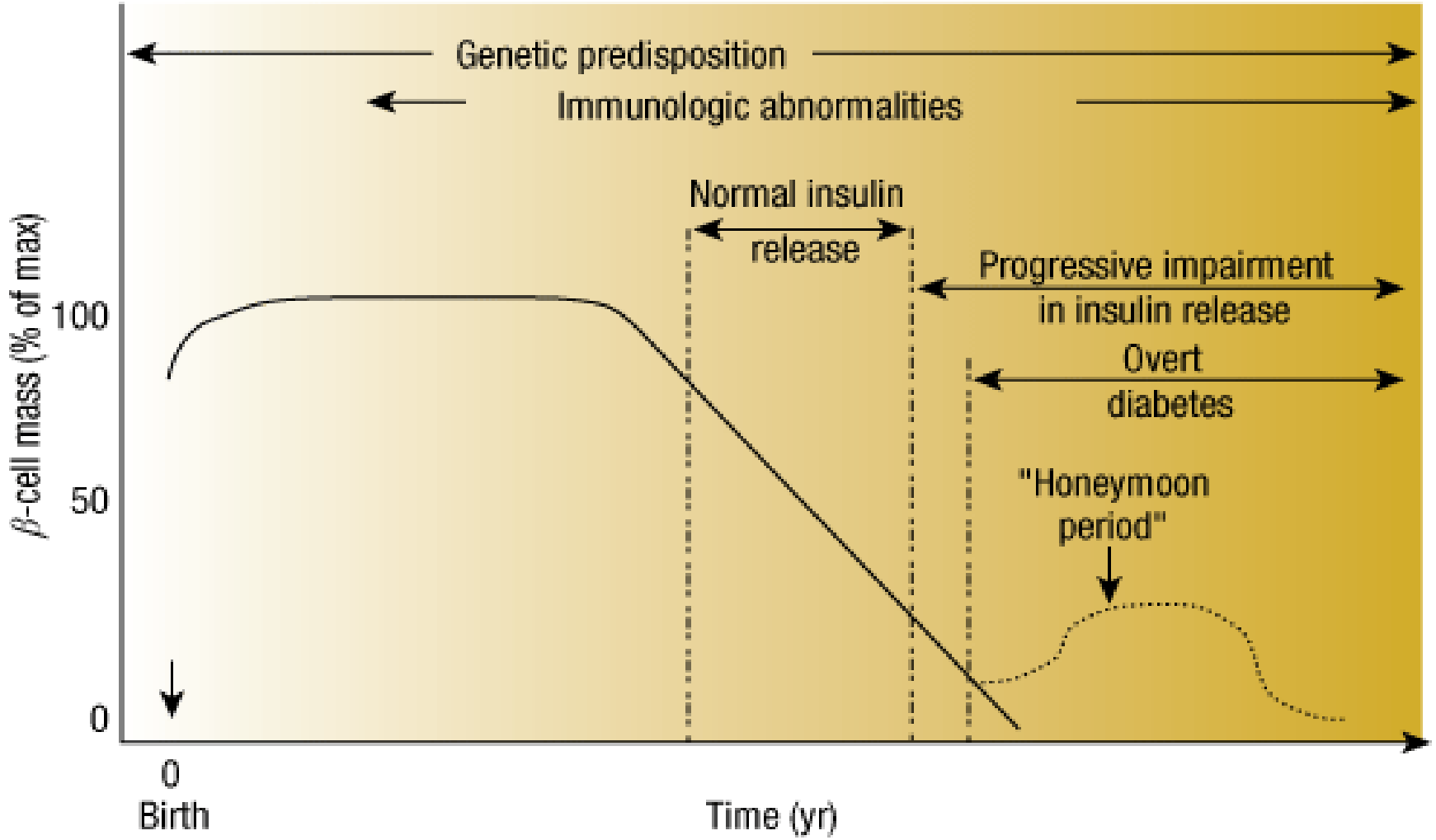
Type 1 DM Pathogenesis



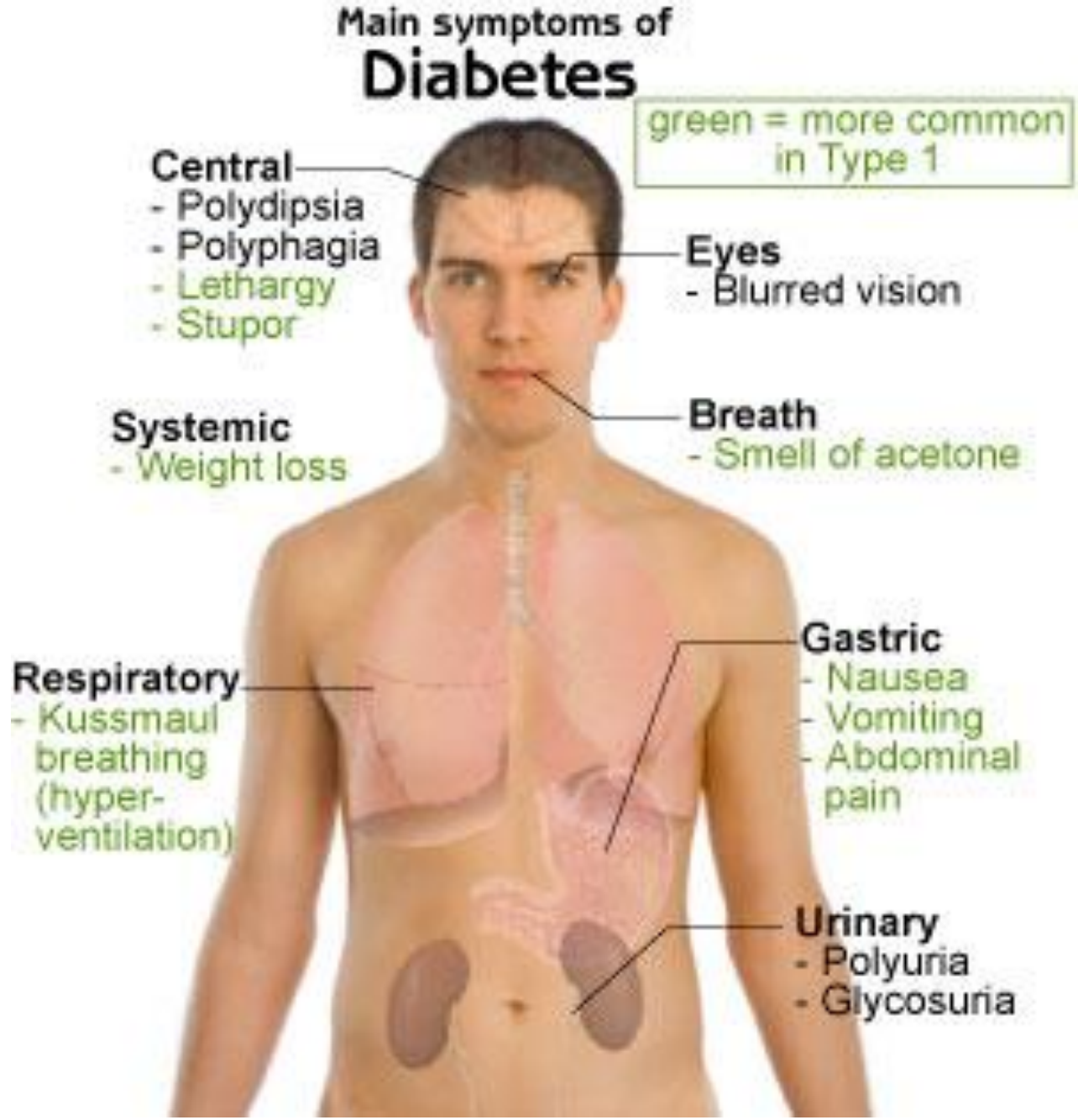
DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A pathophysiologic Approach,* 7th Edition: Http://www.accesspharmacy.com

Symptoms

- The onset is marked by polyuria, polydipsia, polyphagia, and, when severe, ketoacidosis, all resulting from metabolic derangements. ***Since insulin is a major anabolic hormone in the body, deficiency of insulin results in a catabolic state that affects not only glucose metabolism but also fat and protein metabolism.***
- Unopposed secretion of counter-regulatory hormones (glucagon, growth hormone, epinephrine) also plays a role in these metabolic derangements. **The assimilation of glucose into muscle and adipose tissue is sharply diminished or abolished. Not only does the storage of glycogen in the liver and muscle cease, but also reserves are depleted by glycogenolysis.** ***The resultant hyperglycemia exceeds the renal threshold for reabsorption, and glycosuria ensues. The glycosuria induces an osmotic diuresis and thus polyuria, causing a profound loss of water and electrolytes.***

