Hypercalcemia

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Pisit (Duke) Pitukcheewanont, MD
Clinical Director, Pediatric Bone Program
Center for Diabetes, Endocrinology & Metabolism
Children’s Hospital Los Angeles
Associate Professor of Pediatrics
The Keck School of Medicine of USC
The President of Human Growth Foundation

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Pisit Pitukcheewanont, MD, FAAP

Objectives

- Understand the definition of hypercalcemia
- Understand the different diagnoses of hypercalcemia
- Be aware of the treatment for hypercalcemia in children
### Normal range of serum calcium

<table>
<thead>
<tr>
<th>Age</th>
<th>Calcium mmol/L</th>
<th>Calcium mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>2.3-2.65</td>
<td>9.0-10.6</td>
</tr>
<tr>
<td>Age &lt;1 yr</td>
<td>2.25-2.73</td>
<td>9.0-10.9</td>
</tr>
<tr>
<td>1-15 years</td>
<td>2.2-2.7</td>
<td>8.8-10.8</td>
</tr>
<tr>
<td>Adult</td>
<td>2.1-2.55</td>
<td>8.4-10.2</td>
</tr>
</tbody>
</table>

### Forms of Calcium in Serum

- Ionized or free form: 48% - biological active
- Protein-bound form: 40%, mainly 90% albumin;
- Complexed form: 12% such as Phosphate, citrate or bicarbonate
- Clue: remember iCa 50% of total calcium

### Factors affecting serum calcium level

- **Albumin**
  - ↓ albumin 1 mg/dL → ↓ total Ca 0.8 mg/dL
  - Corrected Ca = measured Ca + 0.8 (4 – albumin)

- **pH**
  - ↑ pH 0.1 → ↓ ionized Calcium 0.2 mg/dL
### Urine Calcium/Creatinine Ratio

<table>
<thead>
<tr>
<th>Age</th>
<th>Urine Ca/Cr ratio (mg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 7 mo</td>
<td>0.86</td>
</tr>
<tr>
<td>7 - 18 mo</td>
<td>0.60</td>
</tr>
<tr>
<td>19 mo - 6 yr</td>
<td>0.42</td>
</tr>
<tr>
<td>&gt; 7 yr</td>
<td>0.21</td>
</tr>
</tbody>
</table>


### Definition of hypercalcemia

<table>
<thead>
<tr>
<th>Age &lt; 2 yrs</th>
<th>total Ca &gt; 10.8 mg/dL or 2.7 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 2 yrs</td>
<td>total Ca &gt; 10.5 mg/dL or 2.6 mmol/L</td>
</tr>
</tbody>
</table>

**Calcium** 4 mg/dL = 1 mmol/L.

### Clinical Manifestation

- **Central nervous system effects**
  - Mild tiredness, weakness
  - Lethargy
  - Confusion
  - Coma
- **Renal effects**
  - Polyuria, nocturia
  - Dehydration
  - Nephrolithiasis
  - Renal failure

- **Gastrointestinal effects**
  - Constipation
  - Nausea and vomiting
  - Anorexia

- **Cardiovascular effects**
  - Prolonged QT interval
  - Arrhythmia
Differential Diagnosis

Hypercalcemia in neonate and infant
(< 2 years)

<table>
<thead>
<tr>
<th>PTH disorder</th>
<th>Vitamin D disorder</th>
<th>Abnormality of the calcium sensing receptor (CaSR)</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism: congenital parathyroid hyperplasia</td>
<td>Hypervitaminosis D</td>
<td>Inactivating mutation of CASR</td>
<td>Subcutaneous fat necrosis</td>
</tr>
<tr>
<td>Jansen’s metaphyseal chondrodysplasia</td>
<td>Exogenous: excessive vit D ingestion</td>
<td>Neonatal severe hyperparathyroidism</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td></td>
<td>Endogenous: granulomatous disease, lymphoma</td>
<td></td>
<td>Idiopathic infantile hypercalcemia</td>
</tr>
</tbody>
</table>

Hypercalcemia in childhood and adolescent

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<thead>
<tr>
<th>PTH disorder</th>
<th>Vitamin D disorder</th>
<th>Abnormality of the calcium sensing receptor (CaSR)</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Hypervitaminosis D</td>
<td>Inactivating mutation of CASR</td>
<td>Immobilization</td>
</tr>
<tr>
<td></td>
<td>Exogenous: excessive vit D ingestion</td>
<td>Familial hypocalciuric hypercalcemia</td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td>Endogenous: granulomatous disease, lymphoma</td>
<td></td>
<td>Medications (Thiazide, retinoid derivatives, alkali, etc),</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperthyroidism,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypophosphatasia</td>
</tr>
</tbody>
</table>
Investigations

