HYPOCALCEMIC DISORDERS

PHUWICH HAOHARN
MAHARAT NAKHONRATCHASRIMA HOSPITAL
MARCH 2014
INTRODUCTION

- Normal adult may ingest 1000 mg of Ca$^{2+}$ per day.
- 400 to 500 mg of calcium may be absorbed.
- 300 mg of Calcium from digestive secretions is lost in the stool.
- resulting in the net absorption of only 100 to 200 mg.
The total serum calcium concentration consists of 3 fractions
- 15% bound to multiple organic and inorganic anions such as sulfate, phosphate, lactate, and citrate
- 40% bound to albumin
- 45% circulates as physiologically active ionized Ca
INTRODUCTION

- Serum calcium concentration falls by 0.8 mg/dL for every 1.0 g/dL fall in the serum albumin.

  \[
  \text{Corrected } [\text{Ca}] = \text{Measured total } [\text{Ca}] + (0.8 \times (4.5 - [\text{alb}]))
  \]

- Normal range of total serum calcium: 8.8 - 10.3 mg/dL
UVB exposure to 7-Dehydrocholesterol → D₃ → Liver Enzyme Pathway → Calcidiol (The form measured in the blood (25-OH or hydroxy vitamin D)) → Calcitriol (Active form of vitamin D in the body (1,25-dihydroxy vitamin D)) → Vitamin D is actually a hormone rather than a vitamin → Calcitroic Acid (Inactive form of Vitamin D (24,25-dihydroxy vitamin D)) → Water soluble for excretion from the body

For every 1,000 IU of vitamin D consumed, your blood will increase 10 ng/mL.

Diet Supplement:
- Ergocalciferol D₂ (from ergosterol)
- Cholecalciferol D₃ (from cholesterol)
VITAMIN D

- Calcitriol is primarily stimulated by PTH and hypophosphatemia

The main action of calcitriol
- Increases in bone resorption
- Increase intestinal absorption
Fig 1 | Regulation of serum calcium. Parathyroid hormone and vitamin D normally interact to protect against hypocalcaemia. Problems at any level can lead to low serum calcium, but the most common problems are vitamin D deficiency and hypoparathyroidism.
HYPOCALCEMIC DISORDERS

- Clinical Presentation
- Causes of hypocalcemia
- Treatment of Hypocalcemia
## Clinical Presentation in acute hypocalcemia

<table>
<thead>
<tr>
<th>Neuromuscular irritability</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias (peri-oral, extreamity)</td>
<td>- Prolonged QT intervals</td>
</tr>
<tr>
<td>Muscle twitching</td>
<td>- Arrhythmia</td>
</tr>
<tr>
<td>Carpopedal spasm</td>
<td>- Ventricular arrhythmias are rare</td>
</tr>
<tr>
<td>Trousseau’s sign</td>
<td>- Hypotension</td>
</tr>
<tr>
<td>Chvostek’s sign</td>
<td>- Heart failure</td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>Larygospasm</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Papilledema</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Presentation

- **Chvostek’s sign**
  percussion of the facial nerve below the zygoma, resulting in ipsilateral contractions of the facial muscle

- **Trousseau’s sign**
  3 minutes of occlusive pressure with a blood pressure cuff above SBP 10-20 mmHg resulting in carpal spasm
Clinical Presentation

- Chvostek's sign occurs in about 10 percent of normal subjects.
- Although Trousseau's sign is more specific than Chvostek's sign, both may be negative in patients with hypocalcemia.
Troussseau’s sign

แบ่งได้เป็น 4 ระดับ

• ระดับที่ 1 พบว่าการหดเกรื่องที่เกิดขึ้นนั้นผู้ป่วยสามารถฟื้นได้ค่ำยคนเอง
• ระดับที่ 2 ผู้ป่วยไม่สามารถฟื้นได้แต่ผู้ตรวจสามารถฟื้นได้
• ระดับที่ 3 ผู้ตรวจไม่สามารถฟื้นได้โดยการหดเกรื่องเกิดขึ้นหลังจากเริ่มรัดแขนนานกว่า 1 นาที
• ระดับที่ 4 จะเหมือนระดับที่ 3 แต่การหดเกรื่องเกิดขึ้นหลังจากเริ่มรัดแขนภายใน 1 นาที
Chvostek’s sign

