THYROID GLAND

Hormones:

- 3,5,3',5‘ tetraiodothyronine (thyroxine, T_4)
- 3,5,3' triiodothyronine (T_3)
- 3,3',5‘ triiodothyronine (RT_3)

Iodine:

- **Sources: Iodized table salt, dairy products, fish**
- **Adult RDA: 150 μg**
- **The average dietary intake - 500 μg /day**
- **Dietary intake below 10 μg /day -**

  synthesis of thyroid hormones inadequate

Iodide:

- **a circulating (extrathyroidal) pool - 250 - 750 μg**
- **the total iodide content of the thyroid - 7 500 μg**

Synthesis of Thyroid Hormones

a. Iodide (I^-) pump ("trap") (inhibited by high blood I^- level)

b. Conversion of I^- to I_2,

c. Binding of iodine with thyroglobulin

$\rightarrow$ formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT)

d. Coupling of DIT (MIT) and DIT - oxidative condensation

Conversion of I^- to I_2, binding of iodine with thyroglobulin,

and coupling of MIT (DIT) and DIT are catalyzed by a thyroid peroxidase

e. Storage of the thyroid hormones in the follicular colloid.

Secretion of Thyroid Hormones

a. Formation of pinocytic vesicles

b. Fusion with lysosomes to form digestive vesicles

c. Digestion of thyroglobulin and liberation of the thyroid hormones

d. Deiodination by a thyroid deiodinase of iodinated tyrosine residues, which had not been coupled (MIT, DIT)

Transport of Thyroid Hormones in the Blood

	T_4	T_3
Bound	**99,98%**	**99,8%**
Thyroxine- binding globulin (TBG):	67%	46%
Thyroxine - binding prealbumin (TBPA):	20%	1%
Albumin:	13%	53%
Free	**0,02%**	**0,2%**

Plasma levels

Total	**8 μg/dl**	**0,15 μg/dl**
Free	**2 ng/dl**	**0,3 ng/dl**

Thyroxine	Triiodothyronine
• **Binding affinity of TBG and other plasma proteins**	
6 times greater	
• **Release to the tissues**	
Slower	
• **Biologic half-life**	
Longer (6-7 days)	*1 day*
• **Binding with intracellular proteins**	
Stronger	
• **Latent period**	
2 -3 days	*6 -12 hours*
• **Maximal activity**	
In 10-12 days	*Within 2-3 days*
• **% of thyroid hormones molecules, that bind with cellular thyroid hormone receptor**	
10%	*90%*

Case 1

My old good friend Shirley called me last Monday to invite me to dinner. Shirley is a 43-year-old university teacher. I have known her for over 20 years, since we studied at the University. However we have not met within the last year. I was very surprised that I did not recognize her voice on the phone. It was hoarse and deep as that of a man, especially smoking. Besides Shirley spoke slower than usual and mainly about her complains. She told me that in spite of eating less her weight had increased 16 lb in the last year, but she has attributed her weight gain to "getting older". Later Shirley complained that she has very little energy, always feels weak, tired, and cold (when every one is hot). She also suffers from muscle cramps and stiffness. **When I saw her in the evening, I noticed that Shirley's neck was very full. Her face was slightly edematous and her skin was dry and cold. She added that she was constipated and had too frequent menses.** **I suspected that Shirley had _ _ _ _ _ _ _ _ .**	♦ ***Hoarseness, deep voice*** ♦ ***Slow speech*** ♦ ***↓appetite, weight gain*** ♦ ***↓energy level*** ♦ ***Cold intolerance*** ♦ ***Muscle weakness, cramps, stiffness*** ♦ ***Thyroid enlargement*** ♦ ***Myxedema***

