Physiology team

# 9 Hyper & hypo – parathyroidism

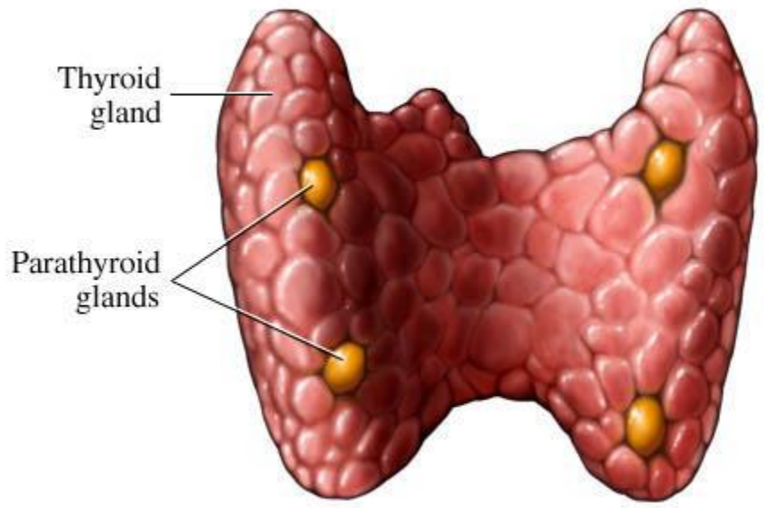
**Sources:**
**Female´s slides**
**GYTON 965-969**

# Parathyroid glands

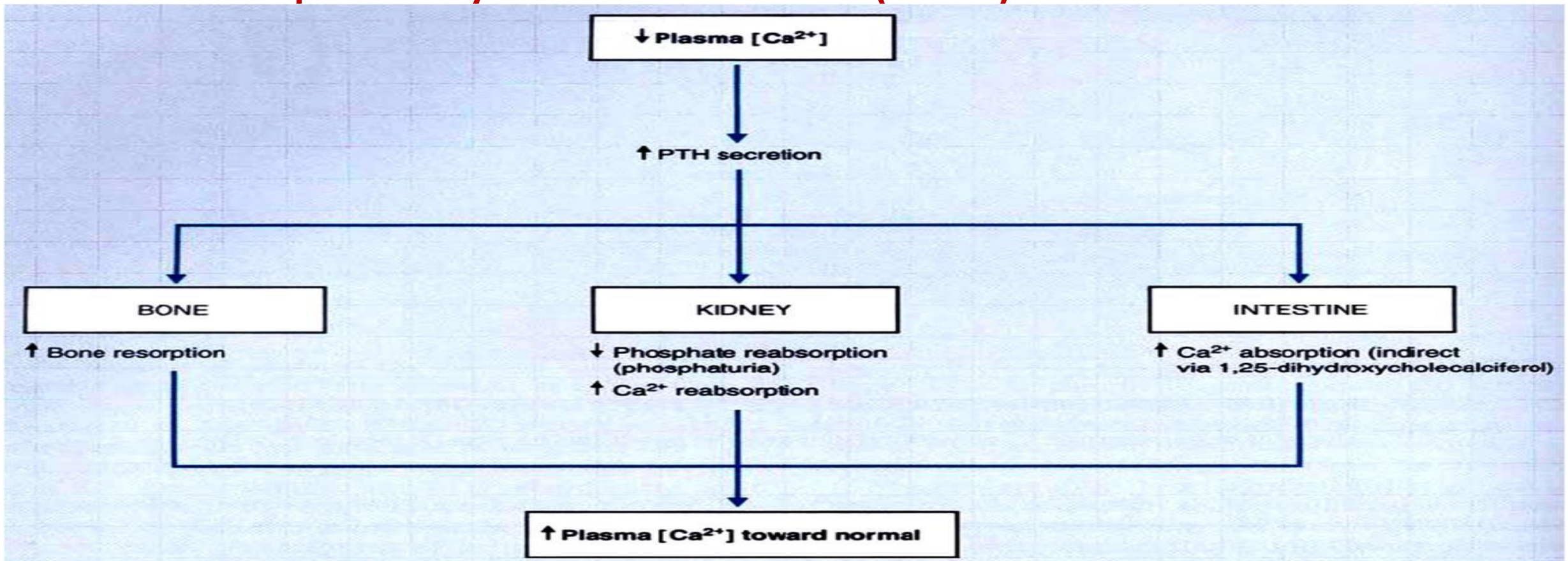
- ✓ Four glands located on the posterior surface of the thyroid gland.
- ✓ Secrete the polypeptide hormone PTH.
- ✓ **Decreased blood level of Ca ⟶ stimulates the Parathyroids to secrete PTH.**

