WALKIN’ ON SUNSHINE…AND SOAKING IN SOME VITAMIN D

OBJECTIVES
• Distinguish the various forms of Vitamin D
• Discuss the metabolism of Vitamin D
• Assess Vitamin D deficiency & risk factors

IN THE BEGINNING…
• Adequate diet in 19th century
  – 12% protein
  – 5% minerals
  – 10-30% fat
  – 60-70% carbohydrates
• What caused diseases such as rickets, scurvy, and beri-beri?

EARLY EXPERIMENTS
• Fed appropriate proportions to animals
  – Low survival
• What was missing from this diet?
• Other findings supported existence of essential micronutrients in diet

CASE OF BERI-BERI
• High incidence among prisoners in Dutch East Indies
• These prisoners were fed predominantly a diet of polished rice
• Providing the hulls of rice got rid of beri-beri
• Conclusion: Polished rice contained toxin that was neutralized by a substance in the hull

SCURVY PREVENTION
• Discovery of substance that prevent scurvy in sailors
  – Substance in citrus fruits
  
  German chemist, Funk, stated that a “vital amine” present in foods was required for health and survival
**STUDY AT UNIVERSITY OF WISCONSIN**

- Experiment on dairy cattle
- Fed four groups same proportions
  - Each group’s entire ration from a single grain – corn, oats, wheat, or mixture
- Outcomes:
  - Corn diet \(\rightarrow\) reproduced & produced large quantities of milk
  - Wheat diet \(\rightarrow\) poor outcomes; many failed to survive
  - Oats diet \(\rightarrow\) results between that of corn and wheat

**FURTHER STUDIES**

- Used white rat to study dietary components
  - Demonstrated that butter fat and cod liver oil contained a factor that prevented eye disease and supported growth
  - This was a fat soluble substance
- Discovered water-soluble factor that prevented neurological disease similar to beri-beri
- Another water soluble factor was found to prevent scurvy

**“THE ENGLISH DISEASE”**

- Sir Edward Mellanby concerned with high incidence of rickets in United Kingdom
  - Could rickets be due to a dietary deficiency?
- Fed Scottish diet (primarily oats) to dogs that were inadvertently kept indoors
  - Developed rickets
  - Cured with cod liver oil
- **Must be Vitamin A!**

**“THE ENGLISH DISEASE”**

- McCollum tested hypothesis about Vitamin A deficiency linked with rickets
- Destroyed the Vitamin A in cod liver oil
  - No longer prevented xerophthalmia or Vitamin A deficiency
  - HOWEVER... still cured rickets

**HEALING RICKETS WITH UV LIGHT**

- Physicians and researchers in Vienna & England noted that sunlight cured rickets
- Study at Univ. of Wisconsin
  - During summer goats had positive calcium balance
  - Goats brought indoors in winter \(\rightarrow\) calcium decreased
  - Sunlight \(\rightarrow\) calcium retention

**HEALING RICKETS WITH UV LIGHT**

- Observation of goats led to further studies with rats
- Irradiated rats, their food, and air in their cages
  - Irradiation in rat and food prevented/cured rickets
- Found that this activity was associated with non-saponifiable lipid fraction
  - Concluded that inactive lipid in diet & skin converted by UV light into active substance
- Process patented \(\rightarrow\) industry had cure for rickets as major medical problem
**Identification of Vitamin D**

- Vitamin D$_3$ isolated from irradiation mixture of ergosterol
- In 1935 → 7-dehydrocholesterol isolated
- In 1937 → Vitamin D$_3$ identified

- D$_3$ natural form of Vitamin D
  - Formed in skin as result of UV irradiation of 7-dehydrocholesterol
  - Is Vitamin D truly at vitamin?
  - Is it normally produced in skin, not in natural foods?

