Vitamin D Deficiency: Impact on Neuropsychiatric Disorders

(page 177 in syllabus)

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Individual Disclosure Statement

Faculty Author/ Presenter

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No other financial relationships to disclose.
Learning Objectives

• Identify populations at risk of vitamin D deficiency

• Identify consequences of vitamin D deficiency
Overview

• Vitamin D physiology
  – Sources
  – Blood levels of 25(OH)D and 1,25(OH)2D
  – Vitamin D receptors (VDR)

• Populations at risk for deficiency

• Replacement therapy and monitoring

• Controversies
  – Bone vs body/brain health
  – Recommended daily requirements
  – Blood levels of 25(OH)D
  – Research on prevention and treatment
Pretest Question 1

Which of the following is **not** associated with vitamin D deficiency?

1. Malabsorption syndromes
2. Inhibition of CYP enzymes
3. Chronic kidney disease
4. Hyperparathyroidism
5. Obesity (BMI > 30 kg/m²)
Pretest Question 2

Which of the following is **not** an action of vitamin D?

1. Vasculoprotection
2. Promotes insulin secretion
3. Reduces inflammation
4. Increases cell proliferation
5. Promotes innate immunity
Vitamin D: The Sunshine Vitamin

• Vitamin D is a steroid hormone (pro-hormone)
  – Made from cholesterol metabolism in skin (activated in liver and kidney); classified as a hormone
  – 25(OH)D is 90-99% bound to vitamin D binding protein
  – 1,25(OH)2D binds to nuclear hormone vitamin D receptors, where it acts as a molecular switch to signal target genes
  – It is estimated that 2,000 genes are primary targets of activated vitamin D
    • May induce expression of CYP3A4
Vitamin D and Whole Body Health

- Rickets
- Osteoporosis/osteomalacia
- Periodontal disease
- Cardiovascular disease: hypertension
- Malabsorption: cystic fibrosis, Crohn’s disease
- Cancer: colon, breast, ovarian, prostate cancer
- Rheumatoid arthritis
- Diabetes: types 1 and 2
- Infectious diseases
- SLE
- Allergies

- Mood disorders
  - Seasonal affective disorder
  - Bipolar disorder
  - Recurrent unipolar disorder
  - Postpartum depression

- Brain development
  - Autism
  - Schizophrenia

- Cognitive disorders
  - Dementia

- Multiple sclerosis
- Parkinson’s disease
- Muscle weakness and pain
- Fibromyalgia
- Headaches
Vitamin D Levels

• 25-hydroxy vitamin D = 25(OH)D
  – Inactive precursor = calcidiol
  – Plasma half-life = 2-3 weeks
  – Usually measured to assess vitamin D deficiency or excess
  – Reference: 10-100 ng/mL
    • May be lower in the winter with low sun exposure
    • 20-30 ng/mL for bone health and 30-100 ng/mL for whole body health (~ 40-60 ng/mL)

• 1,25-dihydroxy vitamin D = 1,25(OH)2D
  – Biologically active = calcitriol
  – Plasma half-life = 4-6 hrs
  – Usually used to evaluate hypercalcemia
  – Reference: 15-60 ng/mL
Vitamin D Receptors (VDRs)

- 1,25(OH)2D binds to VDRs
  - Bone mineral homeostasis (metabolism and calcium/phosphorus homeostasis)
  - Hormone secretion, immune function, cellular proliferation and differentiation
  - VDRs are found in most tissues and cells in the body

- VDR polymorphisms
  - Mutation of VDRs: type 2 vitamin D-dependent rickets (HVDRR) is an autosomal recessive disorder
    - Associated with alopecia and the development of rickets within the first two years of life
    - Failure of 1,25(OH)2D binding to receptors
A certain amount of shortwave ultraviolet B radiation (290-315 nm) must penetrate the outer skin layer in order to produce vitamin D3.
- Arm and leg exposure to sunlight: 3,000 IU vitamin D3
  - Depends on time of day, season, latitude
- Problem: darker skin, obesity, using ≥ 30 SPF sunscreen or protective clothing

Approximately 90% of vitamin D is synthesized in the skin via UV radiation and activated by the kidneys.
- 10% comes from foods such as fatty fish and egg yolks without fortified foods or replacement products.
Vitamin D: D2 vs D3

- Vitamin D2 (ergocalciferol)
  - Produced from ergosterol in a variety of plants and yeast by UVR
  - Lower levels of 25(OH)D than vitamin D3 (30% effective)

