Disorders of calcium homeostasis

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2nd Department of Internal Medicine, Semmelweis University
The role of calcium in normal physiology

Calcium:
- chemical symbol: Ca, ionic form: Ca\(^{2+}\)
- No of protons: 20
- standard atomic weight: 40.078 g/mol
- belongs to alkaline earth metals

The average adult contains approximately 1 kg of calcium in the body

- **bones, teeth** (hydroxyapatite)
  * provide mechanic structure of bones

- **intracellular space**
  * signal transduction (2nd messenger)

- **extracellular compartments**
  * axon excitation
  * signal transmission in synapses
  * myocardium excitation and contraction
  * smooth muscle contraction
  * cofactor in clotting cascade
<table>
<thead>
<tr>
<th>Group</th>
<th>Recommended intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants and children</strong></td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td></td>
</tr>
<tr>
<td>Human milk</td>
<td>300</td>
</tr>
<tr>
<td>Cow milk</td>
<td>400</td>
</tr>
<tr>
<td>7–12 months</td>
<td>400</td>
</tr>
<tr>
<td>1–3 years</td>
<td>500</td>
</tr>
<tr>
<td>4–6 years</td>
<td>600</td>
</tr>
<tr>
<td>7–9 years</td>
<td>700</td>
</tr>
<tr>
<td><strong>Adolescents</strong></td>
<td></td>
</tr>
<tr>
<td>10–18 years</td>
<td>1300&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>19 years to menopause</td>
<td>1000</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>1300</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>19–65 years</td>
<td>1000</td>
</tr>
<tr>
<td>65+ years</td>
<td>1300</td>
</tr>
<tr>
<td><strong>Pregnant women (last trimester)</strong></td>
<td>1200</td>
</tr>
<tr>
<td><strong>Lactating women</strong></td>
<td>1000</td>
</tr>
</tbody>
</table>

<sup>a</sup> Particularly during the growth spurt.
<table>
<thead>
<tr>
<th>Food Items</th>
<th>Serving (oz)</th>
<th>Calcium Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat yogurt</td>
<td>1 cup (8 oz)</td>
<td>415</td>
</tr>
<tr>
<td>Milkshake</td>
<td>1 cup (8 oz)</td>
<td>362</td>
</tr>
<tr>
<td>Pizza, cheese</td>
<td>1/2 cup of 10-inch pizza</td>
<td>355</td>
</tr>
<tr>
<td>Eggnog, nonalcoholic</td>
<td>1 cup (8 oz)</td>
<td>330</td>
</tr>
<tr>
<td>Low fat yogurt with fruit</td>
<td>1 cup (8 oz)</td>
<td>314</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>1/2 cup (3-1/2 oz.)</td>
<td>303</td>
</tr>
<tr>
<td>Skimmed milk (1/2% fat)</td>
<td>1 cup (8 oz)</td>
<td>302</td>
</tr>
<tr>
<td>Whole milk</td>
<td>1 cup (8 oz)</td>
<td>291</td>
</tr>
<tr>
<td>Cheese soup made with milk</td>
<td>1 cup</td>
<td>288</td>
</tr>
<tr>
<td>Swiss cheese</td>
<td>1 slice (1 oz.)</td>
<td>272</td>
</tr>
<tr>
<td>Red salmon</td>
<td>1/2 cup (3-1/2 oz.)</td>
<td>259</td>
</tr>
<tr>
<td>Ricotta</td>
<td>1 ounce</td>
<td>257</td>
</tr>
<tr>
<td>Soft serve ice milk</td>
<td>1 cup</td>
<td>236</td>
</tr>
<tr>
<td>Provolone</td>
<td>1 ounce</td>
<td>214</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1 slice (1 oz.)</td>
<td>204</td>
</tr>
<tr>
<td>Pink salmon</td>
<td>1/2 cup (3-1/2 oz.)</td>
<td>196</td>
</tr>
<tr>
<td>Cheese sauce, homemade</td>
<td>1/4 cup</td>
<td>178</td>
</tr>
<tr>
<td>Mushroom soup made with milk</td>
<td>1 cup</td>
<td>178</td>
</tr>
<tr>
<td>Ice cream or ice milk</td>
<td>1 cup</td>
<td>176</td>
</tr>
<tr>
<td>American cheese</td>
<td>1 slice (1 oz.)</td>
<td>174</td>
</tr>
<tr>
<td>Tomato soup made with milk</td>
<td>1 cup</td>
<td>159</td>
</tr>
<tr>
<td>Mozzarella</td>
<td>1 ounce</td>
<td>174</td>
</tr>
<tr>
<td>Custard or pudding</td>
<td>1/2 cup</td>
<td>145</td>
</tr>
<tr>
<td>Mustard greens, cooked</td>
<td>1/2 cup</td>
<td>138</td>
</tr>
<tr>
<td>Cream pie</td>
<td>1 piece (1/8 pie)</td>
<td>137</td>
</tr>
<tr>
<td>Cottage cheese, creamed</td>
<td>1 cup (8 oz)</td>
<td>136</td>
</tr>
<tr>
<td>Sherbet</td>
<td>1 cup</td>
<td>96</td>
</tr>
<tr>
<td>Oysters, raw</td>
<td>5-8 medium</td>
<td>94</td>
</tr>
<tr>
<td>Broccoli, cooked</td>
<td>1 large stalk</td>
<td>88</td>
</tr>
<tr>
<td>Tofu</td>
<td>2 ounces</td>
<td>73</td>
</tr>
<tr>
<td>Cornbread</td>
<td>1 piece (2 oz.)</td>
<td>65</td>
</tr>
<tr>
<td>Dock (sorrel), cooked</td>
<td>1/2 cup</td>
<td>55</td>
</tr>
<tr>
<td>Flour tortillas</td>
<td>1 each</td>
<td>46</td>
</tr>
<tr>
<td>Corn tortillas</td>
<td>1 each</td>
<td>42</td>
</tr>
<tr>
<td>1/2 &amp; 1/2 cream</td>
<td>2 tablespoons</td>
<td>32</td>
</tr>
<tr>
<td>white bread</td>
<td>1 slice</td>
<td>30</td>
</tr>
</tbody>
</table>

