# WALKIN' ON SUNSHINE…AND SOAKING IN SOME VITAMIN D

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## 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 diary cattle
- Fed four groups same proportions
  - Each group's entire ration from a single grain – corn, oats, wheat, or mixture
- Outcomes:
  - Corn diet → reproduced & produced large quantities of milk
  - Wheat diet → poor outcomes; many failed to survive
  - Oats diet → results between that of corn and wheat

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## 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

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## "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!**

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## "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

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## 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 → calcium decreased
  - Sunlight → calcium retention

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## 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 → industry had cure for rickets as major medical problem

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## IDENTIFICATION OF VITAMIN D

- Vitamin $D_2$ 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?

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## VITAMIN D FORMS

**Ergocalciferol (Vitamin $D_2$)**
- Not naturally occurring in body

**Cholecalciferol (Vitamin $D_3$)**
- Naturally occurring
- Made in skin & found in foods

**Calcidiol (25-hydroxyvitamin $D_3$)**
- Prohormone made in liver
- Low biologic activity
- Major circulating form → often measured

**Calcitriol (1,25-dihydroxyvitamin$D_3$)**
- Activated from made in kidneys

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## ROLE OF VITAMIN D

| | |
|---|---|
| **Ergocalciferol (Vitamin $D_2$)** | Absorption of calcium & phosphorus |
| **Cholecalciferol (Vitamin $D_3$)** | Helps body absorb calcium |
| **Calcidiol (25-hydroxyvitamin $D_3$)** | Not an active form of Vitamin D until the conversion to Calcitriol |
| **Calcitriol (1,25-dihydroxyvitamin$D_3$)** | Increases uptake of calcium from GI tract<br>Enhance effect of PTH on bone<br>**Increases calcium in blood<br>Regulates cell growth<br>Immunomodulation |

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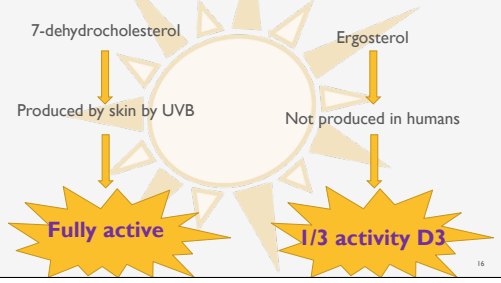
## VITAMIN D3 ≠ VITAMIN D2

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## 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)

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## FOOD SOURCES OF VITAMIN D

**VERY FEW SOURCES**
- Fatty fish (salmon, tuna, mackeral)
- Fish liver oil
- Beef liver, cheese, egg yolks

D3

- Fortified foods → largest food source of Vitamin D
  - Cholecalciferol in milk or juices

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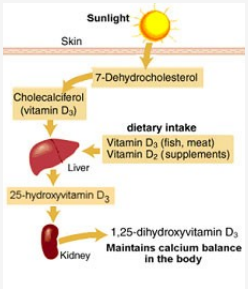


**Vitamin D** is technically **not a vitamin**

(an essential dietary factor)

**Vitamin D** is a **PROHORMONE**

(secosteroid)

produced photo-chemically in the skin from 7-dehydrocholesterol

https://www.fmhs.auckland.ac.nz/en/soph/about/our-departments/epidemiology-and-biostatistics/research/vida-study/about-vitamin-d.html

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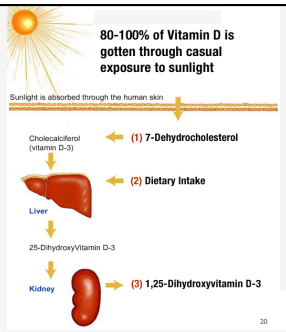
## METABOLISM OF VITAMIN D

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## 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

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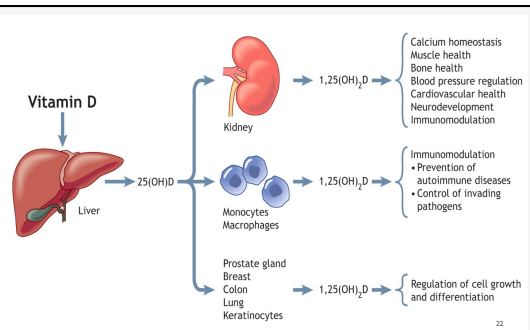


