Disorders of the parathyroid glands

5th Department of Internal Medicine
Comenius University Faculty of Medicine
University Hospital Bratislava
Winter semester 2015/16

Vitamin D

- 7-dehydrocholesterol
- 25-hydroxycholesterol
- 1α-hydroxylase
- Ca absorption
- 1,25(OH)2D
- Ca

PTH Effects on Bone

- PTH stimulates bone resorption
- ↑Ca into ECF
- ↑Ca

PTH Effects on Kidney

- ↓Ca in the urine by stimulating Ca++ reabsorption
- inhibits phosphate reabsorption
- • stimulate production of 1,25(OH)2D

Endocrine Regulation of [Ca++]ECF

1. PTH stimulates the release of Ca++ from bone, in part by stimulating bone resorption.
2. PTH decreases urinary loss of Ca++ by stimulating Ca++ reabsorption.
3. PTH indirectly stimulates Ca++ absorption in the small intestine by stimulating synthesis of 1,25(OH)2D in the kidney.

Parathyroid hormone

- Parathyroid hormone (PTH) plays a key role in the regulation of calcium and phosphate homeostasis and vitamin D metabolism.
- The four parathyroid glands lie behind the lobes of the thyroid. The parathyroid chief cells respond directly to changes in calcium concentrations When serum ionised calcium levels fall, PTH secretion rises.
Hypercalcemia: causes

**With normal or elevated (i.e. inappropriate) PTH levels**
- Primary or tertiary hyperparathyroidism
- Lithium-induced hyperparathyroidism
- Familial hypocalciuric hypercalcaemia, MEN

**With low (i.e. suppressed) PTH levels**
- Malignancy (e.g. lung, breast, renal, ovarian, colonic and thyroid carcinoma, lymphoma, multiple myeloma)
- Elevated 1,25(OH)₂ vitamin D (vitamin D intoxication, sarcoidosis, HIV, other granulomatous disease)
- Thyrotoxicosis, pheochromocytoma
- Paget’s disease with immobilisation
- Milk-alkali syndrome
- Thiazide, Lithium, theophylline
- Glucocorticoid deficiency

Signs/Symptoms
- The classic symptoms are described as ‘bones, stones, psychic moans and abdominal groans’.
- Polyuria and polydipsia, renal colic, lethargy, anorexia, nausea, dyspepsia and peptic ulceration, constipation, depression, drowsiness and impaired cognition.
- Patients with malignant hypercalcaemia can have a rapid onset of symptoms.
- A family history of hypercalcaemia raises the possibility of FHH or MEN.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Ca</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hypercalcemia of malignancy</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism in renal disease</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Hypercalcemia of malignancy
- one of the most common causes of non-PTH-mediated hypercalcemia.
- DX: confirmed by demonstrating an ↑serum concentration of PTH-related protein (PTHrp).
- Levels of PTH and 1,25-dihydroxyvitamin D (calcitriol) are usually appropriately suppressed in these patients.

Management
- **Mild/mod hypercalcemia**: asymptomatic or mildly symptomatic hypercalcemia
- do not require immediate Rx. However maintain adequate hydration and avoid factors that aggravate.
- **Severe hypercalcemia**: Patients require more aggressive treatment.

Severe Hypercalcemia
- Volume expansion – up to 6 l / 24 hours
- Furosemide 40-80 mg every 2-4 hours
- Calcitonin
- Glucocorticoids (HCT 200-300 mg /24 hours)
- Bisphosphonates - zoledronic acid (4 mg i.v.) or pamidronate (30-90 mg i.v. / 8-24 hours)
- Calcimimetics - cinacalcet
- Hemodialysis
- Treatment of underlying condition (parathyreoidectomy in PHPT)
Hyperparathyroidism

<table>
<thead>
<tr>
<th>Type</th>
<th>Serum Ca</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Single adenoma (90%)</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Multiple adenomas (4%)</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Nodular hyperplasia (5%)</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Carcinoma (1%)</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Secondary</td>
<td>Low</td>
<td>raised</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Low</td>
<td>raised</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Low</td>
<td>raised</td>
</tr>
<tr>
<td>Osteomalacia and rickets</td>
<td>Low</td>
<td>raised</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Raised</td>
<td>Not suppressed</td>
</tr>
</tbody>
</table>