Calcium may not be as well absorbed from these foods due to oxalate content:

<table>
<thead>
<tr>
<th>Food Items</th>
<th>Serving (oz)</th>
<th>Calcium Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocoa from mix with milk</td>
<td>1 cup</td>
<td>298</td>
</tr>
<tr>
<td>Chocolate milk</td>
<td>1 cup (8 oz)</td>
<td>284</td>
</tr>
<tr>
<td>Coolard greens, cooked</td>
<td>1/2 cup</td>
<td>152</td>
</tr>
<tr>
<td>Turnip greens, cooked</td>
<td>1/2 cup</td>
<td>138</td>
</tr>
<tr>
<td>Spinach, cooked</td>
<td>1/2 cup</td>
<td>107</td>
</tr>
<tr>
<td>Cocoa from mix water</td>
<td>1 cup (8 oz)</td>
<td>107</td>
</tr>
<tr>
<td>Beet greens, cooked</td>
<td>1/2 cup</td>
<td>99</td>
</tr>
<tr>
<td>Okra, cooked</td>
<td>8-9 pods</td>
<td>92</td>
</tr>
<tr>
<td>Kale, cooked</td>
<td>1/2 cup</td>
<td>89</td>
</tr>
<tr>
<td>Milk chocolate bar</td>
<td>1 bar (1.02 oz)</td>
<td>55</td>
</tr>
<tr>
<td>Green beans, cooked</td>
<td>1/2 cup</td>
<td>31</td>
</tr>
</tbody>
</table>
**Mechanism of extracellular calcium sensing I.**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Cell</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid gland</td>
<td>Chief cell</td>
<td>Inhibition of PTH secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of PTH gene expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of cell proliferation</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>C cell</td>
<td>Enhancement of calcitonin secretion</td>
</tr>
</tbody>
</table>
Mechanism of extracellular calcium sensing II.
Regulation of calcium metabolism
Investigational methods of calcium metabolism I.