แบ่งได้เป็น 4 ระดับ
• ระดับที่ 1 มีการกระตุกเฉพาะบริเวณมุมปาก
• ระดับที่ 2 มีการกระตุกที่บริเวณมุมปากและ alae nasi
• ระดับที่ 3 มีการกระตุกของกล้ามเนื้อ orbicularis oculi ร่วมด้วย
• ระดับที่ 4 มีการกระตุกของใบหน้าทั้งซี่ก
Figure 28-31 Trousseau’s sign. (From Burnside JW, McGlynn TJ. Physical Diagnosis, 17th ed. Baltimore: Williams & Wilkins; 1987:63.)
Ask the patient to relax his facial nerves. Next, stand directly in front of him and tap the facial nerve either just anterior to the earlobe or below the zygomatic arch and the corner of the mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcaemia.
Clinical Presentation
in Chronic hypocalcemia

- Ectopic calcification
- Extrapyramidal sign
- Parkinsonism
- Dementia
- Subcapsular cataract
- Abnormal dentition
- Dry skin

- Growth plate abnormalities in children (rickets)
- Defects in the mineralization of new bone (osteomalacia)
Causes of hypocalcemia

- Parathyroid-Related Disorders
- Vitamin D–Related Disorders
- Other Causes
# Causes of Hypocalcemia

## Parathyroid-Related Disorders

### Absence of the Parathyroid Glands or of PTH

- Congenital
  - DiGeorge's syndrome
  - X-linked or autosomally inherited hypoparathyroidism
  - Autoimmune polyglandular syndrome type 1
  - PTH gene mutations
- Postsurgical hypoparathyroidism
- Infiltrative disorders
  - Hemochromatosis
  - Wilson's disease
  - Metastases
- Hypoparathyroidism following radioactive iodine thyroid ablation

### Impaired Secretion of PTH

- Hypomagnesemia
- Respiratory alkalosis
- Activating mutations of the calcium sensor

### Target Organ Resistance

- Hypomagnesemia
- Pseudohypoparathyroidism
  - Type 1
  - Type 2
### Causes of Hypocalcemia

**Vitamin D–Related Disorders**

- Vitamin D deficiency
  - Dietary absence
  - Malabsorption
- Accelerated loss
  - Impaired enterohepatic recirculation
  - Anticonvulsant medications
- Impaired 25-hydroxylation
  - Liver disease
  - Isoniazid
- Impaired 1α-hydroxylation
  - Renal failure
- Vitamin D–dependent rickets type I
- Oncogenic osteomalacia
- Target organ resistance
  - Vitamin D–dependent rickets type II
  - Phenytoin

**Anti-TB drug.**
- Phenobarbital
- Primidone
- Phenytoin
- Rifampin
- Glutethimide
## Causes of Hypocalcemia

### Other Causes

- Excessive deposition into the skeleton
  - Osteoblastic malignancies
  - Hungry bone syndrome
- Chelation
  - Foscarnet
  - Phosphate infusion
  - Infusion of citrated blood products
  - Infusion of EDTA-containing contrast reagents
  - Fluoride
- Neonatal hypocalcemia
  - Prematurity
  - Asphyxia
  - Diabetic mother
  - Hyperparathyroid mother
- HIV infection
  - Drug therapy
  - Vitamin D deficiency
  - Hypomagnesemia
  - Impaired PTH responsiveness
- Critical illness
  - Pancreatitis
  - Toxic shock syndrome
  - Intensive care unit patients
<table>
<thead>
<tr>
<th>Condition</th>
<th>PTH</th>
<th>Correct Ca</th>
<th>PO4</th>
<th>Mg</th>
<th>25(OH)D</th>
<th>1,25(OH)D</th>
<th>Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoparathyroid</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activating mutation calcium sensing receptor</td>
<td>↑</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo Mg</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH resistance (pseudohypo-parathyroid)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Parathyroid-Related Disorders

Congenital or Inherited Parathyroid Disorders

- DiGeorge’s syndrome resulting in the absence of parathyroid glands
- familial hypoparathyroidism
Parathyroid-Related Disorders

Destruction of the Parathyroid Glands

- Most common - postsurgical hypoparathyroidism
- Transient hypoparathyroidism - common after parathyroidectomy
- Permanent hypoparathyroidism occur after vascular or surgical injury or removal of all parathyroid tissue
Destruction of the Parathyroid Glands

Hypoparathyroidism is a rare complication of radioactive iodine ablation of the thyroid gland in patients with Graves’ disease.