Multiple endocrine neoplasia

<table>
<thead>
<tr>
<th>Features</th>
<th>MEN1</th>
<th>MEN2A</th>
<th>MEN2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alias:</td>
<td>Werm S</td>
<td>Sipple S</td>
<td></td>
</tr>
<tr>
<td>Pancreatic tumors</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Parathyroid hyperplasia</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Angiofibroma/Lipoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Medullary thyroid ca</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mucosal neuma</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Marfanoid habitus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Primary hyperparathyroidism (PHPT)

- overproduction of parathyroid hormone results in elevated levels of plasma calcium
  - Sporadic – 90%
  - Familial – 10% (associated with MEN I, MEN 2A)

Ethiology:
- Single adenoma 80-85%
- Hyperplasia 10-15%
- Carcinoma - rare

PHPT clinical features

- Asymptomatic 80%
- Symptomatic
  - bone changes
    - Renal impairment – stones, nefrokalcinosis
    - Gastrointestinal symptoms – anorexia, nausea, vomitus, ulcerative disease
    - Psychic changes
    - Neuromuscular changes – fatigue, muscle pain and weakness
    - Articular changes
    - Eye changes – calcifications in cornea

Other imaging

- In the early stages there is demineralisation, with subperiosteal erosions and terminal resorption in the phalanges.
- A 'pepper-pot' appearance: lateral X-rays of the skull.
- Reduced bone mineral density, resulting in either osteopenia or osteoporosis. And is assessed by DEXA
- In nephrocalcinosis, scattered opacities within the renal outline.
- There may be soft tissue calcification in arterial walls, soft tissues of the hands and the cornea.

Images

Source: [http://uwmsk.org/residentprojects/hpth.html](http://uwmsk.org/residentprojects/hpth.html)
**PHPT work up**

- **Laboratory:**
  - Elevated S-Ca, i-Ca, U-Ca/24 hours
  - Elevated iPTH
  - 25-OH-D3 to exclude secondary HPT in hyperPTH states

- **Imaging studies:**
  - Ultrasound of the neck – sensitivity for adenoma 69-96%
  - Scintigraphy

**PHPT Treatment**

- **Surgery**
  - Adenoma – extirpation
  - Hyperplasia – resection of 3 and ½ of parathyroid glands / total parathyroidectomy with autotransplantation
  - Indications for surgery
    - Symptomatic
    - Asymptomatic + age (<50y), S-Ca > 0.25 mmol over upper level of normal, GF<60 ml/min, decrease in BMD (T-score/Z-score < -2.5 SDs)
  - Non-surgical
    - Calcimimetics (cinacalcet- MIMPARA) - decrease calcium and PTH levels, but no increase in BMD

**Hypocalcemia**

- Hypocalcaemia is much less common than hypercalcaemia.
- The most common cause of hypocalcaemia is a low serum albumin with normal ionised calcium concentration.

**Hypocalcemia: Clinical manifestation**

- Hypocalcemic tetany: This is characterised by muscle spasms due to increased excitability of peripheral nerves.
- Triad of carpopedal spasm, stridor and convulsions.
- Trousseau’s sign; inflation of a bp cuff on the upper arm to > the SBP is f/b carpal spasm within 3 min.
- Chvostek’s sign: tapping over the branches of the facial nerve produces twitching of the facial muscles.
- “Hungry bones” syndrome – postoperative hypocalcemia is severe and prolonged, despite normal or even elevated levels of PTH

**Differential diagnosis of hypocalcaemia**

<table>
<thead>
<tr>
<th>Hypoalbuminaemia</th>
<th>Total serum calcium</th>
<th>Ionised serum calcium</th>
<th>Serum phosphate</th>
<th>Serum PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinism</td>
<td></td>
<td></td>
<td></td>
<td>or ↑</td>
</tr>
<tr>
<td>Respiratory, e.g. hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic, e.g. Cöeck’s syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td></td>
<td>Variable</td>
<td>or ↓</td>
<td></td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Davidson

**EXAMINATION TIP**

Recognizing carpopedal spasm

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints drooping together, adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the foot.

http://www.fpnotebook.com/legacy/Ortho/Wrist/CrpdlSpsm.htm
Management

- Milder symptoms of neuromuscular irritability (paresthesias) and corrected S. Ca >1.875 mmol/l : initial Rx with oral Ca supplementation.
- 1500-2000 mg of elemental Ca given as calcium carbonate or calcium citrate/d, in divided doses.
- If symptoms do not improve with oral supplementation, iv Ca infusion is required.