1. **Laboratorical investigations**

   **Serum**
   - calcium: 2.23-2.63 mmol/l
     * 47%: bound to blood proteins (90% to albumin)
     * 13%: bound to anions (\( \text{HCO}_3^- \), \( \text{HPO}_4^- \), citrate, lactate)
     * 40%: ionic form
   - ionic calcium: 1.05-1.20 mmol/l
   - albumin: 35-50 g/l
   - phosphate: 0.90-1.40 mmol/l
   - PTH: 10-60 pg/ml
   - 1,25-(OH)_2 Vitamin D: 20-45 pg/ml
   - calcitonin

   **Urine**
   - calcium crystals in urine sediment?

   **Random sample**
   - calcium excretion (≈100-300 mg/day - for an adult (75 kg) with 1000 mg/day calcium intake)

   **Collection for 24hr**
   - Ca/creat clearence (0.01-0.3)

   \[
   \text{Ca/Cr clearance ratio} = \frac{\text{urinary calcium}}{\text{plasma calcium}} \times \frac{\text{plasma creatinine}}{\text{urinary creatinine}}
   \]
Investigational methods of calcium metabolism II.

2. Radiological investigations

- bone X-ray (skull, femur, vertebrae)

- DEXA (for estimating bone mineral density)

- ultrasound (parathyroid glands, renal ultrasound)

- isotope examinations (for estimating the function of parathyroid glands)

- CT (neck-upper mediastinum)
Bone X-ray

Hyperparathyreosis – Osteitis fibrosa cystica

X-ray of normal skull

L1 compression vertebral fracture
Investigational methods of calcium metabolism II.

2. Radiological investigations

- bone X-ray (skull, femur, vertebrae)

- DEXA (for estimating bone mineral density)

- ultrasound (parathyroid glands, renal ultrasound)

- isotope examinations (for estimating the function of parathyroid glands)

- CT (neck-upper mediastinum)
Bone Densitometry

![Bone Densitometry Scan](image1)

**Bone Densitometry Results**

**Name:** CT OSTEO  
**Sex:** F  
**Age:** 59  
**Mondality:** CT  
**Study ID:** CT015  
**Study Time:** 2008-06-19 13:14:35

<table>
<thead>
<tr>
<th>Position</th>
<th>BMD (mg/cm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T12</td>
<td>102.83</td>
</tr>
<tr>
<td>L1</td>
<td>103.38</td>
</tr>
<tr>
<td>L2</td>
<td>111.86</td>
</tr>
<tr>
<td>L3</td>
<td>114.57</td>
</tr>
<tr>
<td>L4</td>
<td>107.68</td>
</tr>
<tr>
<td>Average</td>
<td>108.07</td>
</tr>
</tbody>
</table>

**BMD Result (Non-Segmented Method)  
T-score**  
-2.85  
**Z-score**  
-0.71

**Reference Value**
- Normal: T-Score > -1
- Osteopenia: -2.5 < T-Score < -1
- Osteoporosis: T-Score < -2.5
- Severe Osteoporosis: -2.5, and meanwhile one or more body parts have fracture

**T-Score:** the multiple of the standard deviation compared with the young people

**Z-Score:** the multiple of the standard deviation compared with their peers
Investigational methods of calcium metabolism II.

2. **Radiological investigations**

- bone X-ray (skull, femur, vertebrae)

- DEXA (for estimating bone mineral density)

- ultrasound (parathyroid glands, renal ultrasound)

- isotope examinations (for estimating the function of parathyroid glands)

- CT (neck-upper mediastinum)
Mellékpajzsmirigy ultrahang vizsgálata
Investigational methods of calcium metabolism II.

2. **Radiological investigations**

- bone X-ray (skull, femur, vertebrae)

- DEXA (for estimating bone mineral density)

- ultrasound (parathyroid glands, renal ultrasound)

- isotope examinations (for estimating the function of parathyroid glands)

- CT (neck-upper mediastinum)
Parathyroid scintigraphy

$^{99m}$Tc-sestaMIBI scan

(MIBI = methoxyisobutylisonitrile)
Investigational methods of calcium metabolism II.