- Vitamin D3 (cholecalciferol)
  - Animal/fish sources, supplementation or fortification of dairy
  - Produced from 7-dehydrocholesterol in the skin under the influence of UVB radiation (UVR)
    - Both the intensity of UVR and the level of pigmentation in the skin regulate the rate of D3 formation
  - Stable to heat, light, and storage
  - More active than vitamin D2
## Dietary Reference Intakes for Vitamin D

**IOM Report – 11/30/2010**

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Estimated Average Requirement (IU/d)</th>
<th>Recommended Dietary Allowance (IU/d)</th>
<th>Upper Level Intake (IU/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-6 mos</td>
<td>400</td>
<td>400</td>
<td>1,000</td>
</tr>
<tr>
<td>Infants 6-12 mos</td>
<td>400</td>
<td>400</td>
<td>1,500</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>400</td>
<td>600</td>
<td>2,500</td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>400</td>
<td>600</td>
<td>3,000</td>
</tr>
<tr>
<td>9-13 yrs</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>14-18 yrs</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>19-30 yrs</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>31-50 yrs</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>51-70 yrs</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
<tr>
<td>71+ yrs</td>
<td>400</td>
<td>800</td>
<td>4,000</td>
</tr>
<tr>
<td>14-50 yrs pregnant/lactating</td>
<td>400</td>
<td>600</td>
<td>4,000</td>
</tr>
</tbody>
</table>

Vitamin D deficiency is very common in all age groups. Because few foods contain vitamin D, supplements are recommended. D3 vs D2
- D3 is 87% more potent in raising blood levels of 25(OH)D3

Serum 25(OH)D should be used for patients at risk for deficiency
- Deficient: < 20 ng/mL
- Insufficient: 21-29 ng/mL
- Sufficient: > 30 ng/mL

Endocrine Practice Guidelines

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Daily Requirement</th>
<th>Tolerable Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-6 mos</td>
<td>400-1,000 IU</td>
<td>2,000 IU</td>
</tr>
<tr>
<td>Infants 6-12 mos</td>
<td>400-1,000 IU</td>
<td>2,000 IU</td>
</tr>
<tr>
<td>1-3 yrs</td>
<td>600-1,000 IU</td>
<td>4,000 IU</td>
</tr>
<tr>
<td>4-8 yrs</td>
<td>600-1,000 IU</td>
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<td>10,000 IU</td>
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<td>10,000 IU</td>
</tr>
<tr>
<td>19-50 yrs pregnant/lactating</td>
<td>1,000-2,000 IU</td>
<td>10,000 IU</td>
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</tbody>
</table>

## Natural Sources of Vitamin D2 and D3

<table>
<thead>
<tr>
<th>Sources and Content</th>
<th>Typical Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon, fresh, wild (3.5 oz)</td>
<td>600-1,000 IU (D3)</td>
</tr>
<tr>
<td>Salmon, fresh, farmed (3.5 oz)</td>
<td>100-250 IU (D2 or D3)</td>
</tr>
<tr>
<td>Salmon, canned (3.5 oz)</td>
<td>300-600 IU (D3)</td>
</tr>
<tr>
<td>Sardines, canned (3.5 oz)</td>
<td>300 IU (D3)</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>250 IU (D3)</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>230 IU (D3)</td>
</tr>
<tr>
<td>Cod liver oil (1 tsp)</td>
<td>400-1,000 IU (D3)</td>
</tr>
<tr>
<td>Shitake mushrooms, fresh (3.5 oz)</td>
<td>100 IU (D2)</td>
</tr>
<tr>
<td>Shitake mushrooms, sun-dried (3.5 oz)</td>
<td>1,600 IU (D2)</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20 IU (D2 or D3)</td>
</tr>
<tr>
<td>Exposure to sunlight, UVB (0.5 MED)</td>
<td>3,000 IU (D3)</td>
</tr>
</tbody>
</table>

## Fortified Foods With Vitamin D3

<table>
<thead>
<tr>
<th>Sources and Content</th>
<th>Typical Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified butter</td>
<td>50 IU/3.5 oz (D3)</td>
</tr>
<tr>
<td>Fortified margarine</td>
<td>430 IU/3.5 oz (D3)</td>
</tr>
<tr>
<td>Fortified milk</td>
<td>100 IU/8 oz (D3)</td>
</tr>
<tr>
<td>Fortified yogurts</td>
<td>100 IU/8 oz (D3)</td>
</tr>
<tr>
<td>Fortified cheeses</td>
<td>100 IU/3 oz (D3)</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>100 IU/8 oz (D3)</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>100 IU/serving (D3)</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>100 IU/8 oz (D3)</td>
</tr>
</tbody>
</table>

