Vitamin D
An update on the sunshine vitamin
Goals of this session

- Evaluate data behind a growing list of illnesses associated with Vitamin D deficiency
- Develop a practical approach to screening
- Discuss guidelines for treatment of deficiency and insufficiency

34,000 articles written in 2012

50% of US adults take Vitamin D
Production of the “sunshine” vitamin

- Formed by ultraviolet B (UVB)-mediated photolysis of 7-dehydrocholesterol in the skin
- Pleiotropic hormone with a multitude of cellular effects
  - membrane and nuclear receptors
  - receptor-independent actions
7-dehydrocholesterol
Provitamin D3

Sun 
UV-B radiation
Skin

Vitamin D3

INTESTINE

LUNG

Muscle

Liver

1,25(OH)2D
Biologically active

25OHD3

Kidney
### Vitamin D levels

<table>
<thead>
<tr>
<th>Status</th>
<th>Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>&lt;20 ng/ml</td>
<td>&lt;50 nmol/L</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>20 - 30 ng/ml</td>
<td>50 - 75 nmol/L</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>30 - 88 ng/ml</td>
<td>75 - 220 nmol/L</td>
</tr>
<tr>
<td>Toxicity</td>
<td>88 - 125 ng/ml</td>
<td>&gt;220 nmol/L</td>
</tr>
</tbody>
</table>
### Barriers

<table>
<thead>
<tr>
<th>Physical barriers</th>
<th>Decreased absorption</th>
<th>Decreased production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clothing</td>
<td>Increased skin pigmentation</td>
<td>Aging skin</td>
</tr>
<tr>
<td>Sun screen (SPF 15 or above)</td>
<td>Medications</td>
<td><strong>Decreased bioavailability</strong></td>
</tr>
<tr>
<td>Living in latitudes above 37°N</td>
<td>Fat malabsorption syndromes</td>
<td>BMI &gt;30 kg per m²</td>
</tr>
<tr>
<td>Living in latitudes below 37°S</td>
<td>(Crohn’s, gastric bypass)</td>
<td></td>
</tr>
<tr>
<td>Time of day</td>
<td><strong>Decreased conversion</strong></td>
<td></td>
</tr>
<tr>
<td>Season</td>
<td>Chronic renal disease</td>
<td></td>
</tr>
<tr>
<td>Glass shielding</td>
<td>Severe hepatic disease</td>
<td></td>
</tr>
</tbody>
</table>
Symptoms of deficiency

- Body aches
- Low back pain
- Proximal muscle weakness
- Bone pain over the sternum or tibia
- Severe deficiency - Rickets
Who needs Vitamin D?

- 40-100% community dwelling elderly men and women are deficient in vitamin D
- Increased numbers among those with chronic illness, non-whites, hospitalized or home bound patients
- Boston teens – 24% deficient, 42% insufficient levels

UptoDate Vitamin D deficiency rates 2009
Arch Ped Adolesc Med. 2004; 158:531-7
What does the research say?

• Associated with many illnesses, disease states
• Sorting through the data can be a challenge

Key to grades
A Strong supportive evidence
B Good supportive evidence
C Unclear evidence
D Fair evidence against use
F Good evidence against use
Vitamin D Deficiency

Repletion of vitamin D is recommended in individuals with deficiency.

Check calcium to rule out subclinical hypercalcemia.
Osteomalacia

• 64% postmenopausal women to have Vitamin D levels below 30 ng/ml
• Increased bone turnover markers below 30 ng/ml
• Adequate stores (> 30 ng/ml) have been shown to decrease hip fractures by 16%, reduce non-vertebral fractures by 20%
• Need 1000-1200 mg calcium with Vitamin D to maximize benefit

Falls

• Adequate stores (> 30 ng/ml) have been shown to decrease falls in patients older than 65 years by 19%

• Improves lower extremity function - 8 foot walk test and repeat sit/stand

Osteoporosis

- May be useful in bone loss due to long term corticosteroids or anti-seizure meds
- Reduces the likelihood of fractures
- Most effective with 1000-1200 mg calcium
- No increased risk of death from Vitamin D

Cochrane Summaries, 14 April 2014
Diabetes Mellitus

- Receptor on the β islet cells in the pancreas for Vitamin D
- Inverse relationship between blood glucose, insulin resistance and Vit D levels in young adults
- Serum Vit D levels positively correlate with insulin sensitivity
- Deficiency increases mortality risk in DM2
Fibromyalgia

• Low Vitamin D associated with widespread pain
• Supplementation has been shown to aid in reduction of muscle weakness and pain
• May take up to 3 months of treatment for resolution of symptoms
Depression

- Vitamin D receptors in the hypothalamus
- Inverse relationship with Vit D levels and severity of depression
- Light exposure – not just Vitamin D supplementation - also a cofounding factor
- One study found Vit D better than light therapy