Case 2

Natasha is a 23-year old woman who has always dieted to keep her weight on an "acceptable" level. However, within the last three months she has lost 20 lb in spite of a big appetite. She notes she is "always hot" and wants the thermostat set lower than her apartment mates. She complains of heart palpitations, increased frequency and softening of bowel movements, difficulty sleeping, irritability, and irregular menstrual periods. Besides she easily gets tired. During interview she was restless and she spoke very quickly.	♦ ***Weight loss*** ♦ ***↑appetite*** ♦ ***Heat intolerance*** ♦ ***Palpitations*** ♦ ***↑frequency, softening of bowel movements*** ♦ ***Irregular menstrual periods*** ♦ ***Difficulty sleeping*** ♦ ***Irritability*** ♦ ***Fatigue*** ♦ ***Rapid mentation***
On physical examination Natasha weighted only 110 lb. Her skin was smooth and warm. Her heart rate was 110 beats/min and her arterial pressure was 160/70. She had a tremor in her fingers and hands. Natasha had a wide-eye stare, and her lower neck appeared full; these characteristics were not present in photographs taken 1 year earlier. **Based on her symptoms, I suspected that Natasha had _ _ _ _ _ _ _ _ _ _ _.**	♦ ***Smooth, warm skin*** ♦ ***Tachycardia*** ♦ ***Systolic hypertension*** ♦ ***Tremor in hands*** ♦ ***Ophthalmopathy*** ♦ ***Thyroid gland enlargement - goiter***

THYROID HORMONES

- cause nuclear transcription of large numbers of genes
- ↑ formation of RNA and proteins
  (enzymatic, structural, and others)
- ↑ functional activity throughout the body

↑ BMR;

↑ oxygen consumption and ↑ energy production (ATP and heat)

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Metabolic rate		***Increased***		***Reduced***
	↑ appetite	Sweating	↓ appetite	Obesity
	Weight loss	↓ mass of muscle and fat	Weight gain	Hypothermia
	Heat intolerance		Cold intolerance	
	Relative vitamin deficiency			

EFFECTS ON:

Carbohydrate metabolism

- **↑ rate of absorption from GI tract**
- **↑ all aspects of metabolism**
- **↑ insulin secretion, ↓ half-life of insulin**

EFFECTS ON: **HYPOTHYROIDISM**

Lipid metabolism

- ↑ **synthesis, degradation, and mobilization**
- ↑ **blood FFA level**
- ↓ **blood cholesterol level**

↑ **blood cholesterol level**

↓

severe atherosclerosis

EFFECTS ON:	HYPERTHYROIDISM	HYPOTHYROIDISM
Protein metabolism		
• ↑ synthesis • ↑ breakdown	↑ catabolism Muscle weakness (thyrotoxic myopathy)	Muscle weakness Muscle cramps Muscle stiffness (↑ muscle mass, accumulation of mucopolisaccharides)

EFFECTS ON:	HYPERTHYROIDISM	HYPOTHYROIDISM
Skin		
Connective tissue		
• cause integrity of normal collagen • inhibit synthesis of mucopolisaccharides •↑ degradation of mucopolisaccharides,	Smooth, warm skin	Cool, dry skin Myxedema (nonpitting edema: face, periorbital tissues)

Accumulation of mucopolisaccharides with a "-" charge

↓

Retention of osmotically active cations (Na^+)

↓

Retention of water

↓

Puffiness of skin, compression resistant

EFFECTS ON:	HYPERTHYROIDISM	HYPOTHYROIDISM
Bone, growth		
• Essential for normal growth and skeletal maturation: • Permissive to action of GH • Essential for maturation of epiphyseal growth centres, linear growth of bone, ossification of cartilage, growth of teeth, contours of the face, proportions of the body	Excessive skeletal growth Earlier closure of epiphyses Bone resorption	Retarded growth rate Delayed closure of epiphyses

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Cardiovascular System				
↑ BLOOD FLOW ↑ CARDIAC UOTPUT 1) Indirect effects •↑ number, ↑ affinity of beta-adrenergic receptors in the heart ↓ ↑ heart's sensitivity to chronotropic and inotropic effects of catecholamines Adrenergic stimulation of the heart ↑ Vasodilatation, ↓ diastolic pressure ↑ ↑ heat and CO_2 production 2) Direct effects ↑ myocardial calcium uptake ↑ Na^+,K^+-ATPase activity ↑ α-MHC (myosin heavy chain) level	Palpitation	Tachycardia Arrhythmia Systolic hypertension ↑ pulse pressure Cardiomegaly Congestive heart failure	Angina pectoris	Bradycardia Cardiac enlargement (“myxedema heart” myxedematous pericardial effusion)