Symptoms

- The obligatory renal water loss combined with the hyperosmolarity resulting from the increased levels of glucose in the blood tends to deplete intracellular water, ***triggering the osmoreceptors of the thirst centers of the brain. In this manner, intense thirst (polydipsia)*** appears.
- With a deficiency of insulin, the scales swing from insulin-promoted anabolism to catabolism of proteins and fats. Proteolysis follows, and the gluconeogenic amino acids are removed by the liver and used as building blocks for glucose. ***The catabolism of proteins and fats tends to induce a negative energy balance, which in turn leads to increasing appetite (polyphagia)***, thus completing the classic triad of diabetes: *polyuria*, *polydipsia*, and *polyphagia*. Despite the increased appetite, catabolic effects prevail, resulting in weight loss and muscle weakness. *The combination of polyphagia and weight loss is paradoxical and should always raise the suspicion of diabetes*.


Main symptoms of
Diabetes
green = more common in Type 1
Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor
Eyes
- Blurred vision
Systemic
- Weight loss
Breath
- Smell of acetone
Respiratory
- Kussmaul breathing (hyper-ventilation)
Gastric
- Nausea
- Vomiting
- Abdominal pain
Urinary
- Polyuria
- Glycosuria

Type 1 DM pathogenesis

- **Type 1 diabetes most commonly develops in childhood,** becomes manifest at puberty, and progresses with age.
- **Since the disease can develop at any age**, including late adulthood, the appellation "**juvenile diabetes**" is now considered obsolete. Similarly, the older moniker "insulin-dependent diabetes mellitus" has been excluded from the recent classification of diabetes because insulin dependence is not a consistent distinguishing feature. Nevertheless, **most patients with type 1 diabetes depend on insulin for survival;**
- **Without insulin they develop serious metabolic complications such as ketoacidosis and coma.** A rare form of "idiopathic" type 1 diabetes has been described in which the evidence for autoimmunity is not definitive.

Type 1 DM pathogenesis

- As with most autoimmune diseases, the pathogenesis of type 1 diabetes represents the interplay of **genetic susceptibility and environmental factors**.
- Epidemiologic studies, such as those demonstrating higher concordance rates for disease in monozygotic vs dizygotic twins, have convincingly established a genetic basis for type 1 diabetes. More recently, genome-wide association studies have identified multiple genetic susceptibility loci for type 1 diabetes, as well as for type 2 diabetes. Over a dozen susceptibility loci for type 1 diabetes are now known. Of these, by far the most important is the *HLA locus* on chromosome 6p21; according to some estimates, the HLA locus contributes as much as 50% of the genetic susceptibility to type 1 diabetes.

Diabetic ketoacidosis

- *Diabetic ketoacidosis* **is a serious complication of type 1 diabetes but may also occur in type 2 diabetes,** though not as common and not to as marked an extent.
- **These patients have marked insulin deficiency**, and the release of the catecholamine hormone *epinephrine* blocks any residual insulin action and stimulates the secretion of glucagon.
- The **insulin deficiency coupled with glucagon excess** decreases peripheral utilization of glucose while increasing gluconeogenesis, severely exacerbating hyperglycemia ***(the plasma glucose levels are usually in the range of 500 to 700 mg/dl).*** **Hyperglycemia causes an osmotic diuresis and dehydration characteristic of the ketoacidotic state.**

Diabetic ketoacidosis

- *The second major effect of an alteration in the insulin-to-glucagon ratio is activation of the ketogenic machinery.*
- Insulin deficiency stimulates lipoprotein lipase, with the resultant breakdown of adipose stores, and an increase in levels of free fatty acids. When these free fatty acids reach the liver, they are esterified to fatty acyl CoA.
- *Oxidation of fatty acyl CoA molecules within the hepatic mitochondria produces ketone bodies (acetoacetic acid and β-hydroxybutyric acid).*
- The rate at which ketone bodies are formed may exceed the rate at which they can be utilized by peripheral tissues, leading to *ketonemia* and *ketonuria*.
- If the urinary excretion of ketones is compromised by dehydration, systemic *metabolic ketoacidosis* results. Release of ketogenic amino acids by protein catabolism aggravates the ketotic state

Diabetic Ketoacidosis

Diabetic emergency حالة طارئة

Precipitating factors: السبب

- Insulin omission. ايقاف
- Illness, infection. عدوى، مرض
- Initial DM presentation. أول تشخيص لمرض السكري

Diagnostic laboratory values

- Hyperglycemia.
- Anion gap acidosis. → accumilation Ketone body
- Ketonemia, ketonuria.
- Fluid deficits. نقص
- Na^+, K^+ deficits.