- Serum calcium, ionized calcium, phosphate, magnesium, intact PTH, ALP, 25-OHD, 1,25(OH)_{2}D
- Urine calcium/creatinine ratio
- Film long bones
- Further investigation may be needed eg. FISH for ELN, PTHrP level

Diagnostic Approach to Hypercalcemia

- Hypercalcemia
- Urine Ca/Cr ratio
  - Considering abnormal CaSR
  - Other abnormality

Idiopathic Infantile Hypercalcemia

- Characterized by severe hypercalcemia, failure to thrive, vomiting, dehydration, and nephrocalcinosis.
- CYP24A1 mutations increase sensitivity to vitamin D in patients with idiopathic infantile hypercalcemia.
- Also, it is a genetic risk factor for the development of symptomatic hypercalcemia that may be triggered by vitamin D prophylaxis in otherwise apparently healthy infants.

Williams Syndrome

- Originally described independently by Williams and Beuren in 1961, Williams syndrome (WS)
- Occurs in 1 per 7,500-20,000 births; most cases are sporadic.
- Characteristic triad of anomalies:
  - distinctive facial appearance,
  - supravalvular aortic stenosis (SVAS),
  - mental retardation: 4 areas: cognitive development, language, auditory function, and visuospatial function.

Williams Syndrome

- Onset: birth through adulthood.
- Fetal ultrasonography of neonates with Williams syndrome has revealed multicystic dysplastic kidney in addition to the congenital heart lesions.
- Associated findings on prenatal screening that have been reported include an increased fetal nuchal translucency and low maternal serum alpha fetoprotein (MSAFP) but none of the prenatal findings has been proven to be a diagnostic marker of Williams syndrome.

Hyperparathyroidism

- Uncommon in children
- The incidence of HPT is 2-5 per 100,000
- Female to male ratio 2:1
- Patient usually asymptomatic or presents with non-specific symptoms.
- There is a risk for delay in diagnosis.
Osteitis Fibrosa Cystica

- Irregular, frayed and ill-defined cortical outline, pronounced at radial aspect of middle phalanges → subperiosteal bone resorption
- Multiple lytic lesions → brown tumors (arrows)

Hyperparathyroidism

- Primary Hyperparathyroidism
  - Single adenoma (80%)
  - Multiple gland (10%–15%)
  - Double adenomas (4-5%)
  - A history of head and neck radiation is also a risk factor.

- Secondary Hyperparathyroidism
  - Chronic renal insufficiency
  - Insufficient vitamin D and calcium intake
  - Cholestatic liver disease
  - Iatrogenic causes, such as lithium administration

- Tertiary Hyperparathyroidism
  - Long-standing secondary hyperparathyroidism
Hypervitaminosis D

- Children and infants may develop vitamin D intoxication when receiving more than 2000-4000 units daily.
- This eventually leads to hypercalcemia.
- 25-hydroxyvitamin D level > 100 ng/mL

Hypercalcemia of Malignancy

- 20-30% of cases
- Usually present at diagnosis
- Primarily due to increased bone resorption
- Others: osteolytic metastasis with local release of cytokines (including osteoclast activating factor), PTHrP, extrarenal 1 alpha hydroxylase activity and rarely ectopic PTH secretion

PTHRP producing tumor

- Osteolytic by direct invasion of tumor
- Secretion of humoral factors, usually associated with parathyroid hormone related-peptide (PTHRP)
- Excess 1-alpha hydroxylase activity from tumor
- Release of calcemic cytokines
  - Prostaglandins
  - Interleukin 1, interleukins 6
  - Tumor necrosis factor
Extrarenal 1α-hydroxylase activity

- Extrarenal 1α-hydroxylase expressed in activated macrophages
- Granulomatous disease: Tuberculosis, Sarcoidosis
- Malignancy: Lymphoma
- Fungal Ball: Aspergillosis, Coccidioidomycosis

- The elevated 1,25-dihydroxyvitamin D and hypercalcemia inhibit PTH production, and this exacerbates hypercalciuria

Calcium sensing receptor mutation

- Inactivating mutation
- Homozygous: Neonatal Severe Hyperparathyroidism (NSHPT)
- Heterozygous: Familial Hypocalciuria Hypercalcemia

Familial Hypocalciuric Hypercalcemia

- An autosomal dominant disorder that results from a heterogeneous group of mutations affecting the Calcium Sensing Receptor (CaSR).
- With a less sensitive receptor, PTH continues to be produced even when serum calcium levels are high.
- CaSR activation also reduces renal reabsorption of calcium in a manner independent of PTH.
### Differential Diagnosis of Hypercalcemia