GI illnesses

• Reduced levels common in Crohn’s disease and other inflammatory bowel issues
• One study showed 50% lower risk of flare with 1200 IU daily for one year
• Also may help reduce bone loss while on steroids
• Monitor for hypercalcemia
Increased interest in Vitamin D receptors gene polymorphisms influence cancer by

- Anti-proliferative
- Anti-angiogenic
- Anti-metastatic
- Apoptopic effects
General Cancer Risk Reduction

- Decreases in **all-cause mortality** and cancer-related mortality
- Using trial sequential analysis concluded results could be due to random errors
- Did **not** find firm evidence that vitamin D supplementation decreases or increases cancer occurrence in predominantly elderly community-dwelling women

Cochrane Summaries, February 2014
Breast Cancer Risk Reduction

- Calcitriol significantly inhibits cancer cell growth in vitro especially in breast, colon, prostate and ovarian tissue.
- Highest quartile had 45% reduced risk v. lowest for both Vit D and calcium supplementation.
- Most significant in (ER+ PR+) women but still some effect with (ER+PR-) (ER-PR-).
- Possible explanation for increased risk in darker skinned populations.
Breast Cancer Risk Reduction

• Garland et. al. 2007 - Estimated prevention of 58,000 cases per year with year round levels of 40-60 ng/ml

• Abbas et. al. 2008 - Lower risk of post-menopausal breast cancer
Prostate Cancer Risk Reduction

- Prostate cancer cells have Vit D receptors
- Prospective and retrospective epidemiologic studies show deficiency is associated with risk prostate cancer
Multiple Sclerosis

- Characteristic geographical pattern of disease occurrence and progression
- Appear to be correlated with sun light exposure and lack of vitamin D and are considered to be predisposing factors for MS
- Deficiency is associated with poorer neurologic outcomes

Cochrane Summaries Dec 2010
Polycystic Ovary Syndrome

• Vitamin D influences glucose regulation
• Very small trial – 13 women w PCOS and vitamin D deficiency
  – repletion and calcium supplementation established regular cycles and 2 pregnancies

Asthma

• 616 children serum vitamin D levels associated with airway reactivity, hospitalization, use of anti-inflammatory drugs
• Lower levels inversely associated with recent URI
• JAMA, May 2014, supplementation did not reduce acute exacerbation rates

• Levels of >20 ng/ml translated to a 65% reduce risk
• Seems to be neuroprotective in animal models of Parkinson’s
• 114 people with Parkinson’s given 1200 IU D3 or placebo
  – Those with gene versions called FokI TT and FokI CT showed far less deterioration in their staging
  – Those with FokI CC did not show benefit

Hypertension

- Insufficiency may be linked to high blood pressure
- Blood pressure is often higher during the winter season, at a further distance from the equator, and in people with dark skin pigmentation
- Evidence is unclear. More research is needed in this area.
Coronary Artery Disease

- Deficiency associated with increased risk of CAD particularly <15 ng/ml
- 62% risk cardiovascular event <20ng/ml
- Intolerance of statins also associated with lower Vit D levels – may resolve with replacement of D
Cardiovascular Disease

• Richard Weller, dermatologist from Edinburgh, noted increased CVD risk
• Cardiovascular mortality is linked to the geographic region not the place of origin
• Blocked UVB – no benefit
• Studied skin storage of (NO) and proposed that it was the conversion of (NO) storage molecules to (NO) that caused the reduction in blood pressure

Sunshine

- Direct sun results in Vitamin D production – the amount needed varies greatly by skin pigmentation
- Sunshine may have added benefits including reduction in blood pressure, mental health benefits
Food Sources

- Oily fish – wild salmon (900 IU), sardines (450 IU), tuna (400 IU)
- Vitamin D supplemented foods including cereals, orange juice, dairy – have small amounts – (100 IU in 8oz milk or OJ)
- Mushrooms exposed to UV light (750 IU)
- Beef or calf liver (50 IU)
- Egg yolk (20 IU)
## Food sources of Vitamin D