**Sources of Vitamin D**

<table>
<thead>
<tr>
<th>Pharmaceutical Sources</th>
<th>Vitamin D Content, IU = 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D2 (ergocalciferol)</td>
<td>50,000 IU/capsule</td>
</tr>
<tr>
<td>Drisdol (vitamin D2 liquid)</td>
<td>8,000 IU/cc</td>
</tr>
</tbody>
</table>

**Supplements**

| Multivitamin (D2 or D3)                 | 400; 500; 1,000 IU            |
| Calcium + Vitamin D3                    | 400 IU                       |
| Vitamin D3                               | 400, 800, 1,000; 2,000; 5,000; 10,000; 50,000 IU |
The diagram illustrates the pathway of vitamin D production and its effects on calcium and phosphorus metabolism.

1. **Sun**: UVB light from the sun converts ProD$_3$ to PreD$_3$ in the skin.
2. **Liver**: Vitamin D$_3$ is converted to 25(OH)D.
3. **Kidney**: 25(OH)D is converted to 1,25(OH)$_2$D.
4. **Intestine**: 1,25(OH)$_2$D increases the absorption of calcium and phosphorus.

**Effects**:
- **Increase calcium and phosphorus absorption**
- **Maintain serum calcium and phosphorus**
- **Mobilize calcium stores**
- **Metabolic functions**
- **Bone health**
- **Neuromuscular functions**

**Regulatory Mechanisms**:
- **PTH (+)** increases calcium and phosphorus absorption.
- **Low PO$_4^{2-}$** stimulates 1,25(OH)$_2$D production.

**Dietary Sources**:
- Vitamin D$_3$
- Vitamin D$_2$
Causes of Vitamin D Deficiency

- Diminished cutaneous synthesis
  - Season, latitude, time of day
  - Darker skin, sunscreen, lack of sun exposure
  - Obesity

- Impaired availability of vitamin D
  - Inadequate intake (oily fish, fortified foods, supplements)
  - Lack of fat in the diet for gut absorption
  - Malabsorption disorders
  - Lipase inhibitor (orlistat)
  - Reduced cholesterol levels
    - Cholestyramine, lipid-lowering agents
Causes of Vitamin D Deficiency

- Obesity with storage of vitamin D in fat
- Impaired liver hydroxylation to produce 25(OH)D
- Increased hepatic catabolism of 25(OH)D
  - Carbamazepine, phenobarbital, phenytoin, rifampin, HIV medications
- Impaired renal production of 1,25(OH)2D
Causes of Vitamin D Deficiency

- Abnormal binding proteins
- Abnormal receptor binding
- Genetic variant
  - Cholesterol synthesis
  - Hydroxylation of vitamin D
  - Vitamin D transport

Risk of Vitamin D Deficiency

- Darker skin: African-American and Hispanic
- Winter months/lack of sunlight (UV radiation)
- Lack of fortified foods or supplements
- Elderly
- Infants and children
- Pregnant or lactating women
- Hospitalized/institutionalized patients
- Chronic renal and/or liver disease
- Gastrointestinal diseases, malabsorption, or gastric bypass
- Obesity (BMI > 30 kg/m²)
- Low cholesterol levels for synthesis
- Drugs that affect vitamin D metabolism or absorption (e.g., anticonvulsants, glucocorticoids, antifungal drugs, HIV medications, cholestyramine)

Worldwide Issue

• One billion people worldwide have vitamin D deficiency
  – Lowers life expectancy and may increase mortality rates
• Mostly attributable to people getting less sun exposure because of climate, lifestyle, and concerns about skin cancer
• 1997 Dietary Reference Intake values for vitamin D were established to prevent rickets and osteomalacia
• 2010 Institute of Medicine (IOM) Report increased recommended daily intakes for bone health
  – Current studies suggest we need high serum levels of 25(OH)D to prevent chronic diseases (40-60 ng/mL)