# Regulation of PTH secretion

- Secretion of PTH is inversely related to plasma calcium because Plasma calcium level is the dominant regulator of PTH secretion :
  - ✓ Plasma calcium level less than 3.5 mg/dL ⟶ stimulates PTH secretion
  - ✓ Plasma calcium level more than 5.5 mg/dL ⟶ inhibits PTH secretion



# Effects of parathyroid hormone (PTH)

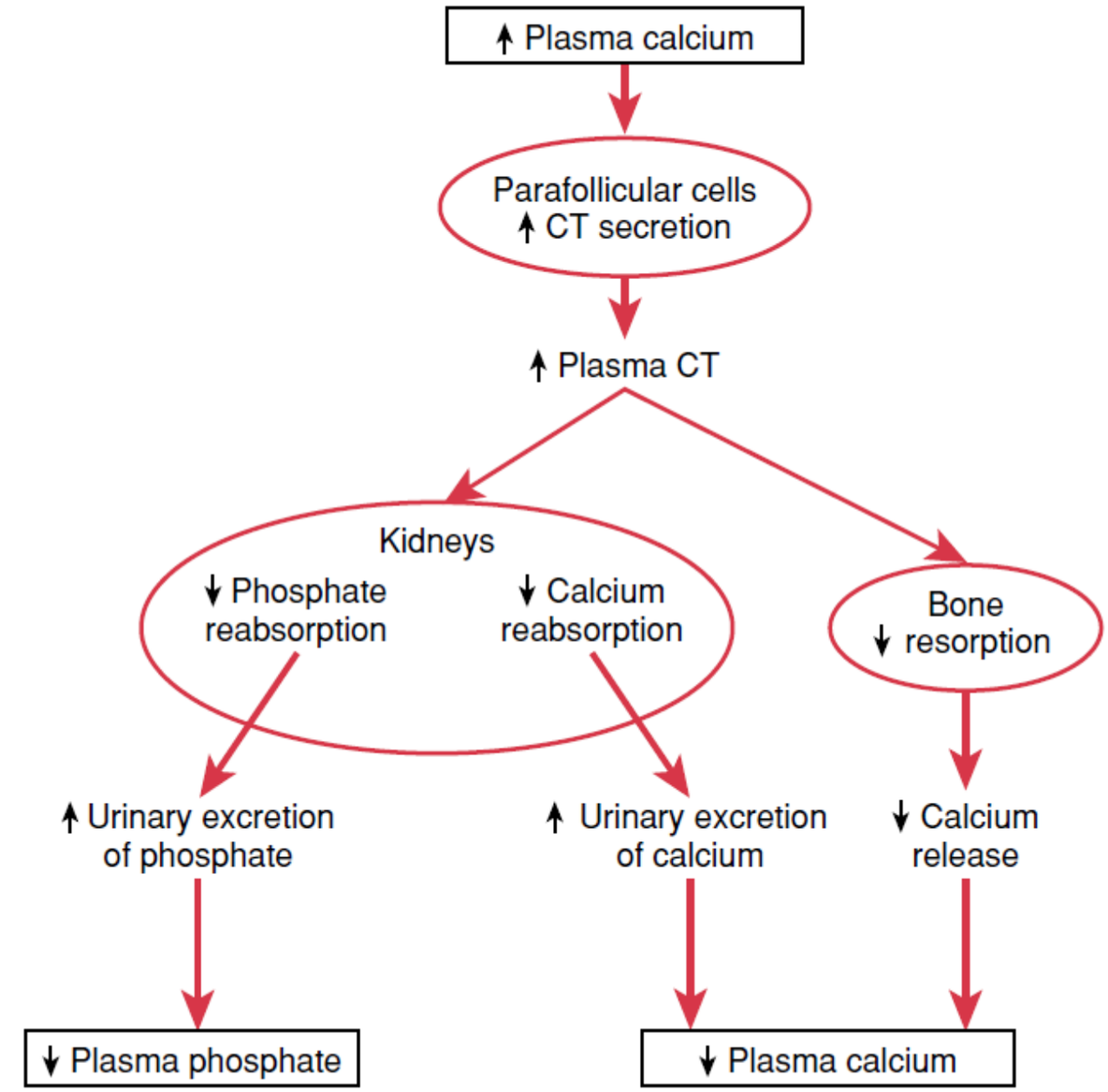



- The main effects of increased PTH secretion in response to decreased extracellular fluid calcium ion concentration:

1. PTH stimulates bone resorption, causing release of calcium into the extracellular fluid (by activation of osteoclasts, and inhibition of osteoblasts)
2. PTH increases reabsorption of calcium and decreases phosphate reabsorption by the renal tubules, leading to decreased excretion of calcium and increased excretion of phosphate
3. PTH is necessary for conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which, in turn, increases calcium absorption by the intestines (so PTH effect on intestine is INDIRECTLY by 1,25-dihydroxycholecalciferol)

# Clacitonin:

- Secreted by the parafollicular cells (C cells) of the thyroid gland.
- **Function:**
  - ✓ Decrease blood Ca++ level very rapidly within minutes.
  - ✓ Opposite effect to PTH
- **Stimulus for secretion:**
  - ✓ Increased plasma calcium concentration




# Effects of calcitonin:

1. **Bones:**
   - ✓ Inhibits osteoclast activity in bones