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## VITAMIN D SYNTHESIS FROM SUNLIGHT

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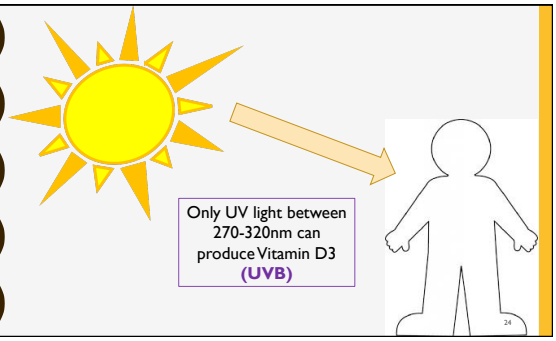


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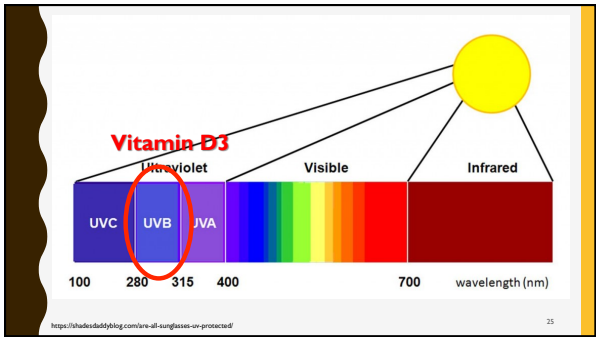
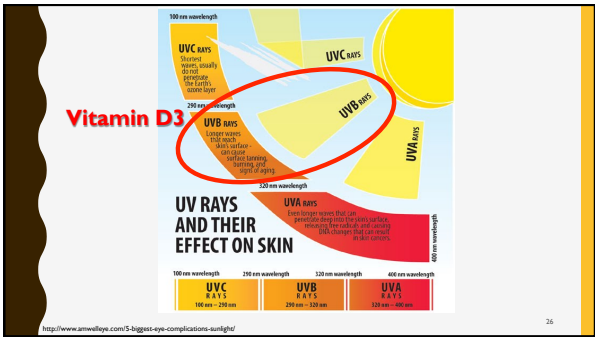



https://shadesdaddyblog.com/are-all-sunglasses-uv-protected/ 25




http://www.amwelleye.com/5-biggest-eye-complications-sunlight/ 26

## WHAT ABOUT TANNING BEDS?

- Produce UVA & UVB
- Studies indicate ~20% skin exposed to sun or tanning bed resulted in increased concentrations of VitaminD3 and 25-(OH)D3
- **Not FDA approved to increase Vitamin D**


Holick, M. (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American Journal of Clinical Nutrition*, 80(6), 1678s-1688s. 27

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

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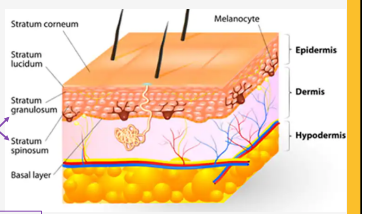
Highest concentrations of 7-dehydrocholesterol

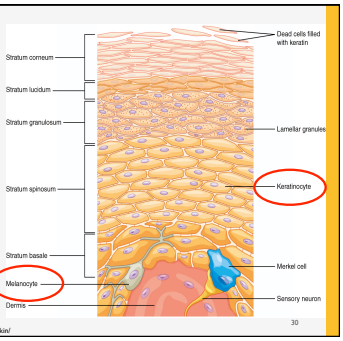



Greatest capacity for production of pre-vitamin D3 and vitamin D3

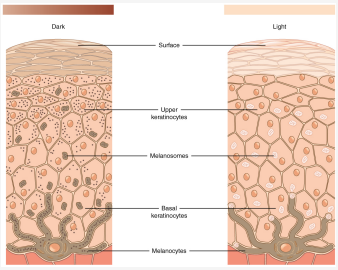
PHOTO: https://lpb.pbslearningmedia.org/resource/49953391-l-science-technology/layers-of-human-skin-melanocyte-and-melanin-science-and-technology/ 29