Result of infiltrative diseases of the parathyroids
  - hemochromatosis
  - Wilson’s disease
  - Metastatic disease
Parathyroid-Related Disorders

Pseudohypoparathyroidism

Idiopathic and inherited forms of PTH resistance are referred to as pseudohypoparathyroidism (PHP)

hypocalcemic
hyperphosphatemic

*Albright’s hereditary osteodystrophy* (AHO) include short stature, rounded face, foreshortened fourth and other metacarpals, obesity, and subcutaneous calcifications.
Figure 28-32  Daughter (left) and mother (right) with pseudo-hypoparathyroidism and Albright's hereditary osteodystrophy.
Figure 28-33: Radiograph of hand from a patient with pseudohypparathyroidism and Albright's hereditary osteodystrophy. Note the shortened fourth metacarpal.
Other Causes of Hypocalcemia

Excessive Deposition into the Skeleton

- Osteoblastic metastases
- Hungry bone syndrome after parathyroidectomy for primary hyperparathyroidism
Other Causes of Hypocalcemia

Human Immunodeficiency Virus Infection

Hypocalcemia is 6-folds more prevalent in HIV-infected patients.

- consequence of antiretroviral, antibiotic and antimycotic therapy
- vitamin D deficiency
- hypomagnesemia
- impaired parathyroid responsiveness to hypocalcemia
Fig 5 | Algorithm for requesting investigations to elucidate the cause of hypocalcaemia
Treatment of Hypocalcemia

**Calcium** — The treatment of hypocalcemia varies with its severity and the underlying cause.

- Hypocalcemia which severely symptomatic require rapid correction of calcium levels with IV calcium therapy.
- Suggest IV calcium therapy in asymptomatic patients with an acute decrease in serum corrected calcium to ≤7.5 mg/dL (1.9 mmol/L).
- Intravenous calcium is NOT warranted as initial therapy for asymptomatic hypocalcemia in patients with impaired renal function.

Uptodate 20.3
Calcium (continue)

- Milder symptoms of neuromuscular irritability and corrected serum calcium $>7.5$ mg/dL
  - Initial treatment with oral calcium supplementation is sufficient. If do not improve, intravenous calcium infusion is required

- Hypocalcemia in concurrent magnesium deficiency, hypomagnesemia should be corrected first

Uptodate 20.3
Vitamin D — When hypoparathyroidism (transient or permanent) or vitamin D deficiency are the cause of hypocalcemia

• intravenous calcium is only transiently effective, and oral calcium may not be well absorbed

• successful management requires the addition of vitamin D, which often permits a lower dose of calcium supplementation
Treatment of Hypocalcemia

Vitamin D

• Initial management of patients with hypoparathyroidism, recommend vitamin D supplementation in addition to calcium

• Calcitriol is the vitamin D metabolite of choice because it does not require renal activation, rapid onset of action, and shorter half-life

• Other: Alfacalcidol, vitamin D (ergocalciferol or cholecalciferol), or dihydrotachysterol

Uptodate 20.3
Treatment of Hypocalcemia

Vitamin D
- Hypocalcemia due to vitamin D deficiency, recommend vitamin D repletion
- Nutritional deficiency (25OHD <20 ng/mL)
  - Initial 50,000 units of vitamin D2 or D3 oral once per week for 6-8 weeks, and then 800 -1000 units of vitamin D3 daily

Uptodate 20.3
Treatment of Hypocalcemia

Permanent hypoparathyroidism

- Goals of therapy are to relieve symptoms, to raise and maintain the serum calcium in the low-normal range (8.0 to 8.5 mg/dL)
- Avoid hypercalciuria (maintain 24-hour urinary calcium below 300 mg)

Uptodate 20.3
Treatment of Hypocalcemia

- Permanent hypoparathyroidism require adequate calcium intake (1.0 to 1.5 g elemental calcium daily).
- Suggest calcitriol rather than recombinant human parathyroid hormone (PTH)
- Recombinant PTH is much more expensive than standard therapy with calcitriol. refractory hypercalciuria, PTH is a reasonable option
Treatment of Hypocalcemia