**Vitamin D Forms**

<table>
<thead>
<tr>
<th>Vitamin D Form</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciferol (Vitamin D$_2$)</td>
<td>Not naturally occurring in body</td>
</tr>
<tr>
<td>Cholecalciferol (Vitamin D$_3$)</td>
<td>Naturally occurring</td>
</tr>
<tr>
<td>Calcidiol (25-hydroxyvitamin D$_3$)</td>
<td>Prohormone made in liver</td>
</tr>
<tr>
<td>Calcitriol (1,25-dihydroxyvitamin D$_3$)</td>
<td>Acted from made in kidneys</td>
</tr>
</tbody>
</table>

**Role of Vitamin D**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciferol (Vitamin D$_2$)</td>
<td>Absorption of calcium &amp; phosphorus</td>
</tr>
<tr>
<td>Cholecalciferol (Vitamin D$_3$)</td>
<td>Helps body absorb calcium</td>
</tr>
<tr>
<td>Calcidiol (25-hydroxyvitamin D$_3$)</td>
<td>Not an active form of Vitamin D until the conversion to Calcitriol</td>
</tr>
<tr>
<td>Calcitriol (1,25-dihydroxyvitamin D$_3$)</td>
<td>Increases uptake of calcium from GI tract</td>
</tr>
<tr>
<td></td>
<td>Enhance effect of PTH on bone</td>
</tr>
<tr>
<td></td>
<td><strong>Increases calcium in blood</strong></td>
</tr>
<tr>
<td></td>
<td>Regulates cell growth</td>
</tr>
<tr>
<td></td>
<td>Immunomodulation</td>
</tr>
</tbody>
</table>

**Vitamin D3 ≠ Vitamin D2**

- 7-dehydrocholesterol → Ergosterol
  - Produced by skin by UVB
  - Not produced in humans
  - Fully active
  - 1/3 activity D3

**Vitamin D3 ≠ 1,25(OH)$_2$Vitamin D$_3$**

- Vitamin D3
  - Biologically inactive
  - Does not bind to VDR
  - Nutritional substance

- 1,25(OH)$_2$D$_3$
  - Steroid hormone
  - Acts through Vitamin D Receptor (VDR)

**Food Sources of Vitamin D**

**Very Few Sources**

- Fatty fish (salmon, tuna, mackerel)
- Fish liver oil
- Beef liver, cheese, egg yolks

- Fortified foods → largest food source of Vitamin D
  - Cholecalciferol in milk or juices
**Vitamin D** is technically not a vitamin (an essential dietary factor).

**Vitamin D** is a PROHORMONE produced photo-chemically in the skin from 7-dehydrocholesterol.

**METABOLISM OF VITAMIN D**

- Renal synthesis of calcitriol
  - Up-regulation by PTH
  - Down-regulation by fibroblast-like growth factor (FGF23)
- Calcitriol
  - Binds to vitamin D binding protein (DBP) → transported to target organs

**VITAMIN D SYNTHESIS FROM SUNLIGHT**

Only UV light between 270-320nm can produce Vitamin D3 (UVB).
WHAT ABOUT TANNING BEDS?

• Produce UVA & UVB
• Studies indicate ~20% skin exposed to sun or tanning bed resulted in increased concentrations of Vitamin D3 and 25-(OH)D3
• Not FDA approved to increase Vitamin D

Both QUANTITY (intensity) and QUALITY (wavelength) of UVB radiation are important determinants in Vitamin D3 synthesis.

Direct correlation between Vitamin D deficiency & latitude which person lives

UVB must activate 7-dehydrocholesterol in the deepest layers of the epidermis.

Highest concentrations of 7-dehydrocholesterol

Greatest capacity for production of pre-vitamin D3 and vitamin D3

Keratinocytes: Excretes keratin which waterproofs & strengthens skin

Melanocytes: Produce melanin (pigment) which darkens the skin


https://opentextbc.ca/anatomyandphysiology/chapter/5-1-layers-of-the-skin/
• Melanin absorbs UV light in 290-320nm range

• Serves as filter for penetration into stratus spinosum & stratum basale

• Melanin competes with 7-dehydrocholesterol for UV absorption

Melanin is an effective natural sunscreen

Darker skin (more melanin) interferes with cutaneous synthesis of Vitamin D

African Americans with dark skin tone require 5-10 times the amount of sunlight necessary to produce similar (though still not as much) serum concentrations of Vitamin D