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Respiratory System				
↑ rate of breathing ↑ depth of breathing ↑ minute ventilation ↑ red blood cells mass	Dyspnea on exertion (weakness of chest wall muscles modest ↓ in left ventricle ejection fraction) Dyspnea (congestive heart failure)	↑ respiratory rate	Dyspnea on exertion (↓ chest wall compliance, ↓ oxygen diffusing capacity)	Pleural effusion

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Gastrointestinal System				
•↑ appetite, food intake •↑ motility of GI tract •↑ rate of secretion of digestive juices	↑ frequency and softening of bowel movements Diarrhea		Constipation	Abdominal distension

EFFECTS ON:

Nervous System

(fetal life, childhood)

Essential for normal growth and development of brain;

- **Growth of cerebral cortex**
- **Proliferation of axons**
- **Branching of dendrites**
- **Synaptogenesis**
- **Cell migration**
- **Myelin formation**

HYPOTHYROIDISM

Congenital Hypothyroidism

Cretinism

Mental retardation

Failure of growth

Thickened facial features

Lower body temperature

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Nervous System *(adults)* ↑ rapidity of cerebration	Rapid mentation Irritability Difficulty sleeping Psychoneurotic tendency (anxiety, extreme worry)	Emotional liability Psychosis	Slow mentation Somnolence Lethargy	Dementia Psychosis

EFFECTS ON:	HYPERTHYROIDISM	HYPOTHYROIDISM
	Symptoms *Signs*	*Symptoms* *Signs*
Neuromuscular		
System		
	Fatigue Tremor	Muscle cramps Muscle stiffness in finger, hands
	↑ speed and amplitude of peripheral nerve reflexes	↓ speed and amplitude of peripheral nerve reflexes
		Stiffness on joints Joints effusion

EFFECTS ON:	HYPERTHYROIDISM		HYPOTHYROIDISM	
	Symptoms	*Signs*	*Symptoms*	*Signs*
Ophthalmologic	Noninfiltrative ophthalmopathy			
manifestations	- Retraction of the upper eyelid (Contraction of the superior tarsal muscle which receives sympathetic innervation)			
		Infiltrative ophthalmopathy - exophthalmos (Oedema, infiltration of the extraocular muscles and connective tissue)		
Endocrine		↑ rate of hormones secretion		
System		↑ tissue need of hormones		
		↑ rate of hormones inactivation		
Reproductive	Irregular menstrual periods		Irregular menstrual periods	
System			Infertility	

CALCIUM METABOLISM

Hormones:

- Parathyroid hormone (PTH)
- 1,25-Dihydroxycholecalciferol (active form of vitamin D_3)
- Calcitonin

THE TOTAL BODY CALCIUM (1 100 g)

- **THE MAJORITY - BONES (1 000 000 mg)**
- **1 % - CELLS (13 000 mg)**
- **0,1% - EXTRACELLULAR FLUID (1 300 mg)**

PHOSPHORUS (TOTAL - 500-800 g):

- **85% - BONES**
- **10-15% - CELLS**
- **1% - EXTRACELLULAR FLUID**

Calcium level : 2,4 mmol/L (9,4 mg/dl)

Distribution of nondiffusible protein-bound calcium, diffusible but un-ionized calcium complexed to anions, and ionized calcium in blood plasma:

- **protein-bound calcium – 41% (1.0 mmol/L)**
- **calcium complexed to anions – 9% (0.2 mmol/L),**
- **ionizes calcium – 50% (1.2 mmol/L)**

Inorganic phosphorus level:

- **3-4 mg/dl (adults)**
- **4-5 mg/dl (children)**

Physiologic Effects of PTH

Primary Hyperparathyroidism - ↑PTH

1. *↑serum [Ca^{2+}] (hypercalcemia) –*
   most important finding that leads to diagnosis
2. *↓serum [phosphate] (hypophosphatemia)*
3. *↑ 1,25$(OH)_2D_3$ level*

ON BONE

↑ Bone resorption

↑resorption

↓

1) Activation of already existing bone cells - osteocytic membrane system

Removal of calcium phosphate salts from amorphous compounds (osteolysis)
(without absorption of fibrous and gel matrix)