**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/ 30




- 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

https://openentextbc.ca/anatomyandphysiology/chapter/5-1-layers-of-the-skin/

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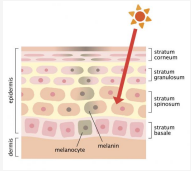
**Melanin is an effective natural sunscreen**

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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

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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**

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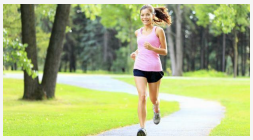
>90% of Vitamin D requirement for most people comes from casual exposure to sunlight

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)



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# ALTERATION OF VITAMIN D3 PRODUCTION

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**Anything that influences penetration of UVB or alters amount of 7-dehydrocholesterol may affect cutaneous productions of Vitamin D3**

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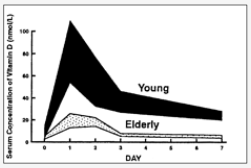
**7-dyhydrocholesterol declines as we age**

- 70 year old & 25 year old exposed to same sunlight exposure
- 70 year old makes ~25% of vitamin $D_3$ as the 25 year old




Holick, M. (2004). Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *The American Journal of Clinical Nutrition, 80*(6), 1678s-1688s.

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**Clouds can eliminate up to 99% UVB radiation**

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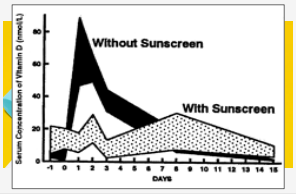
**Sunscreen absorbs UVB and some UVA**

- SPF 8 → reduces capacity of skin to produce vitamin D3 by >95%
- SPF 15 → reduces capacity by >98%

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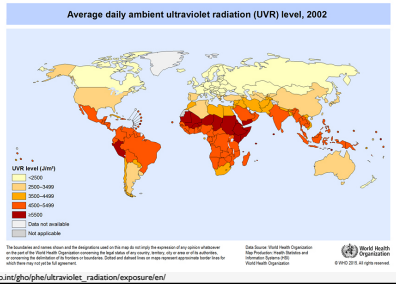
**Latitude** can drastically influence Vitamin D3 production




https://www.who.int/gho/phe/ultraviolet_radiation/exposure/en/

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Markedly decreased UVB in winter months

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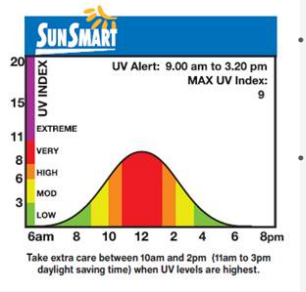


- UVB is at its highest between **10:00AM and 3:00PM** during spring, summer, autumn
- Less cutaneous formation of vitamin D3 in early morning or late evening

https://www.cancercouncil.com.au/23856/cancer-prevention/sun-protection/sunsmart-program-for-primary-schools-and-ohsc/sunsmart-information-and-news/what-is-uv-radiation/

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# ACTIONS OF VITAMIN D

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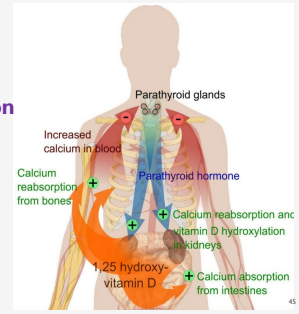
Vitamin D
is best known for
its role in
**calcium regulation**




From: www.medicalsciencenavigator.com

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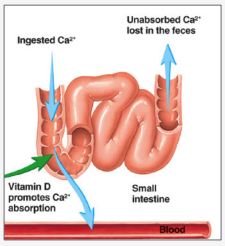


Without Vitamin D3:
10-15% dietary calcium (normal ~30%)
and
60% phosphorus (normal ~80%)
are absorbed

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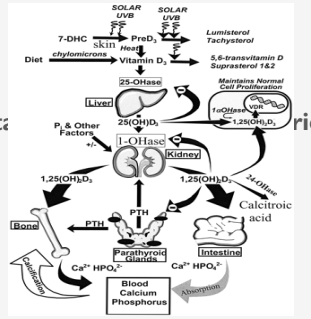