- The initial treatment of hypercalciuria in patients with hypoparathyroidism
  - reducing the dose of calcium and vitamin D
  - addition of thiazide diuretics

Uptodate 20.3
TABLE 28-6

Therapeutic Mineral Ion Preparations

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW*</th>
<th>mg/g</th>
<th>mmol/g</th>
<th>Oral Preparations</th>
<th>Mineral Ion Content</th>
<th>Parenteral Preparations</th>
<th>Mineral Ion Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca carbonate</td>
<td>100</td>
<td>400</td>
<td>10.0</td>
<td>1250 mg†</td>
<td>500 mg</td>
<td>10% soln</td>
<td>93 mg/10 mL</td>
</tr>
<tr>
<td>Ca phosphate</td>
<td>310</td>
<td>383</td>
<td>9.6</td>
<td>1565 mg†</td>
<td>600 mg</td>
<td>22% soln</td>
<td>90 mg/5 mL</td>
</tr>
<tr>
<td>Ca acetate</td>
<td>158</td>
<td>253</td>
<td>6.3</td>
<td>668 mg†</td>
<td>167 mg</td>
<td>10% soln</td>
<td>273 mg/10 mL</td>
</tr>
<tr>
<td>Ca citrate</td>
<td>498</td>
<td>210</td>
<td>6.0</td>
<td>950 mg†</td>
<td>200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca lactate</td>
<td>218</td>
<td>130</td>
<td>4.6</td>
<td>650 mg†</td>
<td>84 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca gluconate</td>
<td>430</td>
<td>93</td>
<td>2.3</td>
<td>1000 mg†</td>
<td>93 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca gluceptate</td>
<td>488</td>
<td>82</td>
<td>2.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca chloride</td>
<td>147</td>
<td>273</td>
<td>6.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg oxide</td>
<td>40</td>
<td>603</td>
<td>24.8</td>
<td>400 mg†</td>
<td>241 mg</td>
<td>10% soln</td>
<td>24 mg/mL</td>
</tr>
<tr>
<td>Mg gluconate</td>
<td>450</td>
<td>54</td>
<td>2.2</td>
<td>500 mg†</td>
<td>27 mg</td>
<td>20% soln</td>
<td>49 mg/mL</td>
</tr>
<tr>
<td>Mg chloride</td>
<td>203</td>
<td>120</td>
<td>4.9</td>
<td>535 mg</td>
<td>64 mg</td>
<td>50% soln</td>
<td>49 mg/mL</td>
</tr>
<tr>
<td>Mg sulfate</td>
<td>246</td>
<td>99</td>
<td>4.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na/K phosphate (neutral)</td>
<td></td>
<td></td>
<td></td>
<td>Capsule</td>
<td>250 mg</td>
<td>8.1 mmol</td>
<td></td>
</tr>
<tr>
<td>K phosphate (neutral)</td>
<td></td>
<td></td>
<td></td>
<td>Capsule</td>
<td>250 mg</td>
<td>8.1 mmol</td>
<td></td>
</tr>
<tr>
<td>Na phosphate (neutral)</td>
<td></td>
<td></td>
<td></td>
<td>soln</td>
<td>94 mg/mL</td>
<td>3.0 mmol/mL</td>
<td></td>
</tr>
</tbody>
</table>

* Molecular weights (MW) shown are for the usual chemical form, including water molecules (e.g., MgSO₄ • 7 H₂O).
† Other formulations exist. Those shown are among those approved in the United States.
‡ Phosphate preparations contain buffered mixtures of monobasic (H₂PO₄⁻) and dibasic (HPO₄²⁻) ions; the phosphorus content therefore is specified in millimoles.

- Oral phosphates contain 7 mEq sodium and potassium per capsule (Na/K form) or 14 mEq potassium per capsule (K form). Parenteral solutions typically contain 4 mEq of sodium or potassium per milliliter.
- MW, molecular weight; soln, solution.

Fig 6 | Algorithm for managing acute hypocalcaemia. In an emergency setting parenteral calcium is likely to be needed. If medium or long term treatment is needed, vitamin D or one of its analogues should be given.\[^{18}\]
Thank you