   - ✓ Stimulates osteoblastic activity in bones
   - ✓ So, bone resorption will decrease leading to increased calcium depositions in bones
2. **Kidney:**
   - ✓ Decreases calcium reabsorption
   - ✓ Leading to increased calcium excretion (in addition to phosphate)

| Abnormalities: | Rickets | Osteomalacia | Renal rickets |
|---|---|---|---|
| occurrence | Children | Adults | Not specific |
| cause | lack of vitamin D leading to calcium/phosphate deficiency in ECF | deficiencies of both vitamin D and calcium occur as a result of steatorrhea (failure to absorb fat) | Due to prolonged kidney disease |
| Features | ▪ **Low plasma calcium and phosphate**<br>▪ **Weak bones** | | Failure of the damaged kidney to form 1,25 dihydroxycholecalciferol (the active form of vitamin D) |
| TETANY related | • **Early stage:** there's no tetany, because PTH stimulate osteoclastic absorption of bone to release Ca to ECF (ECF Calcium level is normal)<br>• **ECF Ca level falls rapidly:** When the bones finally become exhausted of calcium<br>• **blood level of calcium falls below 7 mg/dl:** signs of tetany develop and the child may die of <u>tetanic respiratory spasm</u> | NEVER proceeds to tetany | |
| Bone composition related problem | Inadequate bone mineralization (not related to bone matrix)<br>Mineralizations = Calcium and Phosphate | | |

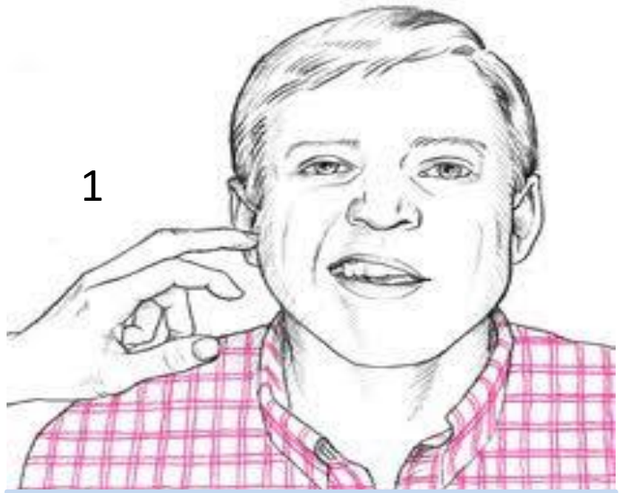
# Abnormalities (continued..)