<table>
<thead>
<tr>
<th>Natural Sources</th>
<th>Approximate IU D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod liver oil</td>
<td>400-1000 IU/tsp</td>
</tr>
<tr>
<td>Salmon, fresh, wild</td>
<td>600-1000 IU/3.5 oz</td>
</tr>
<tr>
<td>Salmon, fresh, farmed</td>
<td>100-250 IU/3.5 oz</td>
</tr>
<tr>
<td>Salmon, canned</td>
<td>300 IU/3.5 oz</td>
</tr>
<tr>
<td>Tuna, canned</td>
<td>230 IU/3.6 oz</td>
</tr>
<tr>
<td>Mackerel, canned</td>
<td>250 IU/3.5 oz</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>300 IU/3.5 oz</td>
</tr>
<tr>
<td>Egg yolks</td>
<td>20 IU/yolk</td>
</tr>
<tr>
<td>Shiitake mushrooms, fresh</td>
<td>100 IU/3.5 oz</td>
</tr>
<tr>
<td>Shiitake mushrooms, sun-dried</td>
<td>1600 IU/3.5 oz</td>
</tr>
<tr>
<td>Breast milk</td>
<td>20 IU/liter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fortified Sources</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified milk</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>100 IU/serving</td>
</tr>
<tr>
<td>Fortified orange juice</td>
<td>100 IU/8 oz</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>100 IU/8 oz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescription Supplements</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D2 capsules (ergocalciferol)</td>
<td>50,000 IU/capsule</td>
</tr>
<tr>
<td>Vitamin D2 liquid (Drisdol)</td>
<td>8000 IU/ml</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (calcitriol [Rocaltril])</td>
<td>0.25, 0.5 mcg and 1.0 mcg/ml</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (calcitriol [Calcijex])</td>
<td>1 mcg/ml for injection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplements Available Over the Counter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamin (D2 or D3)</td>
<td>400 IU</td>
</tr>
<tr>
<td>Vitamin D3 (cholecalciferol) capsules</td>
<td>400, 800, 1000, 2000, 5000 IU/capsule</td>
</tr>
</tbody>
</table>
Supplementation

• US RDA guidelines developed assuming limited light exposure
• D3 (cholecalciferol) increases stores more easily
• 400 IU 0-12 months
• 600 IU for those 1-70 years of age and pregnant or breastfeeding women
• 800 IU for those over 71 years of age
Toxicity

- Excessive solar UV-B irradiation will not cause intoxication because excess vitamin D3 and previtamin D3 are photolyzed into biologically inactive products by the skin.
- Nausea, poor appetite, vomiting, pancreatitis, nephrocalcinosis, vascular calcinosis, metallic taste and headache.
- Toxicity is an elevated vitamin D level greater than 100 ng/mL but the IOM feels there is no benefit to greater than 50 ng/mL and increased risk of side effects.
What are our patients doing?

50%

58% > age 65
Supplemental forms

Prescription
Vitamin D2 (Ergocalciferol) 50,000 IU
Vitamin D2 liquid (Drisdol) 8000 IU/ml
1,25-dihydroxyvitamin D (calcitriol [Rocaltrol]) 0.25, 0.5, 1.0 mcg/ml
1,25-dihydroxyvitamin D (calcitriol [Calcijex]) 1mcg/ml for injection

OTC
Multivitamin (D2 or D3) 400 IU
Vitamin D3 (cholecalciferol) 400, 800, 1000, 2000, 5000
Vitamin D3 (cholecalciferol) drops can be up to 1000 IU/drop
$25-33 billion/year
DNA barcode results from blind testing of the 44 herbal products representing 12 companies.

High risk populations

- More than 35 – 40° N or S of the equator (Hartford is at the 42\(^{nd}\) parallel)
- Darker skin
- Obese
- Little sun exposure
- Elderly
- Glucocorticoid ingestion
- Anti convulsant therapy
- Malabsorption syndromes

Consider testing
Testing

• 25(OH)D serum assay
• Average cost between $75-$175
• Medicare coverage of initial vitamin D level testing is currently limited to:
  – Chronic kidney disease
  – Osteopenia
  – Osteomalacia
  – Hypercalcemia
  – Malabsorption syndromes
  – Rickets

I have never had a problem with using Vitamin D Deficiency – 268.9
Repletion in adults

D2 (Ergocalciferol)
• 50,000 IU orally once weekly for 8 weeks
• Followed by 50,000 IU twice monthly as maintenance

D3 (Cholecalciferol)
• 50,000 IU orally once weekly for 8 weeks
• Followed by 50,000 IU twice monthly as maintenance

*Repeat 25(OH)D testing after 8 weeks
*May need to repeat loading dose of 50,000 for a 2-4 weeks if levels remain low
Repletion in children

D2 (Ergocalciferol)
• 1000-2000 IU/day orally for 8 weeks or
• 50,000 IU orally once weekly for 6 weeks
• Followed by 400-1000 IU/day as maintenance;

D3 Cholecalciferol
• 1000-2000 IU/day orally for 8 weeks or
• 50,000 IU orally once weekly for 6 weeks
• Followed by 400-1000 IU/day as maintenance

*Repeat 25(OH)D testing after 8 weeks
*May need to repeat loading dose of 50,000 for a 2-4 weeks if levels remain low
Summary

• Think about deficiency
• Test high risk patients
• Consider recommending supplementation from September-April in Connecticut for most people
Kathleen N. Mueller, M.D.
Holistic Health Partnering, LLC
Windsor, CT
mueller@holisticmds.net

Center for Integrative medicine
St. Francis Hospital and medical Ctr
kmuelle@stfranciscare.org