2. Radiological investigations

- bone X-ray (skull, femur, vertebrae)

- DEXA (for estimating bone mineral density)

- ultrasound (parathyroid glands, renal ultrasound)

- isotope examinations (for estimating the function of parathyroid glands)

- CT (neck-upper mediastinum)
High resolution CT scan of the neck and chest
DISORDERS ASSOCIATED WITH HYPERCALCEMIA
Definition of hypercalcemia:

Serum calcium $> 2.63$ mmol/l, Ionic calcium $> 1.25$ mmol/l

* mild: $< 2.80$ mmol/l
* moderate: 2.80-3.50 mmol/l
* severe: $> 3.50$ mmol/l

Prevalence of hypercalcemia:

15% of hospitalised patients

(French S. et al; South Med J. 2012 Apr;105(4):231-237)

Symptoms of hypercalcemia:

It depends on:
- the rate of the development
- the severity of the hypercalcemia
- and the elapsed time from the begining

* neuromuscular : weakness, depression, lethargy, coma
* GI : nausea-vomiting, obstipation, lack of appatite
* renal : polyuria-polydipsia (nephrogen DI), renal stones,nephrocalcinosis
* cardiovascular : short QT-interval, calcification of myocardium and valvulus
* skeletal : back pain, spontaneous fractures, bone cysts
1. **Drug-induced hypercalcemia**: tiazid diuretics, lytium, vitamin D, vitamin A, oestrogenes, androgenes

2. **Hypercalcemia associated to malignant diseases**:  
   * the prevalence of hypercalcemia among adult patients with malignant diseases could achieve 10-15%  
   * in these states hypercalcemia acts as paraneoplasia

Causes of PTH-indipendent hypercalcemia I.

- Tumor cell at a distance
- Tumor cell in bone metastasis
- IL-1, IL-6, TNF-beta (MM, squamous cell tumors)
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence (%) of Hypercalcemia of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (with bone metastases)</td>
<td>30–40</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>20–40</td>
</tr>
<tr>
<td>Squamous cell carcinoma of lung</td>
<td>12.5–35</td>
</tr>
<tr>
<td>Squamous cell carcinoma of head and neck</td>
<td>2.9–25</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>3–17</td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>0.6–5.4</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma, high-grade</td>
<td>14–33</td>
</tr>
<tr>
<td>T-cell lymphoma (human T-cell, lymphotrophic virus type 1)</td>
<td>50</td>
</tr>
<tr>
<td>Other malignancies: ovary, liver, pancreas, esophagus, cervix</td>
<td>7</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>7</td>
</tr>
</tbody>
</table>

3. **Hypercalcemia associated to granulomatosus diseases**

Non infectious diseases:
- sarcoidosis
- silicate-induced granulomatosis
- Wegener granulomatosis
- eosinophyl granuloma

Infectious diseases:
- tuberculosis
- candidiasis
- lepra
- histoplasmosis
- coccidiomycosis

4. **Renal insufficiency**
Treatment of PTH-indipendent hypercalcemia

N.B!!!!: The severity of the hypercalcemia and the clinical picture are more dramatic compared to primary hyperparathyroidism (even in malignant diseases)

**Treatment options:**

1. **Fluid supplementation** (3-4l of salt infusion for 24-48 hours)

2. **Inhibition of bone resorption**
   - *Bisphosphonates*
     * zolendronic acid (4mg in 100 ml SA infusion for 30 minutes) - Se creatinine!!
     * pamidronic acid (90mg in 500 ml SA infusion for 4 hours)
       - adverse effects: fever for a few days, flu-like symptoms, myalgia, hypocalcemia, hypophosphatemia
       - the effect develops 4 days after the therapy
       - the duration of the effect is few days-few week
   - *Calcitonin*
     * calcitonin (100 IU in every 6-8 hour in subcutan or intramuscular injection)

3. **Loop diuretics to enhance calciuresis** (after rehidration only!!!!)