| Osteoporosis | |
|---|---|
| Occurrence | Adults, especially in old age |
| Features | • The osteoblastic activity in the bone usually is less than normal<br>• The cause of the diminished bone is excess osteoclastic activity |
| Causes | 1. Lack of physical stress<br>2. Malnutrition<br>3. Lack of vitamin C ( for collagen synthesis )<br>4. Postmenopausal lack of estrogen<br>5. Old age<br>6. Cushing's syndrome |
| Bone composition related problem | Inadequate bone matrix and minerals |

# Disorders of PTH secretion:

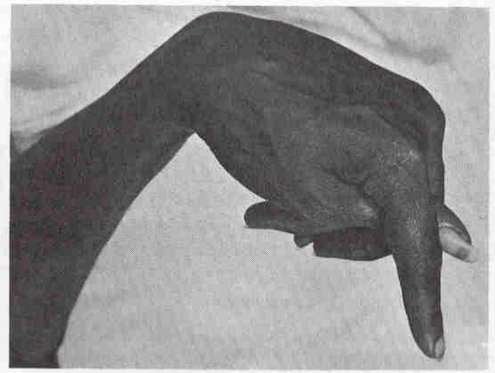
| Hypo-parathyroidism | |
|---|---|
| Causes | 1. **Abnormal parathyroid gland** (reduced or absent synthesis of PTH)<br>2. **By mistake removal of parathyroid gland during thyroid surgery.** |
| Consequences | **Hypo-calcemia** (hypocalacemia can also accompany severe Vit D deficiency) |
| Signs, symptoms and features | • **Positive Chvostek's** (facial muscle twitch) **sign** pic 1<br>• **Positive Trousseau's** (carpal spasm) **sign** pic 2<br>• **Delayed cardiac repolarization with prolongation of the QT interval**<br>• **Paresthesia** (such as tingling and numbness)<br>• **Tetany** |
| Treatment | Calcium carbonate and vitamin D supplements |

1



Tapping the facial nerve as it emerge from the parotid gland in front of the ear, which leads to contraction of facial muscles.

2

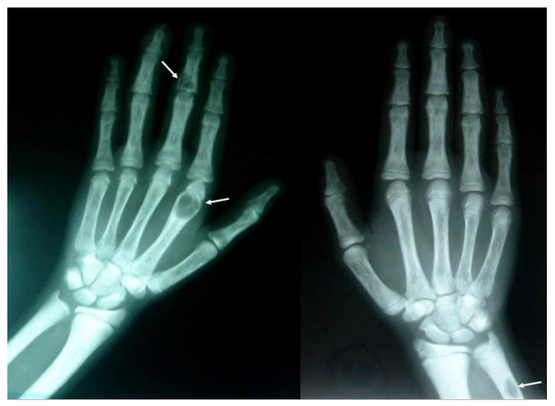


Arresting blood flow to the forearm for few minutes, which leads to flexion of the wrist, thumb and metacarpophalangeal joints

http://youtu.be/kvmwsTU0InQ
(Chvostek's and Trousseau's signs)

ıttp://youtu.be/9BA37LEY9cc
(Hypo-parathyroidism)

# Disorders of PTH secretion:

| | Primary hyper-parathyroidism | Secondary hyper-parathyroidism |
|---|---|---|
| Causes | Tumor of parathyroid glands | Parathyroid glands are normal. May caused by:<br>• Low calcium diet<br>• Pregnancy<br>• Lactation<br>• Rickets<br>• Osteomalcia<br>• Chronic renal failure (↓ 1,25(OH) – vit. D3 synthesis) |
| Consequences | 1. Hyper-calcemia<br>2. Hypo-phosphatemia<br>3. Hyper-calciuria and hyper-phosphaturia | high levels of PTH occur as a compensation for *hypocalcemia* (which not related to parathyroid glands abnormality) |
| Features | • Osteitis fibrosa cystica pic arrows<br>• Calcium containing stones in kidney<br>• Precipitation ترسب of calcium in soft tissues occur when Ca2+ > 17mg/dl. (death can occur) |  |

YouTube http://youtu.be/sD9st1ZPFrQ (Hyper-parathyroidism)

# Summery

## B. Parathyroid hormone (PTH)

- is the major hormone for the regulation of serum [$Ca^{2+}$].
- is synthesized and secreted by the **chief cells** of the parathyroid glands.