Management of severe hypocalcaemia

- 10-20mL 10% ca gluconate i.v. over 10-20 min
- Continuous i.v. infusion may be required for several hrs (equivalent of 10 mL 10% calcium gluconate/hr)
- Cardiac monitoring is recommended.
- If Mg deficiency :50 mmol Mgcl i.v. over 24 hrs

Hypoparathyroidism

- The MC cause is damage to the parathyroid glands (or their bld supply) during thyroid Sx.
- Rarely, hypoparathyroidism can occur as a result of infiltration of the glands, e.g. in haemochromatosis and Wilson's disease.

Pseudohypoparathyroidism

- The disorder is characterized by a lack of responsiveness to PTH, resulting in ↓Ca, ↑Po4, and appropriately ↑PTH.
- Individuals with Albright’s hereditary osteodystrophy have short stature, shortened 4th & 5th metacarpals, rounded facies, and often mild mental retardation.
- The kidney responds as if PTH were absent. The PTH receptor itself is normal, but there are defective post-receptor mechanisms due to mutations.

Management of hypoparathyroidism (peristent/longterm hypocalcaemia)

- Persistent hypoparathyroidism and pseudohypoparathyroidism are Rx with oral calcium salts and vitamin D analogues, either 1α-hydroxycholecalciferol (alfacalcidol) or 1,25-dihydroxycholecalciferol (calcitriol).
- Recombinant PTH is available as SC injection therapy for osteoporosis.
Osteoporosis

Definition of Osteoporosis

- **NIH Consensus Conference**
- Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.
- Osteoporosis is due to:
  - Low peak bone mass
  - Bone loss
  - Both low peak bone mass and bone loss
- Bone strength reflects the integration of two main features:
  - Bone density
  - Bone quality

Fragility Fracture

- A fragility fracture is one that results from mechanical forces that would not ordinarily cause fracture in a healthy young adult.
- This is quantified as forces equivalent to a fall from a standing height or less.
- 1 in 2 women and 1 in 5 men aged 50 will suffer a fragility fracture in their remaining lifetime

The Skeleton is Composed of Cortical and Trabecular Bone

- The skeleton is a dynamic organ comprised of over 200 discrete bones with mechanical, protective, and metabolic functions
- Composed of two types of bone:
  - **Cortical bone**: Outer dense shell (~80% of total skeletal mass)
  - **Trabecular bone**: Network of connecting plates inside the cortical shell (~20% of total skeletal mass)
A Healthy Skeleton Requires a Balance of Bone Resorption and Bone Formation

- Formation: 3 months
- Resorption: 10 days
- When bone turnover is increased, bone loss dominates
- Resting

Bone Mass Rapidly Decreases with the Onset of Menopause

- Menopause occurs for approximately one year during this timeframe

Patterns of Bone Loss is in both sexes

- OSTEOPOROSIS
- OSTEOPOROSIS

Main osteoporotic fractures

- Hip
- Wrist
- Vertebrae

Forms of osteoporosis

- Primary osteoporosis
  - postmenopausal (type 1)
  - senile (type 2)
- Secondary osteoporosis
- Idiopathic osteoporosis
  - in premenopausal women and men
- Idiopathic juvenile osteoporosis
Causes of secondary osteoporosis

Genetic (congenital)
- Cystic fibrosis
- Ehlers-Danlos syndrome
- Glycogen storage disease
- Gaucher disease
- Hemochromatosis
- Homocystinuria
- Hypophosphatasia
- Idiopathic hypercalciuria
- Marfan syndrome
- Menkes steely hair syndrome
- Osteogenesis imperfecta
- Porphyria
- Riley-Day syndrome

Endocrine
- Androgen insensitivity
- Anorexia nervosa/bulimia
- Female athlete triad
- Hyperprolactinemia
- Panhypopituitarism
- Premature menopause
- Turner syndrome
- Klinefelter syndrome

Deficiency states
- Calcium deficiency
- Magnesium deficiency
- Protein deficiency
- Vitamin D deficiency