<table>
<thead>
<tr>
<th></th>
<th>Ca</th>
<th>P</th>
<th>Mg</th>
<th>U Ca/Cr</th>
<th>PTH</th>
<th>PTHrP</th>
<th>25OHD</th>
<th>LSN (OMGH)D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° hyperparathyroidism</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>→</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td>↑</td>
</tr>
<tr>
<td>PTHrP producing tumor</td>
<td>↑</td>
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<td>↓</td>
<td>→</td>
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<td>→</td>
<td>→</td>
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<td>Hypervitaminosis D</td>
<td>↑</td>
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<td>→</td>
<td>↓</td>
<td>→</td>
<td>→</td>
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</tr>
<tr>
<td>Granulomatous disease</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>→</td>
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<td>→</td>
<td>→</td>
<td>↑</td>
</tr>
<tr>
<td>CaSR mutation</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→ → ↑ ↑</td>
</tr>
</tbody>
</table>

### Management

**Lowering high serum calcium level**
- Hydration
- Loop diuretic agent
- Calcitonin
- Bisphosphonate
- Glucocorticoids
- Dialysis

**Treatment the underlying cause**
**Hydration**

*Action:*
- Correct dehydration
- Enhance urinary calcium excretion by increasing GFR and decreasing sodium and water reabsorption at proximal renal tubule

**NSS 1.5-2 maintenance IV**
Adequate rehydration usually decrease serum calcium 1-3 mg/dL.
Monitor I/O closely to avoid fluid overload

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**Loop diuretic agent**

*Action:*
- Facilitated urinary calcium excretion by inhibiting calcium reabsorption at the thick ascending limb of loop of Henle
- *Furosemide 1 mg/kg/dose IV after adequate hydration*

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**Antiresorptive agents**

*Action: inhibit bone resorption*

*Indication:*
- Hypercalcemia of malignancy
- Primary/ metastatic bone tumor
- PTHrP producing tumor

*Calcitonin, bisphosphonate*
Calcitonin

- Salmon calcitonin
- Dose: 2-4 U/kg SC q 4-6 hours
- Onset of action: 4-6 hours
- Duration of action: 24-48 hours
- Decrease serum calcium 1-2 mg/dL
- Its effectiveness may diminish thereafter despite continuous administration (tachyphylaxis)

Bisphosphonate

- Inhibit osteoclast activity
- Pamidronate
- Dose: 0.5-1 mg/kg/dose IV drip in 4-6 hrs
- Onset of action: 1-2 days
- Duration: 2-4 weeks

Corticosteroids

**Action:**
- inhibit intestinal calcium absorption
- inhibit extrarenal 1α-hydroxylation
- inhibit growth of neoplastic lymphoid tissue
- inhibit secretion of mediator by lymphocyte
- inhibit osteoclast function
**Corticosteroids**

**Indication:**
- Hypervitaminosis D
- Endogenous calcitriol production:
  - granulomatous disease eg. TB, sarcoidosis
  - subcutaneous fat necrosis
  - malignancy associated hypercalcemia eg. lymphoma

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**Corticosteroids**

- Hydrocortisone 1-5 mg/kg/dose IV q 6 hrs
- Prednisolone 1 mg/kg/day oral q 8 hrs
  - Usually decrease serum calcium within 2-5 days

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**Ketoconazole**

- Competitive inhibition of mitochondria 1-α hydroxylase enzyme
- Possibly mechanism involving defective up-regulation of the 24-hydroxylase by 1,25-(OH)2D3, and the klotho-FGF23 axis.
- Ketoconazole is a potentially useful and safe agent for treatment of infantile hypercalcemia
- An alternative therapy for hypercalcemic sarcoidosis when corticosteroids are relatively contraindicated.

Calcimimetic drug

- **Cinacalcet**
- An orally active, potent and selective calcium-sensing receptor (CaSR) antagonist (calcilytic)

Cinacalcet

(Schlieper et al. Calcimimetics in CKD: results from recent clinical studies. Pediatric Nephrology, 2008)
Cinacalcet HCL

An analog of NPS R-568 with an improved metabolic profile
- Lowering plasma level of PTH
- Stimulate calcitonin release

Sensipar® (Cinacalcet)

- Calcimimetics
- The first drug in this class to be approved by FDA
- For secondary hyperparathyroidism in chronic renal disease on dialysis and hypercalcemia in pt with parathyroid carcinoma
- Starting dose: 30 mg oral daily

Dialysis

Indication:
- Renal failure
- Heart failure
- Peritoneal dialysis or hemodialysis with calcium poor dialysate or calcium repleted dialysate fluid
Summary

• Hypercalcemia is considered to be an endocrine emergency especially in symptomatic patients (Calcium > 12 mg/dL).

• Identifying the etiology of hypercalcemia is very crucial.

• Hydration with normal saline and diuretic are the first line treatment.

• Anti-resorptive agents therapy could be initiated in some of the hypercalcemic patients. However close monitoring of calcium level is extremely important.

Thank you