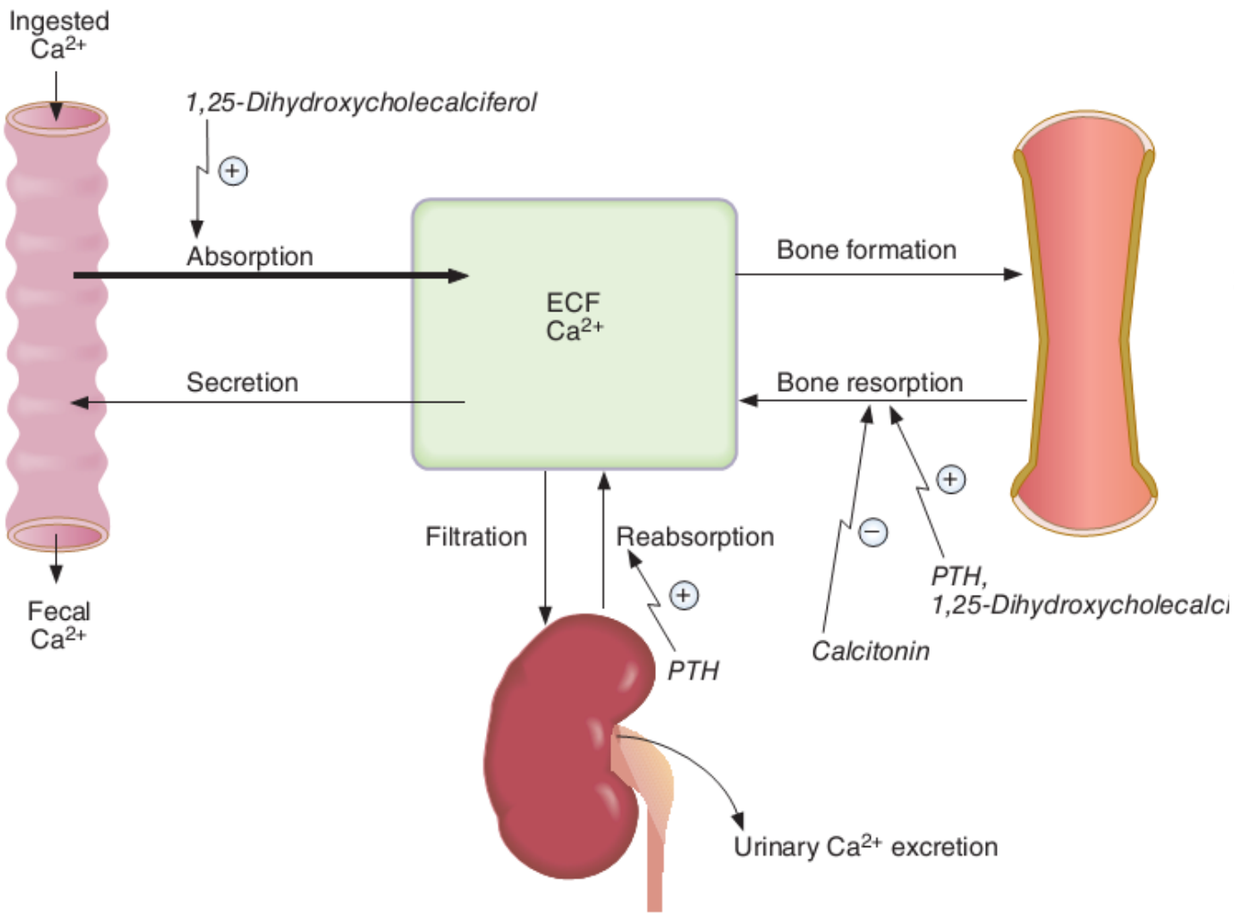



**FIGURE 7-13** Hormonal regulation of $Ca^{2+}$ metabolism. ECF = extracellular fluid; PTH = parathyroid hormone.

### 1. Secretion of PTH

- is controlled by the serum [$Ca^{2+}$] binding to **$Ca^{2+}$-sensing receptors** in the parathyroid cell membrane. **Decreased serum [$Ca^{2+}$] increases PTH secretion**, whereas increased serum $Ca^{2+}$ decreases PTH secretion.
- Decreased serum $Ca^{2+}$ causes decreased binding to the $Ca^{2+}$-sensing receptor, which stimulates PTH secretion.
- Mild decreases in serum [$Mg^{2+}$] stimulate PTH secretion.
- Severe decreases in serum [$Mg^{2+}$] inhibit PTH secretion and produce symptoms of hypoparathyroidism (e.g., hypocalcemia).
- The second messenger for PTH secretion by the parathyroid gland is cAMP.

### 2. Actions of PTH

- are coordinated to produce an **increase in serum [$Ca^{2+}$]** and a **decrease in serum [phosphate]**.
- The second messenger for PTH actions on its target tissues is **cAMP**.

**a. PTH increases bone resorption**, which brings both $Ca^{2+}$ and phosphate from bone mineral into the ECF. Alone, this effect on bone would not increase the serum ionized [$Ca^{2+}$] because phosphate complexes $Ca^{2+}$.

- Resorption of the organic matrix of bone is reflected in **increased hydroxyproline excretion**.

**b. PTH inhibits renal phosphate reabsorption** in the **proximal tubule** and, therefore, increases phosphate excretion **(phosphaturic effect).** As a result, the phosphate resorbed from bone is excreted in the urine, allowing the serum ionized [$Ca^{2+}$] to increase.

- cAMP generated as a result of the action of PTH on the proximal tubule is excreted in the urine **(urinary cAMP)**.

