Vitamin D, Rickets and Osteoporosis

<table>
<tr><th colspan="4">Vitamin D</th></tr>
<tr><td colspan="2">Overview</td><td colspan="2">• Vitamin D is considered a steroid hormone</td></tr>
<tr><td colspan="2">Types</td><td>vitamin D3 (Cholecalciferol)</td><td>vitamin D2 (Ergocalciferol)</td></tr>
<tr><td colspan="2">Sources & distribution</td><td>• <u>Endogenous vitamin precursor:</u>
7-Dehydrocholesterol is converted to vitamin D3 in the dermis and epidermis when exposed to UV in sunlight
• The biologically active form is 1,25-dihydroxycholecalciferol (calcitriol)
• <u>Dietary source:</u>
found in animal tissue
• also available as supplement</td><td>• <u>Dietary source:</u>
Derived from ergosterol which is found in plants
• also available as supplement</td></tr>
<tr><td colspan="2">Daily requirement</td><td colspan="2">Adults: 600 Children: 400 Elderly: 800 (IU/day)</td></tr>
<tr><td rowspan="3">Metabolism and actions</td><td>In skin:</td><td colspan="2">• Cholecalciferol (Vitamin D3) is derived from 7-dehydrocholesterol by the sunlight</td></tr>
<tr><td>In liver:</td><td colspan="2">• Cholecalciferol is converted to 25-hydroxycholecalciferol (calcidiol) by the enzyme 25-hydroxylase</td></tr>
<tr><td>In kidneys:</td><td colspan="2">• The 1-a-hydroxylase enzyme converts 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (calcitriol, which is the <u>biologically active</u> form)
• Active vitamin D is then transported in blood by gc-globulin protein</td></tr>
<tr><td colspan="2">Regulation</td><td colspan="2">Vitamin D synthesis is tightly regulated by plasma levels of phosphate and calcium
• Activity of 1-a-hydroxylase in kidneys is increased by:
◦ Directly increased due to low plasma phosphate
◦ Indirectly increased via parathyroid hormone (PTH) due to low plasma calcium. PTH thus increases vitamin D synthesis in kidneys.
• Activity of 1-a-hydroxylase in kidneys decreases by:
◦ Feed-back inhibition by ↑ 1,25- diOH-D3</td></tr>
<tr><td colspan="2">calcium homeostasis</td><td colspan="2">• Vitamin D has essential role in calcium homeostasis
Calcium homeostasis is maintained by parathyroid hormone (PTH) and calcitonin
• If calcium plasma levels decrease below set point, PTH will ↑ Ca by:
◦ ↑ 1,25- diOH-D3. Which then ↑ Ca mobilization from bone, ↑renal absorption of Ca, ↓ renal excretion of Ca, ↑ Ca absorption from intestine (by ↑ mRNA translation into Ca binding protein, which stimulates Ca absorption from the intestine).
◦ PTH can also directly ↑ Ca mobilization from bone, ↑renal absorption of Ca, ↓ renal excretion of Ca.
• If calcium levels increase above set point, thyroid gland will release calcitonin:</td></tr>
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	• **Calcitonin decreases Ca** by inhibiting Ca mobilization from bone.
Mechanism of action	• Vitamin D action is typical of **steroid** hormones • It binds to **intracellular** receptor proteins. The receptor complex then interacts with target DNA in cell nucleus. This stimulates or represses gene expression.
Functions of vitamin D	1. Regulates **plasma levels** of calcium and phosphate 2. Promotes **intestinal absorption** of calcium and phosphate 3. Stimulates synthesis of **calcium-binding protein** for intestinal calcium uptake 4. **Minimizes loss** of calcium by the kidneys 5. **Mobilizes** calcium and phosphate from **bone** to maintain plasma levels

Deficiency	• Most common deficiency worldwide.
	• High prevalence in Saudi Arabia due to:
	  • Low dietary intake
	  • Insufficient exposure to Sun
	• Circulating level of **>75 nmol/L** is required for beneficial health effects
	• Deficiency may lead to rickets, osteomalacia, and osteoporosis.

Rickets	
Nutritional rickets	Inherited rickets
• A disease in children causing net demineralization of bone *(while **Osteomalacia** is demineralization of bones in adults)* • Continued formation of collagen matrix of bone with incomplete bone mineralization. • Bones become **soft and pliable** • Causes skeletal deformities including **bowed legs** • Patients have low serum levels of vitamin D	• Vitamin D-dependent rickets (types 1 and 2) • Rare types of rickets due to genetic disorders • Causing vitamin D deficiency
Features: large forehead, stunned growth, odd curve to spine or back, wide joints at elbow, ankle or wrist, odd shaped legs, wide bones, large abdomen, odd shaped ribs and breast bone.	
Causes	
Vitamin D deficiency because of: • Poor nutrition • Insufficient exposure to sunlight • Renal osteodystrophy (causes decreased synthesis of active vitamin D in kidneys) • Hypoparathyroidism (hypocalcemia)	mainly because of **genetic defects** in: • Vitamin D synthesis • Vitamin D receptor (no hormone action)
Diagnosis of rickets	

Measuring serum levels of:

- 25-hydroxycholecalciferol, PTH, Calcium, Phosphate, Alkaline phosphatase

Treatment

- Vitamin D and calcium supplementation

Osteoporosis

- Bone matrix **composition is normal** but **bone mass** per unit volume is **reduced**
- Increases fragility of bones & Increases susceptibility to fractures
- Crush fractures of vertebral bodies, collapsed vertebrae may present as "Dowager's hump"

Primary osteoporosis:	Secondary osteoporosis may be caused by:
• Post-menopausal women (they lose more bone mass than men)	Drugs, Immobilization, Smoking, Alcohol, Cushing's syndrome, Gonadal failure, Hyperthyroidism, GI disease

Diagnosis

- WHO standard: Serial measurement of bone mineral density
- Biochemical tests (calcium, phosphate, vitamin D) alone cannot diagnose or monitor primary osteoporosis, but **can diagnose Secondary osteoporosis** (due to other causes).
- The test results overlap in healthy subjects and patients with osteoporosis

Bone formation markers

1. Osteocalcin
   - Produced by osteoblasts during bone formation & resorption **(bone turnover)**
   - Involved in bone remodeling process
   - **Short half-life of few minutes**
2. Bone-specific alkaline phosphatase
   - Present in osteoblast plasma membranes
   - Helps osteoblasts in bone formation
   - A Non-specific marker, as its isoenzymes are widely distributed in other tissues
3. P1NP (Procollagen type-1 amino-terminal propeptide)
   - Produced by osteoblasts. Involved in the process of type 1 collagen formation
   - Blood levels are highly responsive to osteoporosis progression and treatment

Bone resorption markers

CTX-1 (Carboxy-terminal cross-linked telopeptides of type 1 collagen)

- A component of type-1 collagen
- Released from type-1 collagen during bone **resorption**
- Blood and urine levels are highly responsive to post-resorptive treatment
- **Levels vary largely by circadian variation**

Treatment

- In confirmed cases of osteoporosis, treatment options are unsatisfactory
- **Oral calcium, estrogens, fluoride therapy** may be beneficial
- **Bisphosphonates** inhibit bone resorption that slows down bone loss

Prevention
• Prevention from childhood is important • Good diet and exercise prevent osteoporosis later • Hormone replacement therapy in menopause may prevent osteoporosis

Done by: لولوة الصغير