Indications for 25(OH)D Levels

- Rickets
- Osteomalacia/osteoporosis
- Chronic kidney disease
- Hepatic failure
- Malabsorption syndrome
  - Cystic fibrosis
  - Inflammatory bowel disease
  - Crohn’s disease
  - Bariatric surgery
  - Radiation enteritis
- Hyperparathyroidism
- Some lymphomas
- African-American/Hispanic
- Pregnant/lactating women
- Older adults with hx of falls or nontraumatic fractures
- Obesity (BMI > 30 kg/m²)
- Granuloma-forming disorders
  - Sarcoidosis
  - Tuberculosis
  - Histoplasmosis
  - Coccidiomycosis
  - Berylliosis
- Medications
  - Antiseizure, glucocorticoids, HIV medications, antifungals, cholestyramine

<table>
<thead>
<tr>
<th>Serum Levels (ng/mL)</th>
<th>Health Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 (&lt; 25 nmoL/L)</td>
<td>Associated with vitamin D deficiency and rickets in infants and young children</td>
</tr>
<tr>
<td>10-20 (25-50 nmoL/L)</td>
<td>Generally considered inadequate for bone and overall health in healthy adults</td>
</tr>
<tr>
<td>20-30 (50-75 nmoL/L)</td>
<td>Generally considered adequate for bone health: IOM recommended 20-30 ng/mL</td>
</tr>
<tr>
<td>&lt; 30-32 (&lt; 75-80 nmoL/L)</td>
<td>Insufficiency for overall health</td>
</tr>
<tr>
<td>32-100 (80-250 nmoL/L)</td>
<td>Proposed as desirable for overall health and disease prevention: 40-60 ng/mL target levels</td>
</tr>
<tr>
<td>&gt; 200 (&gt; 500 nmoL/L)</td>
<td>Considered potentially toxic, leading to hypercalcemia, hypercalciuria, nephrolithiasis, hyperphosphatemia, soft tissue calcification</td>
</tr>
</tbody>
</table>
Vitamin D Toxicity

• Extremely rare

• Doses > 50,000 IU/d raises 25(OH)D more than 150 ng/mL
  – Associated with hypercalcemia and hyperphosphatemia
  – High calcium doses increase risk

• Doses of 10,000 IU/d D3 for up to 5 months does not cause toxicity

**Actions of Vitamin D**

- Inhibits parathyroid hormone secretion
- Promotes insulin secretion
- Neuroimmunomodulator
  - Promotes innate immunity (activates T cells)
  - Inhibits adaptive immune response
  - Inhibits cell proliferation
  - Reduces inflammation
  - Promotes wound healing
- Neuroprotective function

Skeletal/Muscular Vitamin D Deficiency

- Rickets $\rightarrow$ bone deformity
- Osteomalacia $\rightarrow$ bone/muscle pain
- Osteopenia $\rightarrow$ osteoporosis
- Bone fractures/falls
  - Calcium + vitamin D = ↓ falls in elderly
- Periodontal disease $\rightarrow$ tooth loss
- Muscle weakness/aches/pain
  - Often misdiagnosed as fibromyalgia or chronic fatigue syndrome

Holick MF. Curr Drug Targets 2011;12:4-18;
Nonskeletal Vitamin D Deficiency

• Cancer
  – Colon, breast, ovarian, pancreatic, lymphoma, prostate(?)
  – Melanoma

• Cardiovascular
  – Hypertension

• Autoimmune/immune
  – Multiple sclerosis, type 1 diabetes, rheumatoid arthritis, autoimmune thyroid disease, Crohn’s disease, asthma
  – Interstitial lung disease: systemic lupus, scleroderma, Sjögren’s syndrome
  – Infections: HIV, tuberculosis, viral infections, UTIs
  – Allergic reactions: allergies, hives

• Dermatological (psoriasis, acne)
Vitamin D Deficiency in the Brain

• Neurodevelopment
  – Neurocognitive development, attention deficit disorder, autism spectrum disorder

• Mood
  – Depression, seasonal affective disorder, bipolar disorder, PMS, postpartum depression

• Psychosis
  – Schizophrenia

Vitamin D Deficiency in the Brain

- Parkinson’s disease
- Alzheimer’s disease/dementia
- Multiple sclerosis
- Migraines/headaches
- Seizures
- Strokes
- Blindness/macular degeneration

Nimitphong H, Holick MF. Curr Opin Clin Nutr Metab Care 2011;14:7-14;
Most American Children Are Not Getting Enough Vitamin D

- Lack of synthesis of vitamin D from sun exposure and use of sunscreen in summer months
  - Caucasians may make enough with adequate outdoor UVB exposures if they do not use sunscreen

- Importance of vitamin D supplements and fortified foods
  - US Food and Drug Administration

Godar DE et al. Environ Health Perspect 2011;Epub ahead of print;DOI:10.1289/ehp.1003195.
Vitamin D and Perinatal Health