Drug-induced osteoporosis
- Anticonvulsants
- Antipsychotic drugs
- Antiretroviral drugs
- Cyclosporines and tacrolimus
- Cytotoxic drugs
- Furosemide
- Glucocorticoids
- GnRH analogs
- Heparin
- Lithium
- Selective serotonin reuptake inhibitors

Bone Densitometry
- Non-invasive test for measurement of BMD
- Major technologies
  - Dual-energy X-ray Absorptiometry (DXA)
  - Quantitative Ultrasound (QUS)
  - Quantitative Computerized Tomography (QCT)
- Many manufacturers
- Numerous devices
- Different skeletal sites

Main causes of secondary osteoporosis
- Endocrine disorders
- Cushing syndrome
- Hyperthyroidism
- Hyperprolactinemia
- Hypogonadism
- GH deficiency
- Diabetes mellitus
- Gastrointestinal disorders
- Drug-induced osteoporosis

Physical examination

Osteoporosis
- Osteoporosis
- Height loss
- Body weight
- Kyphosis
- Humped back
- Tooth loss
- Skinfold thickness
- Grip strength

Vertebral fracture
- Vertebral fracture
- Arm span-height difference
- Wall-occiput distance
- Rib-pelvis distance

Diagnosis of osteoporosis

OSTEOPOROSIS

DIAGNOSIS OF OSTEOPOROSIS

Physical examination

Bone Densitometry
DXA

- “Gold-standard” for BMD measurement
- Measures “central” or “axial” skeletal sites: spine and hip
- May measure other sites: total body and forearm
- Extensive epidemiologic data
- Correlation with bone strength in-vitro
- Validated in many clinical trials
- Widely available

Using T-scores vs. Z-scores

T-scores
- WHO diagnostic classification in postmenopausal women and men age 50 and older
- WHO classification with T-score cannot be applied to healthy premenopausal women, men under age 50, and children

Z-scores
- For use in reporting BMD in healthy premenopausal women, men under age 50, and children
- Z-score ≤ -2.0 or less is defined as “below the expected range for age”
- Z-score above -2.0 is “within the expected range for age”

Which Skeletal Sites Should Be Measured?

Every Patient
- Spine – L1-L4
- Hip – Total Hip – Femoral Neck

Some Patients
- Forearm (33% radius, 1/3 radius)
- If hip or spine cannot be measured
- Hyperparathyroidism
- Very obese

Osteoporotic fracture and BMD

Further Independent Risk Factors for Fracture

- Risk factors:
  - Age
  - Low BMD
  - Previous fractures
  - Low BMI
  - Prior history of fracture
  - Family history of hip fracture
  - Current smoking
  - High intake of alcohol
  - Rheumatoid arthritis
  - Glucocorticoid therapy

Diagnosis of Osteoporosis Using Central DXA: WHO Definition

- DXA: Dual Energy X-ray Absorptiometry
- Normal bone density
- Osteopenia
- Osteoporosis
1. To diagnose osteoporosis
2. To predict fracture risk
3. To monitor therapy
The FRAX® tool has been developed by WHO to evaluate fracture risk of patients. The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In its most sophisticated form, the FRAX® tool is computer-driven and is available on website.

- Provides individualized **absolute risk** over a 10-year period (similar to Gail model for risk of breast cancer or Framingham model for risk of cardiovascular disease)
- Hip fracture
- Major osteoporotic fracture
- Guidelines regarding **when** to intervene are emerging

**FRAX™ Fracture Risk Assessment**

**Biochemical Markers of Bone Turnover**

- **Resorption markers**
  - Pyridinoline (Pyr)
  - Deoxypyridinoline (dPyr)
  - Amino terminal telopeptide of type I collagen (NTX)
  - Carboxy terminal telopeptide of type I collagen (CTX)

- **Formation markers**
  - Osteocalcin (OC)
  - Bone-specific alkaline phosphatase (BAP)
  - Amino terminal propeptide of type I collagen (PINP)
  - Carboxy terminal propeptide of type I collagen (PICP)

**Monitoring of treatment**

- **Measurement of bone mass by DXA**
  - 12 months after beginning of treatment and then at 24-month intervals as needed

- **Biochemical markers of bone turnover**
  - At 3 and 6 months after therapy initiation

- **Clinical examination**
  - After initiating of therapy in 1 month to reevaluate and to assess tolerance and thereafter at 3 months, 6 months and 1 year

- **25-hydroxyvitamin D**
  - Should be measured after 3-4 months of adequate supplementation and should not be repeated if an optimal level (at least 75 nmol/l) is achieved.