**c. PTH increases renal $Ca^{2+}$ reabsorption** in the **distal tubule,** which also increases the serum [$Ca^{2+}$].

**d. PTH increases intestinal $Ca^{2+}$ absorption** indirectly by stimulating the production of 1,25-dihydroxycholecalciferol in the kidney (see VII C).

# Summery

**3. Pathophysiology of PTH** (Table 7-12)

**a. Primary hyperparathyroidism**

- is most commonly caused by **parathyroid adenoma.**
- is characterized by the following:

**(1)** ↑ serum [$Ca^{2+}$] (hypercalcemia)
**(2)** ↓ serum [phosphate] (hypophosphatemia)
**(3)** ↑ urinary phosphate excretion (phosphaturic effect of PTH)
**(4)** ↑ urinary $Ca^{2+}$ excretion (caused by the increased filtered load of $Ca^{2+}$)
**(5)** ↑ urinary cAMP
**(6)** ↑ bone resorption

**b. Humoral hypercalcemia of malignancy**

- is caused by **PTH-related peptide (PTH-rp)** secreted by some malignant tumors (e.g., breast, lung). PTH-rp has all of the physiologic actions of PTH, including increased bone resorption, increased renal $Ca^{2+}$ reabsorption, and decreased renal phosphate reabsorption.
- is characterized by the following:

**(1)** ↑ serum [$Ca^{2+}$] (hypercalcemia)
**(2)** ↓ serum [phosphate] (hypophosphatemia)
**(3)** ↑ urinary phosphate excretion (phosphaturic effect of PTH-rp)
**(4)** ↓ serum PTH levels (due to feedback inhibition from the high serum $Ca^{2+}$)

**c. Hypoparathyroidism**

- is most commonly a result of **thyroid surgery**, or it is **congenital**.
- is characterized by the following:

**(1)** ↓ serum [$Ca^{2+}$] (hypocalcemia) and **tetany**
**(2)** ↑ serum [phosphate] (hyperphosphatemia)
**(3)** ↓ urinary phosphate excretion

**d. Pseudohypoparathyroidism type Ia—Albright's hereditary osteodystrophy**

- is the result of **defective $G_s$ protein** in kidney and bone, which causes end-organ **resistance to PTH.**
- **Hypocalcemia** and **hyperphosphatemia** occur (as in hypoparathyroidism), which are not correctable by the administration of exogenous PTH.
- Circulating **PTH levels are elevated** (stimulated by hypocalcemia).