- Vitamin D deficiency is present in 40-80% of pregnant women
- 70% of children in US are deficient in vitamin D
- Early deficiency may increase the risk of many chronic diseases
  - Osteomalacia, rickets, multiple sclerosis, heart disease, type 1 diabetes, asthma, cancer, and mental illness

Vitamin D and Pregnancy

- Recent IOM recommendation for vitamin D3 supplementation during pregnancy and breastfeeding is low (600 IU/day)
  - Recommendations of up to 4,000 IU/day without sun exposure or risk factors
  - A daily dose of 400 IU D3 raises 25(OH)D by 2.8-4.8 ng/mL

- Estimates of vitamin D deficiency in pregnant women are between 5-50%, with African-American women at a much higher risk
  - Supplements may improve fetal growth and infant weight

Vitamin D and Neurodevelopment

- Brain development in utero depends on mother’s vitamin D levels
  - Sun exposure, dietary intake, or supplements

- Brain development after birth depends on sun exposure and vitamin D dietary intake or supplements
  - Increased risk of food and environmental allergies and asthma

Vitamin D and Neurodevelopment

• Increases nerve growth factor in the brain
  – Nootropic or brain-enhancing

• Vitamin D receptors appear in a wide variety of brain tissue early in brain development

• Estrogen and testosterone have different effects on vitamin D metabolism
  – Estradiol has enhancing effects on vitamin D metabolism, whereas testosterone does not
  – Higher rates of autism, ADHD, and Tourette syndrome in boys
Vitamin D and Neurodevelopment

- Prepregnancy to first 24 months of a child’s life has profound effects on human health
- Higher fish consumption during pregnancy has been associated with better infant cognition: vitamin D and omega-3 fatty acids
- Lower maternal seafood consumption has been associated with increased risk of lower verbal IQ, poor outcomes for social behaviors, fine motor skills, communication, and social development
Vitamin D and Neurodevelopment

- Government recommendations for infants, children, pregnant women, and young adults are too low without sun exposure
- Prenatal vitamins and infant drops contain 400 IU of vitamin D3 and may be inadequate for infant development
- Sun protection during pregnancy and for children increases the risk of vitamin D deficiency
- Children and adolescents who do not drink vitamin D fortified milk or eat oily fish may be vitamin D deficient without supplementation
Infant Formula vs Breast Milk

- Infant formula is fortified with vitamin D3
- Human milk varies with sun exposure and D3 intake
  - Breast milk contains the 25-hydroxycholecalciferol form of vitamin D (less active)
  - The liver in infants is not that functional for the first hydroxylation of cholecalciferol
  - Requires up to 4,000 units/day of vitamin D3 supplementation in mother to achieve healthy levels in infants
- Breastfed babies should be supplemented with vitamin D3 immediately after birth

Vitamin D: Pregnancy/Infancy

- Premature labor and preeclampsia
- Increased risk of low birth weight
- Rickets, weaker bones, fractures
- Defects in tooth enamel, dental caries
- Hypocalcemic seizures or tetany
- Type I diabetes
- Asthma
- Allergies
- Viral bronchitis and pneumonia in first year of life
- Anemia with low hemoglobin
- Multiple sclerosis in adulthood
- Neurodevelopmental disorders

Signs of Vitamin D Deficiency

• Gastrointestinal: malabsorption, GERD
• Autoimmune: allergies, asthma, type 1 diabetes
• Bone/muscular: dental caries, bone fractures, osteomalacia, osteoporosis, muscular pain or sprains
• Neuropsychiatric:
  – Developmental disorders
  – Attention deficit disorder
  – Mood disorders: depression, bipolar disorder
  – Psychotic disorders: schizophrenia
  – Headaches
Autism Spectrum Disorders

- Increased rates of autism in blacks (or dark-skinned individuals who immigrated to the north) vs whites
- Increased rates of autism in northern latitudes
- Increased rates of autism births in the winter, especially in March, when vitamin D levels are low
  - Storage of vitamin D may be lowest in March after a long winter with little sunlight exposure
- Children conceived in winter have increased risk of being diagnosed with autism (December – March)

Mood Disorders: Depression

• Association between low vitamin D levels and depression:
    • Reduction in depressive symptoms for over 800 IU D3 in postmenopausal women
Mood Disorders: Depression

- **Equivocal results**

- **No benefit of high doses (500,000 IU D3/yr for 3-5 yrs) in women 70 yrs and older**
Children (N=67) with severe mental health disorders, including psychosis, had twice the rate of vitamin D deficiency as mentally healthy children

- < 20 ng/ml 25(OH)D = deficiency
  - 21% (1 out of 5)
- < 30 ng/mL 25(OH)D = insufficiency
  - 61% (2 out of 3)

“The prevalence of vitamin D deficiency (43%) was most common in children with psychotic disorders compared to other mental health disorders.”

