Vitamin D and HIV

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Vitamin D synthesis and metabolism

UVB → Skin → ProD → PreD → Vitamin D3 → Liver → 25(OH)D → Kidney → 1,25(OH)2D → Intestines → Bone → Increase calcium and phosphorus absorption → Mobilize calcium stores → Maintain serum calcium and phosphorus

Diet
- Limited dietary sources of vitamin D:
  - Fortified milk
  - Fortified orange juice
  - Salmon and other fatty fish
  - Vitamin supplements

Bruce W. Hollis, and Carol L. Wagner CMAJ 2006;174:1287-1290
Functions of Vitamin D

Vitamin D

Liver

25(OH)D

Kidney

1,25(OH)_2D

Calcium homeostasis
Muscle health
Bone health
Blood pressure regulation
Cardiovascular health
Neurodevelopment
Immunomodulation

Immunomodulation
- Prevention of autoimmune diseases
- Control of invading pathogens

Prostate gland
Breast
Colon
Lung
Keratinocytes

1,25(OH)_2D

Regulation of cell growth and differentiation

Bruce W. Hollis, and Carol L. Wagner CMAJ 2006;174:1287-1290
Based on Institute of Medicine (IOM)

- Vitamin D deficiency – 25 hydroxyvitamin D < 20ng/ml
- Vitamin D insufficiency - 25 hydroxyvitamin D – 21 to 29 ng/ml

Other Osteoporosis organizations- NOF, IOF favor a minimum level of 30 ng/ml for skeletal health

Prevalence of Vitamin D deficiency

- NHANES (2005-2006) -41.6% adults had 25(OH)D <20ng/ml
- Vitamin D deficiency is common in Australia, the middle east, India, Africa and South America
Prevalence of Vitamin D deficiency in HIV infected individuals
• Ranging between 70.3 to 83.7 %

Risk Factors for Vitamin D deficiency in HIV infected individuals

In addition to traditional risk factors

• Malnutrition and reduced intake of fortified foods
• Malabsorption
• Frequent hospitalizations
• HIV infection – chronic inflammation, ↑TNF –α, ↓ PTH
• Effects of antiretroviral therapy

Effects of antiretroviral therapy on Vitamin D

Protease inhibitors – Darunavir and Ritonavir

- Inhibit 1α and 25 α –hydroxylation
- Reduction of 25 hydroxyvitamin D to active 1,25 dihydroxy Vitamin D

Non–nucleoside reverse transcriptase inhibitors (NNRTI)

- Efavirenz reduces the expression of the cytochrome P450 enzyme CYP2R1 which is involved in converting vitamin D3 into 25 hydroxyvitamin D
- Efavirenz upregulates CYP24 which converts active vitamin D to inactive metabolites

Wohl DA et al. Antivir Ther 2014;19:191-200
Nucleotide analogue reverse transcriptase - Tenofovir

- Increased PTH
- Elevated vitamin D binding protein
- Reduced free 1,25 dihydroxyvitamin D levels
- Functional vitamin D deficiency

Overton et al, Ann Intern med 2015;62:815-824
Consequences of Vitamin D deficiency

• Decrease in intestinal calcium and phosphorus absorption of dietary calcium and phosphorus
  - only 10-15% of dietary calcium and 60% phosphorus are absorbed vs 30-40% of calcium and 80% of phosphorus

• Secondary hyperparathyroidism
  - mobilizes calcium from bones
  - increase in osteoclastic activity with low BMD

• Phosphaturia caused by secondary hyperparathyroidism
  - Low normal/low serum phosphorus level
  - Inadequate calcium-phosphorus production with defective mineralization of skeleton

Holick et al JCEM, July 2011, 96(7):1911-1930
Clinical manifestations of Vitamin D deficiency

- Mild Vitamin D deficiency may be asymptomatic
- Severe Vitamin D deficiency (25hydroxyvitamin D <10 ng/ml) when prolonged leads to osteomalacia
- Bony pain and tenderness
- Proximal muscle weakness
- Diffuse muscle pain
- Difficulty walking –waddling gait
- Recurrent falls
- Fracture
Evaluation of severe Vitamin D deficiency

- Basic metabolic panel
- Serum Calcium, Phosphorus
- Alkaline phosphatase
- Parathyroid hormone
- Celiac antibodies
- X rays to evaluate bony pain

- Screening is recommended only in individuals at risk for deficiency – HIV infected patients on antiretroviral therapy, HIV infected patients with low BMD, osteoporosis and fragility fracture