4. **Glucocorticoids** (inhibition of 1-alpha-hydroxilase in macrophags in granulomatous diseases)
   - *Hydrocortison* (200-300 mg/day iv. For 3-5 days)

5. **Dialysis**
Prevalence of PHPT:

- North-America: 1/1000
- North-Europe: 3-4/1000
- in the population older than 75 years: 20/1000
- women:men=2-3:1

Pathology of parathyroid glands causing PHPT:

- single adenoma (80-85%)
- double adenoma (1-2%)
- hyperplasia (10-15%)
- carcinoma (<1%)
- cyst (1-3%)
Histology of parathyroid adenoma

Normal parathyroid gland

Parathyroid adenoma
Symptoms of PHPT

Skeleton:
- bone pain
- fractures
- decrease of BMD: osteopenia/osteoporosis
- osteitis fibrosa cystica

Joints:
- arthralgy

Muscles:
- weakness of proximal muscles
- muscle atrophy

Renal:
- renal stones
- nephrocalcinosis
- nephrogenic diabetes insipidus
- renal insufficiency

Gastrointestinal:
- peptic ulcer
- acute pancreatitis

Psychiatric:
- depression

Rare: **Hypercalcemic crisis!!**

Causes:
- parathyroid npl. hemorrhage/necrosis
- infectio
- exsiccosis
Osteitis fibrosa cystica
## Changes in clinical picture of PHPT

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal stones</td>
<td>57 (%)</td>
<td>51 (%)</td>
<td>37 (%)</td>
<td>17 (%)</td>
</tr>
<tr>
<td>Skeletal symptoms</td>
<td>23 (%)</td>
<td>10 (%)</td>
<td>14 (%)</td>
<td>1.4 (%)</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>NA</td>
<td>36 (%)</td>
<td>40 (%)</td>
<td>39 (%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.6 (%)</td>
<td>18 (%)</td>
<td>22 (%)</td>
<td>80 (%)</td>
</tr>
</tbody>
</table>

John P. Bilezikian and Shonni J. Silverberg
Reviews in Endocrine & Metabolic Disorders 2000; 237-245
Diagnosis of PHPT - Laboratorical investigations

Elevated or normal PTH concentration **AND** hypercalcaemia

Other changes in calcium metabolism:

- Urine calcium excretion: increased
- Serum phosphate: normal / decreased
- 1,25-(OH)2 Vitamin D: increased
- Alkalikus foszfatáz: increased / normal

Diagnosis of PHPT – Radiological investigations

- CT, MRI: sensitivity: 50-70%
- Ultrasound: sensitivity: 40-80%
- 99mTc-sestamibi substraction isotope: sensitivity for single adenoma: 90%
  for the diagnosis of ectopic parathyroid tissue
$^{99m}$Tc-sestaMIBI scan

Parathyroid Tumor

(MIBI = methoxyisobutylisonitrile)
1. Asymptomatic PHPT (80% of all cases !!!)

Table 2. Guidelines for Monitoring Patients with Asymptomatic PHPT Who Do Not Undergo Parathyroid Surgery: A Comparison of Current Recommendations With Previous Ones

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>Biannually DXA, annually (forearm)</td>
<td>Biannually DXA, annually (3 sites)</td>
<td>Annually DXA, every 1–2 y (3 sites)</td>
<td>Annually Every 1–2 y (3 sites), a x-ray or VFA of spine if clinically indicated (e.g., height loss, back pain)</td>
</tr>
<tr>
<td>Skeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>eGFR, annually; serum creatinine, annually</td>
<td>eGFR, not recommended; serum creatinine, annually</td>
<td>eGFR, not recommended; serum creatinine, annually</td>
<td>eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT</td>
</tr>
</tbody>
</table>
2. Symptomatic PHPT

Surgical removal of the pathologic parathyroid tissue

Rubin et al. Natural History of Primary Hyperparathyroidism
J Clin Endocrinol Metab, 2008, 93:3462–3470
Familial syndromes with PHPT

More than one parathyroid gland are affected in 15% of all cases and half of them is a part of a familial syndrome (5-8% of all cases)