Zhang M et al. Presented at: 164th Annual Meeting of the American Psychiatric Association; NR01-67; May 2011; Honolulu, HI.
Schizophrenia

- **Decreased Risk**
  - Increased sun exposure
  - Vitamin D supplementation during first year of life (for males only)

- **Increased Risk**
  - Black skin
  - Winter births (December – March)
  - Low levels of 25(OH)D

Cognition

- Vitamin D has vasculoprotective roles in the brain
- Vitamin D deficiency is associated with cognitive impairment in elderly women, all-cause dementia, Alzheimer’s disease, stroke (with and without dementia symptoms), and cerebrovascular disease
  - Vitamin D supplements may improve or maintain cognition
  - Important role in brain function and development

Alzheimer’s Disease: 2010 Report

- African-Americans are about twice as likely to have Alzheimer's disease than whites, and Hispanics are about 1.5 times more likely than whites to develop the disease.
- No known genetic factor for these differences.
- High blood pressure and diabetes are more prevalent in the African-American and Hispanic communities.
- No mention of darker skin color or possible link with vitamin D deficiency.

Parkinson’s Disease

- Vitamin D insufficiency (lower 25(OH)D levels ≤ 30 ng/mL) reported in patients with PD compared to controls
  - Lower sun exposure and decreased activity outside

- More severely affected PD patients had a higher prevalence of 25(OH)D deficiency than less severely affected patients with a shorter disease duration

Multiple Sclerosis

• Possible association between the amount of sunlight that children are exposed to and whether or not they will develop MS as adults

• Most cases of this degenerative neural disorder are in the temperate regions of the world, where the sunlight is rarely intense

• Children growing up in tropical and subtropical regions rarely develop MS regardless of where their ancestors came from

Multiple Sclerosis

• Decreased Risk
  – Increased sun exposure during early life
  – UV exposure and 25(OH)D inversely associated with MS relapse
  – Fall births
  – White skin lowers prevalence of MS disability
  – Consumption of fish 3-4 times a week
  – Intake of vitamin D is inversely associated with MS risk

• Increased Risk
  – Darker-skinned immigrants in higher latitudes
  – Spring births
  – Low fish intake and high meat/dairy products intake

Macular Degeneration

• Chronic, late-onset disease due to degeneration of the macula
  – Leading cause of irreversible vision loss in developed countries
  – Affects approximately 8.5 million Americans aged 40 yrs and older
  – No cure for the condition

• Vitamin D may protect against age-related macular degeneration (AMD)
  – Reduces inflammation

Potential Benefits of Vitamin D

• Skeletal
  – Improved bone density and fewer fractures and falls

• Nonskeletal
  – Lowered mortality rate – elderly women in institutions
  – Reduced risk of cancer
  – Reduced risk of multiple sclerosis
  – Reduced risk of allergy and asthma
  – Reduced risk of infections
  – Reduced risk of renal disease
  – Reduced musculoskeletal pain
  – Reduced risk of mental illness

Summary

• Vitamin D deficiency is very common and a potentially serious problem

• Requires population-based screening of serum 25(OH)D levels
  – High-risk and critically ill patients
  – Serum levels 30-100 ng/mL (~ 40-60 ng/mL)

• Supplements should be titrated to achieve serum levels
  – Vitamin D2 vs D3
  – Daily vs weekly vs monthly dosing
  – Monitor upper limits closely: > 10,000 IU/d D3 or > 100 ng/mL 25(OH)D
Research Questions

- Serum 25 (OH)D levels: what is the best for bone vs whole body health?
- Is there a safe level of sun exposure that provides sufficient vitamin D levels but does not increase the risk of skin cancer?
- Does high doses of calcium plus vitamin D cause toxicities (e.g., hypercalcemia, kidney stones)?
- Does vitamin D induce CYP3A4 enzymes and increase the metabolism of CYP3A4 substrates?
- Studies needed for preventative and treatment effects of vitamin D on mortality, cardiac disease, cancer, diabetes, autoimmune disorders, infections, and neuropsychiatric disorders