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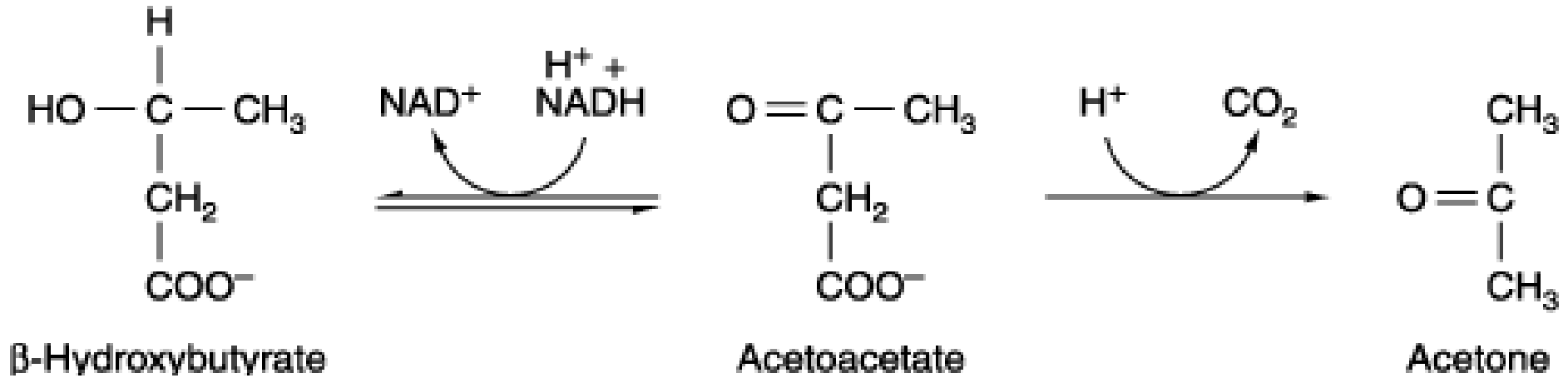

- Ketogenesis due to insulin deficiency leads to increased serum levels of ketones, and ketonuria.
- Acetoacetate, β-hydroxybutyrate: ketone bodies produced by the liver; organic acids that cause metabolic acidosis.
- Respiration partially compensates; reduces PCO_2: when pH < 7.20, deep, rapid respirations (Kussmaul breathing).
- Acetone: minor product of ketogenesis; can smell fruity odor on the breath of diabetic ketoacidosis patients.

Classification

Type 2 diabetes

- ***Type 2 diabetes*** is caused by **a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic β cells** ("relative insulin deficiency").
- Approximately 90% to 95% of diabetic patients have type 2 diabetes, and the vast majority of such individuals are **overweight.**
- Although classically considered "**adult-onset," the prevalence of type 2 diabetes in children and adolescents is increasing at an alarming pace**

Risk factors for type 2 DM

- ✓ BMI ≥ 25.
- ✓ Physical inactivity.
- ✓ 1st degree relative with DM.
- ✓ High risk ethnic group (latino, african american, native american, asian american, pacific islander).
- ✓ IFG, IGT.
- ✓ HTN: ≥ 140/90 mmHg or on therapy for HTN.
- ✓ CV disease.
- ✓ HDL < 35 mg/dl.
- ✓ Triglycerides > 250 mg/dl.
- ✓ Delivery of > 9 lb baby.
- ✓ History of GDM.
- ✓ Insulin resistance:
  - ✓ Acanthosis nigricans, severe obesity
- ✓ Polycystic ovary syndrome.