Vita riety

The American Journal of Clinical Nutrition, Volume 80, Issue 6, December 2004, Pages 1678S–1688S, https://doi.org/10.1093/ajcn/80.6.1678S

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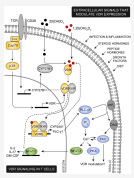
# VITAMIN D RECEPTORS



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

Adipose – adrenal – bone – bone marrow – brain – breast – cancer cells – cartilage – colon – eggshell gland – epididymis – hair follicle – intestine – kidney – liver – lung – lymphocytes – muscle – osteoblast – ovary – pancreas B cells – parathyroid – parotid – pituitary – placenta – prostate – retina – skin – stomach – testes – thymus – thyroid - uterus

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## 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

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## VITAMIN D DEFICIENCY

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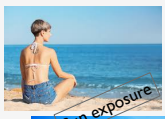
## FACTORS AFFECTING VITAMIN D





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Recognized as **MAJOR** health problem for adults >50 years of age

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

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## 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

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## 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

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**Vitamin D deficiency appears to be associated with a wide range of diseases**

(A direct causal relationship remains unclear)

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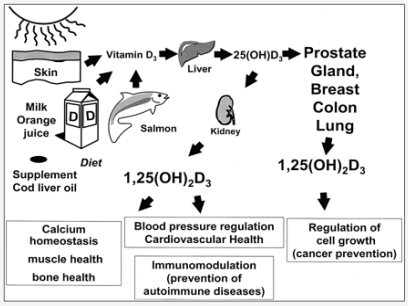


*The American Journal of Clinical Nutrition*, Volume 80, Issue 6, December 2004, Pages 1678S–1688S, https://doi.org/10.1093/ajcn/80.6.1678S

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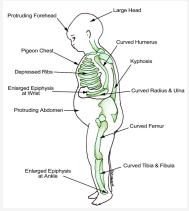
## EFFECT ON BONES

Osteopenia
Osteomalacia (children & adults)
Rickets (children)

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## 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$D_3$

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## 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

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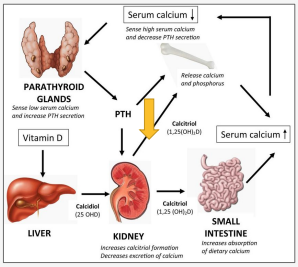
## HYPERPARATHYROIDISM

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## 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**

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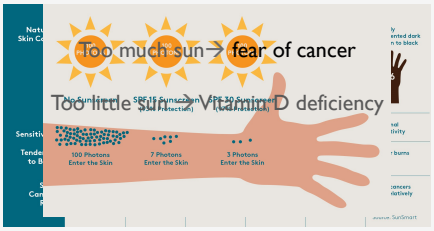
## CONTROVERSY

**Sunscreen or no sunscreen?**

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## HOW MUCH VITAMIN D DO WE NEED?

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## RECOMMENDED DAILY INTAKE

- Two sets of guidelines
  - Institute of Medicine (IOM)
  - Endocrine Society

| | Ages 1-18 | Ages 19-70 | Ages 71+ |
|---|---|---|---|
| | RDA (IU/day) | RDA (IU/day) | RDA (IU/day) |
| IOM | 600 | 600 | 800 |
| Endoc. Society | 600-1000 | 1500-2000 | 1500-2000 |

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## US ENDOCRINE SOCIETY CLASSIFICATION

| Vitamin D Status | Vitamin D levels<br>serum 25(OH)vitaminD |
|---|---|
| Deficiency | <20 ng/mL |
| Insufficiency | 21-29 ng/mL |
| Sufficiency | >30 ng/mL |
| Toxicity | >150 ng/mL |

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| Source | Approx Vitamin D content |
|---|---|
| Salmon | |
| Fresh, wild (3.5 oz) | 600-1000 IU |
| Fresh, farmed (3.5 oz) | 100-250 IU |
| Canned (3.5 oz) | 300-600 IU |
| Sardines, canned (3.5 oz) | 300 IU |
| Mackeral, canned (3.5 oz) | 250 IU |
| Tuna, canned (3.6 oz) | 230 IU |
| Fortified milk (8 oz) | 100 IU |
| Fortified orange juice (8 oz) | 100 IU |
| Infant formula (8 oz) | 100 IU |
| Exposure to sunlight | 3000 IU |