<table>
<thead>
<tr>
<th>Familial Syndrome</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplex endocrine neoplasia type 1 (MEN1)</td>
<td>30-40/million</td>
</tr>
<tr>
<td></td>
<td>2% of all cases</td>
</tr>
<tr>
<td>Multiplex endocrine neoplasia type 2A (MEN2A)</td>
<td>40/million</td>
</tr>
<tr>
<td>Hyperparathyreosis-jaw tumor syndrome (HPT-JT)</td>
<td></td>
</tr>
<tr>
<td>Familial isolated primary hyperparathyroidism (FIHP)</td>
<td></td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia (FHH)</td>
<td></td>
</tr>
</tbody>
</table>

- FHH: Familial hypocalciuric hypercalcemia
- FIHP: Familial isolated primary hyperparathyroidism
- HPT-JT: Hyperparathyreosis-jaw tumor syndrome
- MEN1: Multiplex endocrine neoplasia type 1
- MEN2A: Multiplex endocrine neoplasia type 2A
- PHPT: Primary hyperparathyroidism
MEN-1

Major symptoms:

- primary hyperparathyroidism 95%
- pancreas islet cell tumor 40%
- hypophysis tumor 30%

Minor symptoms:

- carcinoid tumor, adrenal neoplasia,
- lipoma, kollagenoma, angiofibroma

Genetic background:

Gene: MEN-1 (10 exon) - 11q13 chromosome
Protein: menin protein - 610 aminoacid
- transcription
- genom stability
- cell proliferation

No of known mutations: >500, De novo mutations: >10%
Genotype-fenotype relationship: none

Machens et al, Clin Endocrinol, 2007, 613-622
MEN-2A

Symptoms: Penetrancia

- medullar thyroid carcinoma 90%
- phaeochromocytoma 50%
- PHPT 30%

PHPT occur in 15-20% of all patients
Clinical picture of PHPT is similar to the sporadic PHPT cases – milder than that in MEN-1 syndrome

Genetic background:
Gene: RET protooncogene - 10q11 chromosome - 22 exons
Protein: - receptor tirozin-kinase
- differentiation and migration of cells originated from ganglia
- activating mutations causes continuous activation of the receptor without ligand binding

90-95% of the mutations are on the exons 10-11. Hot spot: codon 634.
Genotype-fenotype relationship!!!!
HPT - JT syndrome

Major symptoms:

Hyperparathyroidism 90%
(usually all 4 parathyroid glands are affected)
cystic parathyroid tumor 20%
parathyroid carcinoma 15%
Multifocal fibro-osseal jaw tumor 30%

Minor symptoms:

Bilateral renal cysts 10%
Wilms' tumor, hamartomas <6%

Genetic background:

Gene: HRPT2 - 1q25 chromosome - 17 exons
Protein: parafibromin - 531 amino acids
- tumor suppressor protein,
- regulation of the transcription, histone modification and cell proliferation
### Summary of familial PHPT syndromes

![Diagram showing MEN1, MEN2a, FIHPT, and HPT-JT]

#### Table 4: Summary of special features of HPT in tumour susceptibility disorders and the consequent surgical management strategies

<table>
<thead>
<tr>
<th>Feature</th>
<th>Disorder</th>
<th>Recommended management</th>
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</thead>
<tbody>
<tr>
<td>High penetrance and early onset</td>
<td>MEN1, HPT-JT</td>
<td>HPT assist in diagnosis of syndrome, consider early surgery</td>
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<tr>
<td>Multiple parathyroid tumours, recurrence common</td>
<td>MEN1, MEN2A, HPT-JT, FIHPT</td>
<td>Subtotal/total parathyroidectomy, cryopreservation, intraoperative PTH assay, reoperations, lifelong follow up</td>
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<tr>
<td>Increased risk of parathyroid cancer</td>
<td>HPT-JT</td>
<td>Consider early and aggressive surgery</td>
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<tr>
<td>Associated tumours of the neck</td>
<td>MEN1, MEN2A</td>
<td>Thymectomy in MEN1 to prevent thymic carcinoma.</td>
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<tr>
<td></td>
<td>HPT-JT</td>
<td>Thyroidectomy and lymphadenectomy in MEN2A to prevent/treat MTC</td>
</tr>
<tr>
<td>Other associated tumours</td>
<td>MEN1, MEN2A, HPT-JT</td>
<td>Radiographic and biochemical protocols for tumour surveillance, lifelong follow up</td>
</tr>
</tbody>
</table>
FHH