Prediabetes

Levels of blood glucose proceed along a continuum. Individuals with fasting glucose concentrations less than 100 mg/dl, or less than 140 mg/dl following an OGTT, are considered to be euglycemic. **However, those with fasting glucose concentrations greater than 100 mg/dl but less than 126 mg/dl, or OGTT values greater than 140 mg/dl but less than 200 mg/dl, are considered to have impaired glucose tolerance, also known as "pre-diabetes."**

Pre-diabetic individuals have a significant risk of progressing to overt diabetes over time, with as many as 5% to 10% advancing to diabetes mellitus per year. In addition, **pre-diabetics are at risk for cardiovascular disease, as a result of the abnormal carbohydrate metabolism as well as the coexistence of other risk factors such as low levels of high-density lipoprotein, hypertriglyceridemia, and increased plasminogen activator inhibitor-1 (PAI-1).**

Complications

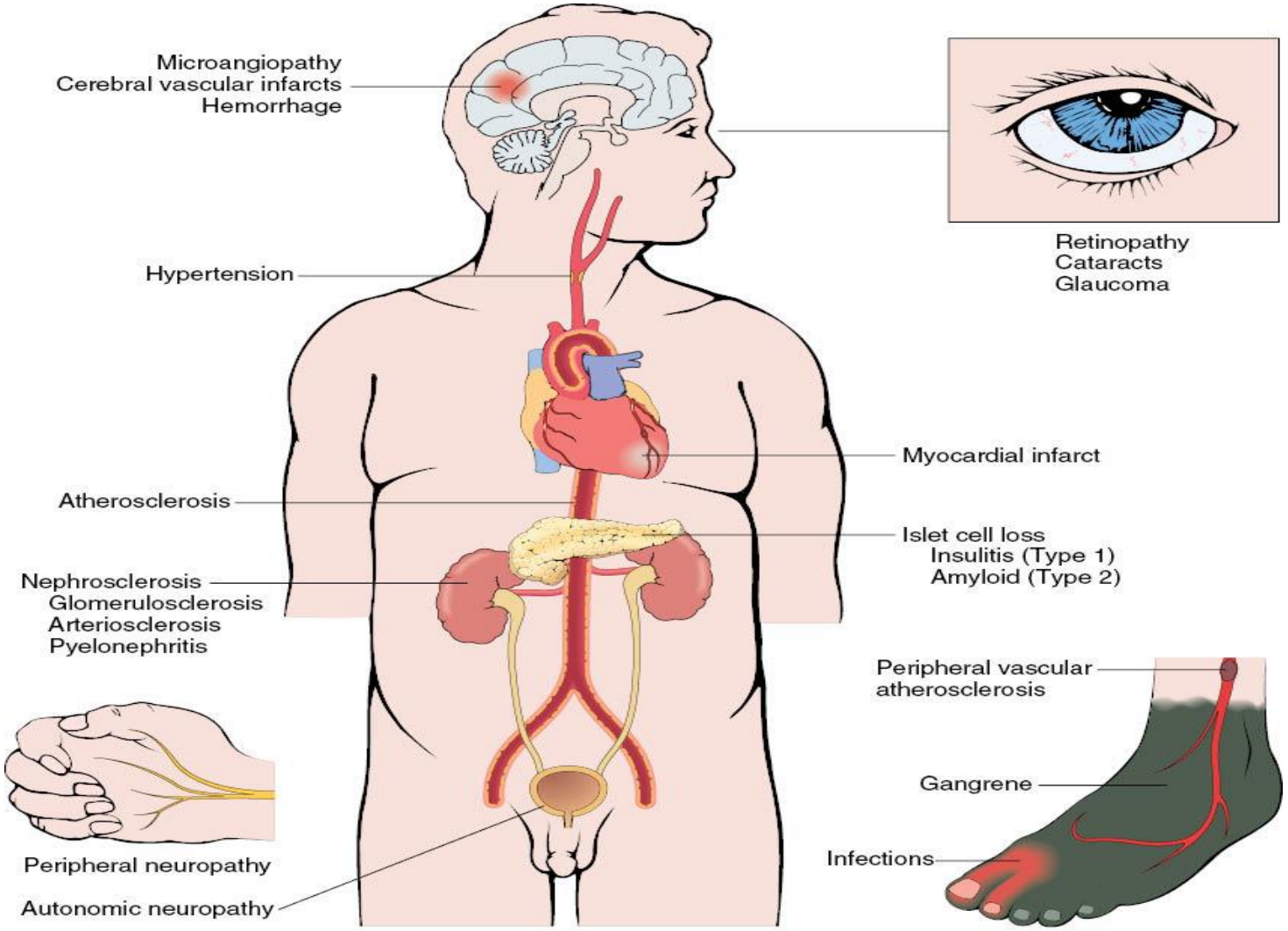

FIGURE 24–32 Long-term complications of diabetes.

Thank You