MILD - bone deposition can compensate for reabsorption
SEVERE- bone reabsorption outstrips deposition

The organic matrix:

- **Collagen fibres (90-95%)**
- Homogenous medium – ground substance (extracellular fluid, proteoglycans: chondroitin sulphate and hyaluronic acid)

osteitis fibrosa cystica:

- *subperiosteal resorption (radial side of middle phalanges)*
- *bone cysts, fractures*

Calcium salts deposition:

- **crystalline forms – hydroxyapatite crystals -$Ca_{10}(PO_4)_6(OH)_2$,**
- **a few per cent of calcium salts (0,4-1 % of total bone calcium) - amorphous forms (absorbed readily and exchangeable)**

2) Activation of osteoclasts - secretion of:

- **Proteolytic enzymes, acids (citric acid, lactic acid)**

Resorption of organic matrix → ↑ urinary excretion of hydroxyproline

Physiologic Effects of PTH

Primary Hyperparathyroidism - ↑PTH

1. *↑serum [Ca^{2+}] (hypercalcemia)*
2. *↓serum [phosphate] (hypophosphatemia),*
3. *↑ 1,25$(OH)_2D_3$ level*

ON KIDNEY

♦ **↑ reabsorption of calcium**
(late distal tubules, collecting tubules, early collecting ducts, possibly ascending loop of Henle)

• *↑ reabsorption ,↑urinary excretion of Ca^{2+}*

Plasma calcium:

- **41% bound to plasma proteins (not filtered)**
- **59%- filtered - near 99% of filtered calcium reabsorbed:**
  - **90% proximal tubules, loop of Henle, early distal tubules**
  - **10% - late distal tubules, collecting tubules, early collecting ducts**

reabsorption dependent on PTH!

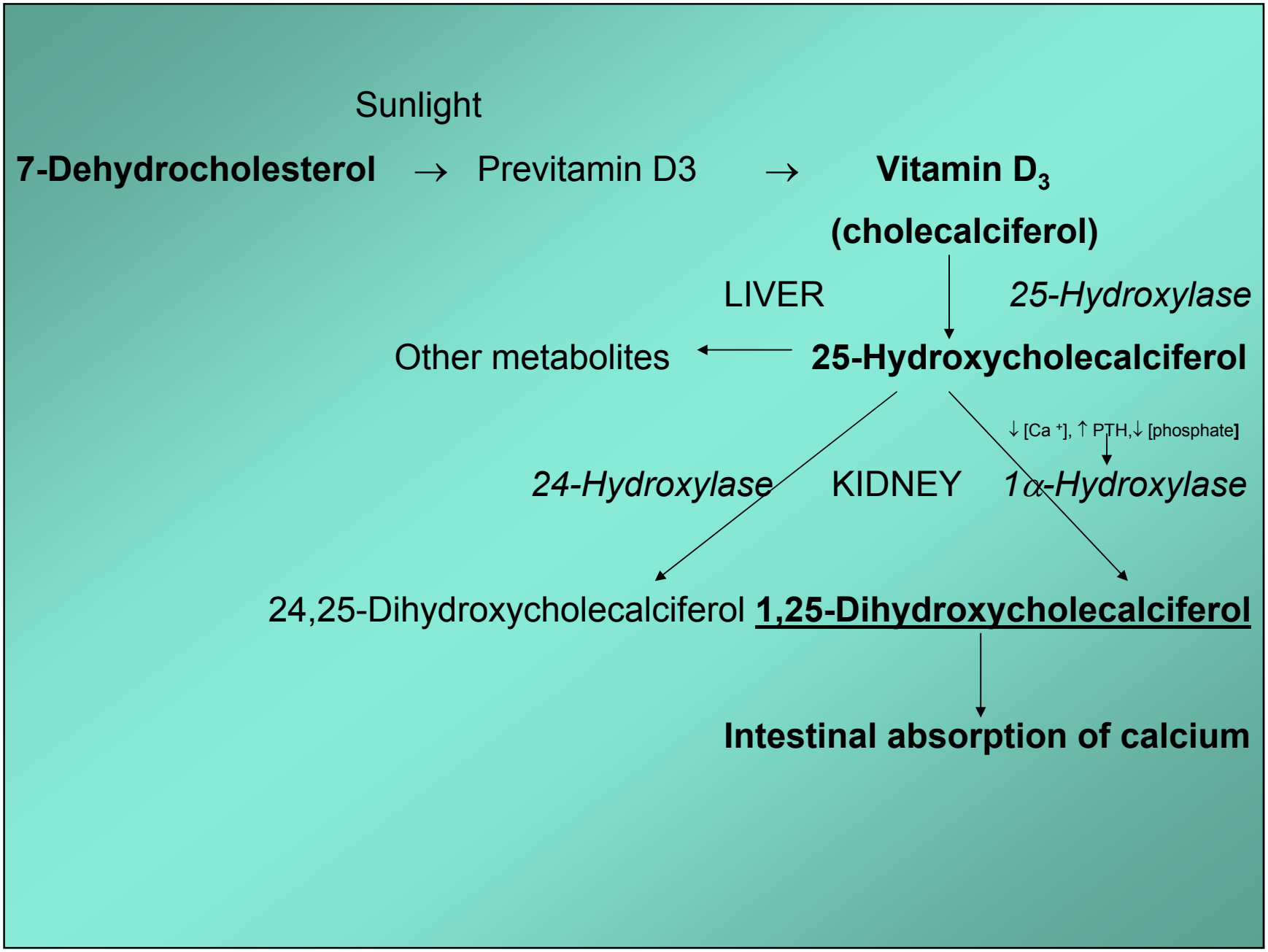
1) Extreme tendency to form kidney stones
(calcium phosphate, calcium oxalate)
2) *Renal interstitium - calcium deposition*
(nephrocalcinosis)