**The Burden of Osteoporosis**
Osteoporosis is a Prevalent Disease

Affects 200 million women worldwide:

- 1/3 of women aged 60 to 70
- 2/3 of women aged 80 or older

Approximately 20-25% of women over the age of 50 have one or more vertebral fractures:

- United States: 25%
- Australia: 20%
- Western Europe: 19%
- Scandinavia: 26%
- Denmark: 21%
- Slovakia: 15%

Prior Fractures Predict Future Fractures

Women with a prior fracture have an 86% increased risk of any subsequent fracture.

1 in 5 postmenopausal women with prior vertebral fracture will have another vertebral fracture within 1 year.

45% of women with hip fracture report prior fragility fracture.

Women with prior fracture have approximately 2-fold higher risk of suffering a hip fracture.

Consequences of hip fracture

One year after hip fracture

- 80% Unable to carry out at least one independent activity of daily living
- 60% Unable to walk independently
- 40% Permanent disability
- 30% Death within one year
- 20% Unable to carry out at least one independent activity of daily living

Consequences of osteoporosis

- Acute & chronic pain
- Breathing difficulties
- Problems with digestion
- Depression
- Possible long-term nursing care
- Surgical complications
- Increased mortality

Principles of the Care for a Patient with Osteoporosis

- General principles
  - elimination of known risk factors of osteoporosis
  - reduction of risk of fall [various barriers, bad sight, drugs ...]
  - modification of eating habits and physical activity

- Supporting therapy
  - physical therapy, physiotherapy, analgetics, myorelaxants

- Specific therapy

OSTEOPOROSIS

TREATMENT

OF

OSTEOPOROSIS
Summary of Evidence for Fracture Risk Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral</th>
<th>Nonvertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonine</td>
<td>Yes</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Yes</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Yes</td>
<td>No effect demonstrated</td>
<td>No effect demonstrated</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Teriparitide</td>
<td>Yes</td>
<td>Yes</td>
<td>No effect demonstrated</td>
</tr>
</tbody>
</table>


Osteoporosis Therapies and Patient Adherence

Less than 50% of patients persist with their osteoporosis therapy for more than 1 year

Patients initiating therapy
- Side effects
- Safety concerns
- Health problems
- Lack of results
- Cost
- Inconvenient dosing
- Withdrawn by others

Patients continuing therapy
- Lack of motivation

OSTEOPOROSIS
VITAMIN D

Vitamin D and Calcium Insufficiency-Related loss of Bone Quality

- Age-related vitamin D and calcium insufficiency
- Negative calcium balance
- Insufficient supply of calcium
- Impaired mineralization
- Loss of bone quality in women and men

Effects of vitamin D

- Cardiovascular events
- Arterial hypertension
- Metabolic syndrome
  - Diabetes mellitus
  - Obesity
  - Dyslipidemy
- Autoimmunity
  - Intestinal bowel disease
  - Inflammatory diseases
  - Sclerosis multiplex
  - Psoriasis

VDR localisation

<table>
<thead>
<tr>
<th>System</th>
<th>Tissue – cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td>esophagus, stomach, intestinal cells, hepatocytes</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>myocytes, vascular smooth muscle, endotel</td>
</tr>
<tr>
<td>Kidneys</td>
<td>proximal and distal tubules</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>thyroid, parathyroid, pancreas</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>testes, ovarium, placenta, uterus, endometrium</td>
</tr>
<tr>
<td>Immunity</td>
<td>thymus, bone marrow, B, T lymphocytes</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>alveoli</td>
</tr>
<tr>
<td>Skeleton</td>
<td>osteoblasts, osteocytes, chondrocytes</td>
</tr>
<tr>
<td>Muscles</td>
<td>muscle fiber, fibroblasts, collagen</td>
</tr>
<tr>
<td>Skin</td>
<td>epidermis, hair follicles</td>
</tr>
<tr>
<td>CNS</td>
<td>neurones, glia, globus astrocytes</td>
</tr>
</tbody>
</table>