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## DIETARY SUPPLEMENTS

$D_2$

$D_3$

- Differ in chemical structure
- Manufactured differently
- Identical metabolism
- Both raise 25(OH)D levels
- At nutritional doses, both are equivalent
- At high doses, $D_2$ is less potent

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## VITAMIN D TOXICITY

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## PREVENTION OF EXCESS VITAMIN D

Melanin accumulation

Conversion to inactive metabolites

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Excessive sun exposure & excessive food intake DO NOT cause Vitamin D toxicity

Toxicity most likely to occur from high intake of dietary supplements

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## 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)

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## TOLERABLE UPPER INTAKE LEVELS

| Age | Upper Intake |
|---|---|
| 0-6 mos. | 1000 IU |
| 7-12 mos. | 1500 IU |
| 1-3 yr. | 2500 IU |
| 4-8 yr. | 3000 IU |
| 9-18 yr. | 4000 IU |
| >19 yr. | 4000 IU |

**Generally, not recommended to take >2000 IU in supplement form without medical advice**

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## 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

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## MY TAKE HOME MESSAGE…


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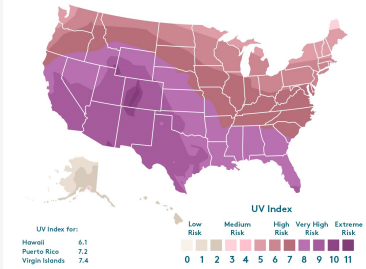
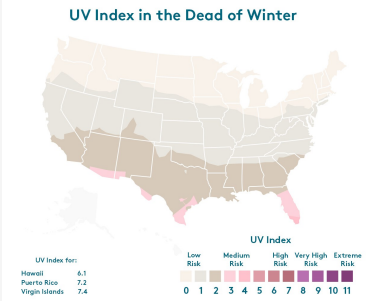
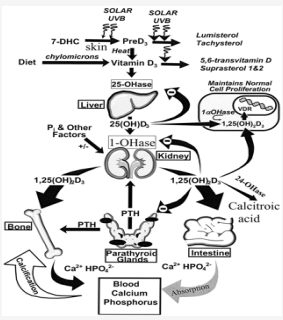


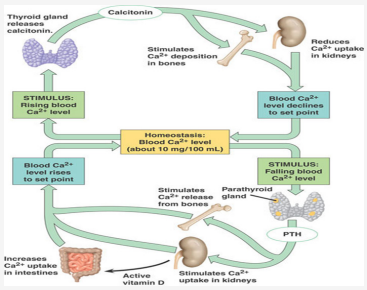

76




77




78


Thyroid gland releases calcitonin.
Calcitonin
Stimulates $Ca^{2+}$ deposition in bones
Reduces $Ca^{2+}$ uptake in kidneys
STIMULUS: Rising blood $Ca^{2+}$ level
Blood $Ca^{2+}$ level declines to set point
Homeostasis: Blood $Ca^{2+}$ level (about 10 mg/100 mL)
Blood $Ca^{2+}$ level rises to set point
STIMULUS: Falling blood $Ca^{2+}$ level
Stimulates $Ca^{2+}$ release from bones
Parathyroid gland
PTH
Increases $Ca^{2+}$ uptake in intestines
Active vitamin D
Stimulates $Ca^{2+}$ uptake in kidneys

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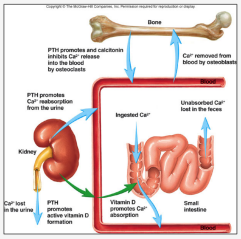
Bone
PTH promotes and calcitonin inhibits $Ca^{2+}$ release into the blood by osteoclasts
$Ca^{2+}$ removed from blood by osteoblasts
Blood
PTH promotes $Ca^{2+}$ reabsorption from the urine
Ingested $Ca^{2+}$
Unabsorbed $Ca^{2+}$ lost in the feces
Kidney
$Ca^{2+}$ lost in the urine
PTH promotes active vitamin D formation
Vitamin D promotes $Ca^{2+}$ absorption
Small intestine
Blood

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