In ideal atmospheric conditions, with clear skies, 30 minutes of whole body exposure (pale skin) to sunlight without clothes or sunscreen may result in synthesis of 10,000-20,000IU of Vitamin D

This quantity is enough to supply the body’s full needs

>90% of Vitamin D requirement for most people comes from casual exposure to sunlight

Exposure of arms & legs for 10-30 minutes between 10am-3pm twice per week is often adequate (depends on time of day, season, latitude, skin tone)

ALTERATION OF VITAMIN D3 PRODUCTION
Anything that influences penetration of UVB or alters amount of 7-dehydrocholesterol may affect cutaneous productions of Vitamin D3.

7-dehydrocholesterol declines as we age:
- 70 year old & 25 year old exposed to same sunlight exposure
- 70 year old makes ~25% of vitamin D₃ as the 25 year old

Clouds can eliminate up to 99% UVB radiation.

Sunscreen absorbs UVB and some UVA:
- SPF 8 → reduces capacity of skin to produce vitamin D₃ by >95%
- SPF 15 → reduces capacity by >98%

Latitude can drastically influence Vitamin D₃ production

Markedly decreased UVB in winter months.
• UVB is at its highest between 10:00AM and 3:00PM during spring, summer, autumn
• Less cutaneous formation of vitamin D3 in early morning or late evening

**ACTIONS OF VITAMIN D**

Vitamin D is best known for its role in calcium regulation

Without Vitamin D3:
10-15% dietary calcium (normal ~30%) and 60% phosphorus (normal ~80%) are absorbed

**VITAMIN D RECEPTORS**

• 36 tissues express VDR
• Potential to produce biological response depends on availability of Vitamin D3

IT’S MORE THAN JUST CALCIUM REGULATION...

• The activity of Vitamin D3 expands beyond the regulation of calcium homeostasis
• Currently recognized to play vital roles in:
  – Adaptive immunity
  – Tumor suppression
  – Insulin secretion by β-pancreatic cells
  – Cardiac and blood pressure regulation
  – Brain and fetal development

VITAMIN D DEFICIENCY

FACTORS AFFECTING VITAMIN D

- Sun exposure
- Kidney disease
- Skin color
- Malabsorption syndrome

An estimated ONE BILLION people worldwide across all ethnicities and age groups have a vitamin D deficiency.

VIT D DEFICIENCY HIGHEST AMONGST:

- Elderly
- Institutionalized (67%)
- Hospitalized (57%)
- 2/3 of healthy young adults in Boston were vitamin D deficient at end of winter

A GLANCE AT THE DATA...

- >50% African Americans in US at risk
- Young adults that seldom see daylight or always use sunscreen at risk
- Boston → 84% African American men and women over age 65 were deficient
- Women and children in Saudi Arabia → high prevalence of osteomalacia and rickets
- 32% students & doctors at Boston Medical Center were vitamin D deficiency at end of winter
Vitamin D deficiency appears to be associated with a wide range of diseases

(A direct causal relationship remains unclear)

EFFECT ON BONES

Osteopenia
Osteomalacia (children & adults)
Rickets (children)

VITAMIN D & CANCER

• Levels of 25-hydroxyvitamin D <20ng/mL associated with 30-50% increased risk and higher mortality rate from colon, prostate, and breast cancer

• Nurses Health Study (~33,000 subjects)
  – Inverse relationship between colorectal cancer and median 25-hydroxyvitamin D, but not 1,25(OH)2 vitamin D3

LIVING AT HIGHER LATITUDES

• Increased cases of Type 1 diabetes, Crohn's disease, Multiple Sclerosis
  – Living below 35° latitude first 10 years of life ↓ risk of MS 50%

• Increased risk of hypertension and CV disease

• Increased incidence of schizophrenia and depression

HYPERPARATHYROIDISM
IMMUNE SYSTEM IMPAIRMENT

• VDR expressed on B cells, T cells, and Ag presenting cells
  – All capable of synthesizing ACTIVE vitamin D
• Modulates immune cell function
• Influences natural & adaptive immunity
  • Lack of vitamin D → poor immune function

CONTROVERSY

Sunscreen or no sunscreen?