Classification of vitamin D saturation

- **KALCIDIOL (25-OH vitD)**
  - Deficiency: 9 ng/ml (22.5 nmol/l)
  - Light deficiency: 20 ng/ml (50 nmol/l)
  - Insufficiency: 30 ng/ml (75 nmol/l)
  - Optimum: 30 – 80 ng/ml
  - Toxicity: 150 ng/ml (375 nmol/l)

Recommended daily intake in women older than 50 years

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Vitamin D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOF</td>
<td>1200 mg/day 800 – 1000 IU/day</td>
</tr>
<tr>
<td>ICF</td>
<td>1300 mg/day 800 – 1000 IU/day</td>
</tr>
<tr>
<td>WHO/FAO</td>
<td>1300 mg/day 600 – 800 IU/day</td>
</tr>
</tbody>
</table>

Endocrinology of gonads

- Male hypogonadism
- Female hypogonadism
- Hyperandrogenism in females

Male sex hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Testicular secretion</th>
<th>Adrenal secretion</th>
<th>Periarterial secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>&lt;1</td>
<td>&gt;5</td>
<td>75</td>
</tr>
<tr>
<td>Androstendion</td>
<td>10</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Estradiol</td>
<td>1</td>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>DHEA</td>
<td>&gt;10</td>
<td>&lt;10</td>
<td>80</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Androgen</th>
<th>Androgenic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>262</td>
</tr>
<tr>
<td>Androstenedion</td>
<td>107</td>
</tr>
<tr>
<td>Estradiol</td>
<td>12</td>
</tr>
<tr>
<td>DHEA, DHEAS</td>
<td>3</td>
</tr>
</tbody>
</table>

Testosterone

- Produced in Leydig cells (95%) and adrenals (5%)
- In blood:
  - 60% bound to sex hormone binding globulin (SHBG)
  - 38% bound to albumin
  - 2% free (active)
- It is converted to dihydrotestosterone in tissues
- Production is regulated by pituitary (luteinazing hormone)
Effects of testosterone

- Sexual differentiation
- Spermatogenesis
- Libido
- Effect on CNS, cognitive function
- Effect on blood coagulation
- Effect on cardiovascular system

Male hypogonadism

- Clinical syndrome associated with inadequate production of testosterone (androgen deficiency) and lowered amount of spermatozoa production

Classification of hypogonadism

1) Primary
- Klinefelter syndrome
- Inè chrom. defekty (XY/XX, XXY, XXXXY,...)
- Anorchism
- Kryptorchism
- Leydig cells aplasia
- Noonan syndrome
- „Adult seminiferous tubule failure”
- „Adult Leydig cell failure”
- Defect testosterone synthesis
- other (trauma, RAT, drugs,...)

2) Secondary
- Panhypopituitarism
- Defect of LH + FSH production
  - Kallmann sy
  - Prader-Williho sy
  - Laurence-Moon sy
  - Bardet-Biedl sy
  - Gordon-Holmes sy
- Inactive LH production
- Hyperprolaktinemia
- Hypothalamic disorders
  (stress, alcohol, malnutrition)
- Cushing sy

3) Defect of androgen receptors

Diagnosis of hypogonadism

- Clinical symptoms typical for hypogonadism
  +
- Inadequately low total testosterone levels
- (never treat just lab test!)

Clinical symptoms of hypogonadism

<table>
<thead>
<tr>
<th>Typical</th>
<th>Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbance of sexual differentiation, azoospermia</td>
<td>Low energy, motivation</td>
</tr>
<tr>
<td>Reduced libido</td>
<td>Depression</td>
</tr>
<tr>
<td>Reduced exciton</td>
<td>Impaired concentration and memory</td>
</tr>
<tr>
<td>Orygmatomia</td>
<td>Sleep disturbance</td>
</tr>
<tr>
<td>Reduced sexual hair (pubic, face)</td>
<td>Mild anosmia</td>
</tr>
<tr>
<td>Small testes</td>
<td>Higher fat mass</td>
</tr>
<tr>
<td>Low BMD</td>
<td>Lower physical activity</td>
</tr>
<tr>
<td>Reduced muscle strength</td>
<td>„Hot flushes”</td>
</tr>
</tbody>
</table>
Klinefelter syndrome