**Symptoms:**
Symptomless hypercalcemia, normal or slightly elevated PTH concentration **AND** relative hypocalciuria (Ca/kreat clearence<0.01)

**Prevalence:**
- Australia 1:31250 32/million
- Scotland 1:15625 64/million

**Genetic background:**
- **Gene:** CaSR gene - 3q13.3-q21- coding region: exon2-7
- **Protein:** CaSR - 1078 aminoacid
  - senses the extracellular calcium concentration

**Effects of gene mutations:**

**Usually no need for surgical therapy!!**
Differential diagnosis of the disorders with hypercalcemia
(Serum calcium > 2.55 mmol/l, Ionic calcium > 1.35 mmol/l)

1. Detailed clinical and familial anamnézis
2. Physical examination
3. Exclusion of drugs causing hypercalcemia (Vitamin D, thiazid diuretics, lithium)

**Decreased PTH concentration**
- PTH-independent hypercalcemia

**Normal PTH concentration**
- CaCr-clearance < 0.01
  - No symptoms
  - Severe neonatal symptoms

**Increased PTH concentration**
- CaCr-clearance > 0.01
  - PHPT → Familial PHPT (5 %)
  - Search for other endocrine tumor in patient and in relatives

- Sporadic PHPT (95 %)
  - Symptomless
  - Symptoms
    - Regular controls
    - Parathyroid surgery

- FHH
- NSHPT

Genetic analysis for CaSR gene mutations, if:
1. isolated, symptomless hypercalcemic patients
2. CCCR is between 0.01-0.02

- Genetic analysis: RET gene mutations → MEN2A
- Genetic analysis: MEN1 gene mutations → MEN1
- Genetic analysis: HRPT2 gene mutations → HPT-JT

- MTC
- Phaeo
- Hypophysis tumor
- GEP tumor
- Jaw tumor
- Vese cyst, Wilms tumor
- No other tumor
- FIH
DISORDERS ASSOCIATED WITH HYPOCALCEMIA
Definition of hypocalcemia:

Serum calcium < 2.23 mmol/l, Ionic calcium > 1.05 mmol/l

Prevalence of hypocalcemia:

15-88 (?) % of hospitalised patients (depends on the methods…)
(French S. et al; South Med J. 2012 Apr;105(4):231-237)

Symptoms of hypocalcemia:

It depends on:
- the rate of the development
- the severity of the hypocalcemia
- and the elapsed time from the beginning

* neuromuscular: enhanced excitation in neurons
  paresthesia, tetania, laryngospasmus, bronchospasmus
* neurol-psych: intracran. calcification (basal ggl, cortex), change in personality, parkinsonism, psychosis
* skin: dry skin, atopic ekzema, caries
* GI: dysphagia, abdominal pain, colica in bile ducts
* pulm: dyspnoe, wheezing
* cardiovascular: longer QT-interval, congestive heart failure, cardiomyopathy
Causes of hypocalcemia

**Insufficient Vitamin D synthesis or effect**
Diet mistake, malabsorption, hepatic failure-cirrhosis, chronic renal insufficiency

**Insufficient PTH synthesis - Hypoparathyroidism**
Iatrogen: neck irradiation, neck surgery (thyroid!!!)

Infiltrative / destructive diseases: haemochromatosis, sarcoidosis, Wilson-disease, amyloidosis

Genetic disease: DiGeorge-szindróma

**Magnesium insufficiency**

**PTH resistance**

**APS-1 syndrome:**
- Hypoparathyroidism
- Addison-disease
- mucocutan candidiasis

- diabetes mellitus type 1
- autoimmune thyroid disease
- chronic active hepatitis
- alopecia
- vitiligo

**Acute pancreatitis**