**e. Chronic renal failure**

- Decreased glomerular filtration rate (GFR) leads to decreased filtration of phosphate, phosphate retention, and **increased serum [phosphate].**
- Increased serum phosphate complexes $Ca^{2+}$ and leads to **decreased ionized [$Ca^{2+}$].**
- **Decreased production of 1,25-dihydroxycholecalciferol** by the diseased renal tissue also contributes to the decreased ionized [$Ca^{2+}$] (see VII C 1).
- Decreased [$Ca^{2+}$] causes **secondary hyperparathyroidism.**
- The combination of increased PTH levels and decreased 1,25-dihydroxycholecalciferol produces **renal osteodystrophy,** in which there is increased bone resorption and osteomalacia.

**f. Familial hypocalciuric hypercalcemia (FHH)**

- autosomal dominant disorder with decreased urinary $Ca^{2+}$ excretion and increased serum $Ca^{2+}$
- caused by **inactivating mutations** of the $Ca^{2+}$-sensing receptors that regulate PTH secretion.

# Summery

table 7-12 Pathophysiology of PTH

| Disorder | PTH | 1,25-Dihydroxy-cholecalciferol | Bone | Urine | Serum [$Ca^{2+}$] | Serum [P] |
|---|---|---|---|---|---|---|
| Primary hyperparathyroidism | ↑ | ↑ (PTH stimulates 1α-hydroxylase) | ↑ Resorption | ↑ P excretion (phosphaturia)<br>↑ $Ca^{2+}$ excretion (high filtered load of $Ca^{2+}$)<br>↑ urinary cAMP | ↑ | ↓ |
| Humoral hypercalcemia of malignancy | ↓ | — | ↑ Resorption | ↑ P excretion | ↑ | ↓ |
| Surgical hypoparathyroidism | ↓ | ↓ | ↓ Resorption | ↓ P excretion<br>↓ urinary cAMP | ↓ | ↑ |
| Pseudohypoparathyroidism | ↑ | ↓ | ↓ Resorption (defective $G_s$) | ↓ P excretion<br>↓ urinary cAMP (defective $G_s$) | ↓ | ↑ |
| Chronic renal failure | ↑ (2°) | ↓ (caused by renal failure) | Osteomalacia (caused by ↓ 1,25-dihydroxy-cholecalciferol)<br>↑ Resorption (caused by ↑ PTH) | ↓ P excretion (caused by ↓ GFR) | ↓ (caused by ↓ 1,25-dihydroxy-cholecalciferol) | ↑ (caused by ↓ P excretion) |

cAMP = cyclic adenosine monophosphate; GFR = glomerular filtration rate. See Table 7-1 for other abbreviation.

# MCQs

| | | | |
|---|---|---|---|
| **Q1** | **What is the stimulation of parathyroid to secrete PTH?**<br>A. Increased blood level of Ca<br>B. Decreased blood level of Ca<br>C. Increased blood level of phosphate | **Q4** | **Tetany caused by:**<br>A. Hyper-parathyroidism<br>B. By mistake removal of parathyroid gland during thyroidectomy (Hypo-parathyroidism) |
| **Q2** | **Calcitonin secretion will inhibit if:**<br>A. Plasma calcium level less than 3.5 mg/dL<br>B. Plasma calcium level more than 3.5 mg/dL<br>C. Plasma calcium level more than 5.5 mg/dL | **Q5** | **Hypo-parathyroidism characterized by which signs?**<br>A. osteitis fibrosa cystica<br>B. Chvostek and Trousseau<br>C. shortened QT interval |
| **Q3** | **An effect of PTH:**<br>A. Decreased excretion of phosphate<br>B. Increased excretion of calcium<br>C. increased calcium absorption by the intestines | **Q6** | **Adenoma of parathyroid gland is a cause of:**<br>A. Primary hyper-parathyroidism<br>B. Hypo-parathyroidism<br>C. Secondary hyper-parathyroidism |

1-B 2-A 3-C 4-B 5-B 6-A

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# Endocrine Block