Examination of patient with hypogonadism

- Physical examination
- Lab tests
- Spermogram
- Testicular biopsy
- Genetics

Physical examination

- Reduced men hair
- “hypogonadal facies”
- Gynecomastia
- Eunuchoid habitus (when onset before puberty)
- Genital examination (volume on Prader orchidometer min 15 ml)

Lab tests

- Total testosterone
- Free testosterone when indicated
- FSH
- LH
- PRL
- TSH

Other tests

- LHRH test (when hypothalamic disorder is suspected)
- Genetics (susp. Klinefelter syndrome)
- Pituitary MRI (in secondary hypogonadism)
- DXA

Treatment

- 2 problems:
  - Clinical symptoms of hypogonadism
    - Testosterone substitution
  - Fertility
    - Spermatogenesis induction
Testosterone treatment - contraindications
- Prostate cancer, breast cancer
- Hematocrit > 50%
- Sleep apnoe syndrome
- Heart failure
- Prostate nodules, or PSA 4 ng/ml or PSA 3 ng/ml with high risk of prostate cancer after urologist agreement

Testosterone medication
- T enanthen alebo cypionate 75-100 mg i.m. weekly or 150-200 mg every 2 weeks
- T patches á 5 mg 1-2 daily
- T gel 1% 5-10 g
- 30 mg bucal T every 12 hours
- Subcutaneous T every 3-6 months
- Oral T undekanoate, i.m. T undekanoate

Take home message - male hypogonadism
- Primary (genetic or urologic disorders)
- Secondary (hypothalamic, pituitary disorders)
- Diagnosis: total T, free T, FSH, LH, PRL, TSH, spermiogram, urologic, genetic tests, pituitary MRI
- Treatment:
  - causal treatment (e.g. surgery)
  - Testosterone subst. or fertility induction

Case report 1
- 55 years old patient was sent to endocrinology room with weakness, low libido and low total testosterone in lab. Urologic examination was negative. What will you do:
  - A) testosterone substitution
  - B) check FSH, LH, PRL a TSH
  - C) Send the patient to genetic tests
  - D) nothing - testosterone declines usually with age

Case report 1
- In patient we found very low level of FSH and LH. PRL and TSH is in normal range. What is the next step:
  - A) it is primary hypogonadism I will send the patient to genetic tests
  - B) it is primary hypogonadism I will send the patient to testes biopsy
  - C) it is secondary hypogonadism I will order pituitary MRI
  - D) it is secondary hypogonadism I will send the patient to genetic tests

Case report 1
- On MRI we found pituitary tumor 3x2 cm without optic nerve compression. Next step is?
  - A) evaluation of other pituitary hormones
  - B) send the patient for surgery
  - C) I will prescribe testosterone patches
  - D) I will send the patient for genetic tests
Case report 1

- In other pituitary tests we found panhypopituitarism
- After hormonal pre-treatment he absolved transsphenoidal surgery
- Histology: nonfunctioning adenoma
- 2 months after surgery the patient had normal hormonal levels without any medication

Female hypogonadism

Female sex hormones

- Estradiol
  - Most potent
  - Production: ovaries
- Estron
  - Postmenopausal
  - Production: ovaries + peripheral tissues
- Progesterone
  - Produced in corpus luteum

Menstrual cycle

Effects of estrogens

- Sexual differentiation
- Menstrual cycle
- Body changes during pregnancy
- Saving calcium for bones (osteoporosis prevention)
- HDL rise, TAG decline
- Activation of coagulation

Female hypogonadism

- Primary
  - Prepubertal (genetic syndromes)
  - Postpubertal (premature ovarian failure)
- Secondary
  - Pituitary or hypothalamic dysfunction
Premature ovarian failure (POF)

- Amenorrhea and estrogen deficiency associated with high levels of gonadotropins in women younger than 40 years

Causes of POF

- Chromosomal abnormalities (60%)
- Autoimunity (20%)
- Others (20%)

Other causes of POF

- Iatrogenic
  - ChT, RAT, drugs
- Metabolic disorders
  - (galactosemia)
- Infections
  - mumps, CMV, HIV, shigella
- Idiopathic
  - Environmental factors

Genetic causes of hypogonadism

- Turner syndrome /45X/+ mosaic
- Trisomy X /47XXX/
- Gene mutations
  - Swyer syndrome /XY gonad. dysgenesis/
  - Savage syndrome
  - Genetic mutations of LH, FSH and their receptors