♦ **↓reabsorption of phosphate → ↑phosphate excretion (phosphaturic effect)**
(inhibition of Na^+ - phosphate cotransporter - early proximal tubules)

• *↑urinary phosphate excretion*

♦ **↑ reabsortion of magnesium ions, hydrogen ions**

♦ **↓ reabsortion of sodium, potassium, and amino acids**


Sunlight
7-Dehydrocholesterol → Previtamin D3 → Vitamin D3
(cholecalciferol)
LIVER
25-Hydroxylase
Other metabolites
25-Hydroxycholecalciferol
↓ [Ca +], ↑ PTH,↓ [phosphate]
24-Hydroxylase
KIDNEY
1α-Hydroxylase
24,25-Dihydroxycholecalciferol
1,25-Dihydroxycholecalciferol
Intestinal absorption of calcium

HYPERPARATHYROIDISM

PRIMARY HYPERPARATHYROIDISM

PTH level ↑

1,25 $(OH)_2$ D_3 ↑ (PTH stimulates 1α-hydroxylase)

BONE ↑ resorption

URINE ↑ P excretion (phosphaturia)
↑ Ca^{2+} excretion (high filtered load of Ca^{2+})

Serum [P] ↓

Serum [Ca^{2+}] ↑ - **HYPERCALCEMIA**

↓

GI System Loss of appetite, loss of weight, nausea, and constipation
Hypersecretion of gastric acid – peptic ulcer
↑ frequency of pancreatitis

CV System

Nervous System

HYPOPARATHYROIDISM

HYPOPARATHYROIDISM

Causes - Idiopathic (parathyroid glands absent, hypoplastic),
- Surgical hypoparathyroidism (most common)

PTH level	↓
1,25 $(OH)_2$ D_3	↓
BONE	↓ resorption
URINE	↓ P excretion
Serum [P]	↑
Serum [Ca^{2+}]	↓ - **HYPOCALCEMIA**

Nervous System ↑ permeability of neuronal membranes to Na^+ → ↑ excitability of nervous system → **TETANY**

Muscular system Muscle cramps, stiffness, contractions – "carpopedal spasm": "obstetrical hand", plantar flexion of toes

Latent tetany - positive results of provocative tests:

- Chvostek`s sign – a twitch of facial and upper lip muscles produced by a sharp tap given over the facial nerve
- Trousseau`s sign – "carpopedal spasm" induced by a sharp reduction of blood flow obtained with a blood pressure cuff