HOW MUCH VITAMIN D DO WE NEED?

RECOMMENDED DAILY INTAKE

• Two sets of guidelines
  – Institute of Medicine (IOM)
  – Endocrine Society

<table>
<thead>
<tr>
<th>Source</th>
<th>Approx Vitamin D content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon</td>
<td></td>
</tr>
<tr>
<td>Fresh, wild</td>
<td>600-1000 IU</td>
</tr>
<tr>
<td>Fresh, farmed</td>
<td>100-250 IU</td>
</tr>
<tr>
<td>Canned</td>
<td>300-600 IU</td>
</tr>
<tr>
<td>Sardines</td>
<td>300 IU</td>
</tr>
<tr>
<td>Mackeral</td>
<td>250 IU</td>
</tr>
<tr>
<td>Tuna</td>
<td>230 IU</td>
</tr>
<tr>
<td>Fortified milk</td>
<td>100 IU</td>
</tr>
<tr>
<td>Fortified orange</td>
<td>100 IU</td>
</tr>
<tr>
<td>Infant formula</td>
<td>100 IU</td>
</tr>
<tr>
<td>Exposure to sunlight</td>
<td>3000 IU</td>
</tr>
</tbody>
</table>

US ENDOCRINE SOCIETY CLASSIFICATION

<table>
<thead>
<tr>
<th>Vitamin D Status</th>
<th>Vitamin D levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>21-29 ng/mL</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>&gt;30 ng/mL</td>
</tr>
<tr>
<td>Toxicity</td>
<td>&gt;150 ng/mL</td>
</tr>
</tbody>
</table>
DIETARY SUPPLEMENTS

- Differ in chemical structure
- Manufactured differently
- Identical metabolism
- Both raise 25(OH)D levels
- At nutritional doses, both are equivalent
- At high doses, D₂ is less potent

VITAMIN D TOXICITY

PREVENTION OF EXCESS VITAMIN D

Melanin accumulation
Conversion to inactive metabolites

Excessive sun exposure & excessive food intake DO NOT cause Vitamin D toxicity
Toxicity most likely to occur from high intake of dietary supplements

TOXICITY

- Doses >50,000 IU can raise serum 25(OH)D to 300 ng/mL
- Doses >10,000 IU daily may cause kidney & tissue damage
- Doses of 5000 IU daily raised serum 25(OH)D to 100-150 ng/mL
- Leads to hypercalcemia, vascular & tissue calcification, damage to heart, kidney, and blood vessels
- Symptoms unlikely at daily intakes <10,000 IU (but there may be adverse effects over time)

TOLERABLE UPPER INTAKE LEVELS

<table>
<thead>
<tr>
<th>Age</th>
<th>Upper Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mos.</td>
<td>1000 IU</td>
</tr>
<tr>
<td>7-12 mos.</td>
<td>1500 IU</td>
</tr>
<tr>
<td>1-3 yr.</td>
<td>2500 IU</td>
</tr>
<tr>
<td>4-8 yr.</td>
<td>3000 IU</td>
</tr>
<tr>
<td>9-18 yr.</td>
<td>4000 IU</td>
</tr>
<tr>
<td>&gt;19 yr.</td>
<td>4000 IU</td>
</tr>
</tbody>
</table>

Generally, not recommended to take >2000 IU in supplement form without medical advice
IN SUMMARY...

- Vitamin D is a steroid hormone that is synthesized in the SKIN when activated by SUNLIGHT (UVB).
- Although Vitamin D is best known for its role in bone formation, receptors are found all over the body → NUMEROUS FUNCTIONS.

MY TAKE HOME MESSAGE...

- SOAK UP THE SUN

UV Index in the Middle of Summer

UV Index in the Dead of Winter