Turner syndrome

- Monosomy of X
- Incidence 1:3000
- Short stature, gonad. dysgenesis, anomalies uropoet. system, heart, aortal defects
Clinical signs of ovarian failure

- Amenorrhea
- Symptoms of estrogen deficiency (hot flushes, osteoporosis etc)

Diagnosis of POF

- High FSH, LH
  - FSH is higher than 40 mIU/l
- Low estradiol
- Karyotype
- Pelvic ultrasound
- DXA
- Screening of autoimmune diseases (celiakia, DM 1, Hashimoto dis., Addison dis.)

Treatment of female hypogonadism

- HST (estrogens)
- Fertility
  - Usually problematic issue
  - Ovarian stimulation in IVF usually not successful
  - Donors of oocytes
  - Glucocorticoids in autoimmune ovarian failure

Take home message: female hypogonadism

- Classification
  - Primary (POF)
  - Secondary (pituitary, hypothalamus)
- Diagnosis
  - Estradiol, FSH, LH - 3-5 day of cycle, TSH, PRL / dif dg amenorhea also androgen/s, gynecol. exam, genetics
- Treatment
  - Treat the cause if possible
  - HST
  - Induction of fertility when desired

Female hyperandrogenic diseases

- Polycystic ovarian syndrome (PCOS) - 95%
- Tumors producing androgens (ovarian, adrenal)
- Congenital adrenal hyperplasia
PCOS

- Prevalence 5-10%
- Overproduction of androgens in ovaries and adrenals associated with insulin resistance
- Exact patomechanism is not known

Clinical signs of PCOS

- Anovulation, oligomenorrhea- amenorrhea
- Hirsutism
- Acne
- Alopecia

Scale of hirsutism according to Ferriman- Gallway score

Diagnostic criteria of PCOS

- Clinical and/or lab signs of hyperandrogenism
- Oligomenorrhea- amenorrhea
- Polycystic ovaries on ultrasound
- For diagnosis you need 2 of 3 criteria

Lab tests in PCOS

- Elevated testosterone (total and free)
- Elevated adrenal androgens (DHEAS, androstendion)
- Elevated LH (not specific)
- Elevated insulin level

Differential diagnosis

- Androgens producing tumors
  - Older women, quick onset of clinical signs
- Congenital adrenal hyperplasia
  - Typically elevated 17 OH progesterone
Treatment of PCOS

• Causal treatment? (pathogenesis not known)

• We solve 2 problems:
  – Treatment of hirsutism
    – HAK, cyproteron acetate
  – Ovulation induction
    – Clomiphene citrate

Take home message: female hyperandrogenism

• Causes: PCOS /95%, CAH, adrenal and ovarian tumors

• Clinical signs: oligo/amenorhea, hirsutism

• Diagnosis
  – Lab.: testosterone- total and free, FSH, LH, DHEAS, androstendion, 17-OH progesterone, kortisol
  – Imaging: CT, MRI, ovarian ultrasound

• Treatment: depends on the cause

Case report 2

• 22 year old women was sent to endocr. room with oligomenorhea

• Menarche in 13, till 20 regular cycle

• Objective examination: overweight, hirsutism in linea alba, breast and face

• Gynecol. ultrasound: normal

Case report 2

• Which lab test do we need to evaluate oligomenorhea:
  – A) FSH, LH, estradiol, testosterone, DHEAS, androstendion, 17-OH progesterone, kortisol, TSH, PRL
  – B) only androgens: testosterone, DHEAS, androstendion, 17-OH progesterone
  – C) FSH, LH, estradiol, testosterone, DHEAS, androstendion, 17-OH progesterone

Case report 2

• We found elevated levels of testosterone, DHEAS and androstendion, all other tests were normal. What are we going to do:
  – A) MRI of adrenals to exclude adrenal tumors
  – B) MRI of pituitary to exclude pituitary tumors
  – C) genetics for Turner syndrome

Case report 2

• We know the lab test and now we also know that the MRI of adrenals was negative. What is the diagnosis in this patient:
  – A) Congenital adrenal hyperplasia
  – B) Cushing syndrome
  – C) PCOS
  – D) Ovarian tumor