Holick et al JCEM, July 2011, 96(7):1911-1930
## Recommended Daily Vitamin D intakes

<table>
<thead>
<tr>
<th>Life stage group</th>
<th>IOM Estimated average requirement</th>
<th>IOM RDA</th>
<th>Upper limit</th>
<th>Endo society Daily requirements</th>
<th>Endo society Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (19-70 yrs)</td>
<td>400 IU/d</td>
<td>600 IU/d</td>
<td>4000 IU/d</td>
<td>1500 -2000 IU/d</td>
<td>10,000 IU/d</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>400 IU/d</td>
<td>800 IU/d</td>
<td>4000 IU/d</td>
<td>1500 -2000 IU/d</td>
<td>10,000 IU/d</td>
</tr>
<tr>
<td>Pregnancy and lactation</td>
<td>400 IU/d</td>
<td>600 IU/d</td>
<td>4000 IU/d</td>
<td>1500 -2000 IU/d</td>
<td>10,000 IU/d</td>
</tr>
</tbody>
</table>

*Holick et al JCEM, July 2011,96(7):1911-1930*
Recommendations for treatment of Vitamin D Deficiency

• All adults who are vitamin D deficient be treated with 50,000 IU of Vitamin D2 or Vitamin D3 once a week for 8 weeks followed by maintenance dose of 1500-2000 IU/day of Vitamin D3

• Obese adults, patients with malabsorption syndromes and patients on medications affecting Vitamin D metabolism need 2-3 times higher doses to treat vitamin D deficiency

• Liquid forms of Vitamin D2 (8000 IU/ml) available

• IM injections are extremely painful and hard to obtain in US
Monitoring for Vitamin D

• 25(OH)D is best indicator to monitor vitamin D status typically 1 month after repletion of high dose ergocalciferol

• 1,25 dihydroxyvitamin D does not reflect vitamin D status-can be normal or even elevated in vitamin D deficiency due to secondary hyperparathyroidism

• Measurement of 1,25 dihydroxyvitamin D is useful in
  • Chronic kidney disease
  • Hereditary phosphate losing disorders
  • Oncogenic osteomalacia
  • Vitamin D resistant rickets
  • Chronic granulomatous disorders such as sarcoidosis and lymphomas
Vitamin D and Calcium attenuate bone loss with Antiretroviral therapy initiation-A Randomized trial

- 48 week prospective, randomized, double-blind, placebo controlled study

- To evaluate the effect of vitamin D3 plus calcium supplementation on bone loss associated with antiretroviral therapy

- 79 adults with antiretroviral therapy-naïve HIV received vitamin D3 (4000 IU) plus 500mg of calcium carbonate twice daily and 86 received placebo

- Antiretroviral therapy initiated was EFV/FTC/TDF

Overton et al, Ann Intern med 2015;62:815-824
Vitamin D and Calcium attenuate bone loss with Antiretroviral therapy initiation - A Randomized trial

- Supplementation with high dose Vitamin D3 (4000 IU) and calcium carbonate (1000mg) with ART initiation increased 25 (OH)D levels (median change 28.6 ng/ml)

Overton et al, Ann Intern med 2015;62:815-824
Vitamin D and Calcium attenuate bone loss with Antiretroviral therapy initiation - A Randomized trial

- Attenuated increases in bone turnover markers and bone loss at the hip and lumbar spine by about 50% at 48 weeks

**Figure 3. Percentage of BMD change from baseline to 48 wk.**

- Vitamin D3 plus calcium supplementation mitigates the BMD loss seen with initiation of EFV/FTC/TDF (efavirenz/emtricitabine/tenofovir)
Take home points

• There is increased prevalence of vitamin D deficiency in HIV infected patients from malnutrition, malabsorption and certain antiretroviral agents
• Screening is recommended in individuals at risk for deficiency—HIV infected patients on antiretroviral therapy, HIV infected patients with low BMD, osteoporosis and fragility fracture
• Most organizations favor 25 hydroxyvitaminD level more than 30ng/ml for optimal skeletal health
• All adults who are vitamin D deficient should be treated with 50,000 IU of Vitamin D2 or Vitamin D3 once a week for 8 weeks followed by maintenance dose of 1500-2000 IU/day of Vitamin D3
• A recent study has shown Vitamin D3 plus calcium supplementation mitigates the BMD loss seen with initiation of EFV/FTC/TDF
Thank you