Vitamin D and HIV-infection

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Vitamin D and HIV infection

• Metabolism vitamin D
• Functions vitamin D
• Vitamin D deficiency
  • Global
  • HIV-infection
• Vitamin D supplementation study
  • Metabolic effects
  • Immunological effects
Vitamin D metabolism is complex and depends on CYP450 activity, 1,25OHVD is the active metabolite that binds to vitamin D receptor

Functions vitamin D

VDR present on bone, skin, parathyreoid gland, pancreas, adipose tissue, immune system, CNS

- Calcium phosphate homeostasis
- Bone mineralisation
- Diabetes
- Psoriasis
- Cognitive impairment, MS
- Auto-immune disorders,
- Cancer
- Infections: TB !! HIV (Sanchez dela Torre JID 2008 and Mehta, JID 2009)
Vitamine D and immunemodulation

Vitamine D receptor monocytes/macrophages

• 1α-hydroxylase in APC (macrophagen)
• 24-hydroxylase in macrofaag

Vitamine D (\textit{in-vitro} 1,25(OH)\textsubscript{2}D\textsubscript{3} stimulation PBMCs):

• ↓ Th1 celrespons (IFN\gamma, TNF\alpha)
• ↑ Th2 celrespons (IL-10, IL-4, IL-5)
• ↑ CD4\textsuperscript{+}CD25\textsuperscript{+} regulatoire T-cellen (IL10, TGF\beta)

Vitamin D deficiency

Plasma level of 25(OH)VD is the marker vitamin D status !
Plasma levels 1,25(OH) VD reflect P450 (27B1) activity ?
Differences in assays methodology
Age, gender, ethnicity, latitude, clothing, nutrition, skin pigment, culture, living conditions, season,...
Vitamin D deficiency

Optimal level of 25(OH)VD is unknown!
Plasmalevel 25(OH)VD related to health consequences?
- Suppression PTH or calcium absorption
- Bone mineral density
- Fractures
- Inflammation....

Definition:
- Vitamin D insufficiency: 25-50 nmol/L → Muscle weakness
- Vitamin D deficiency: < 25 nmol/L → Falls
- Severe VD deficiency: < 12.5 nmol/L: Rickets, osteomalacia

Global problem, especially India, China, Middle East
Europe: South > North
Immigrants: Netherlands 22% turkish women undetectable (van der Meer IM A J Clin Nutr 2006)

General
- Age
- Sex
- BMI
- Ethnicity
- Vitamin D intake
- Sunexposure
- Medication eg anti-epileptica, corticosteroïden

Additional for HIV
- HIV virus
- HIV medication?
- ↓ Production by monocytes?
- ↑ Usage by macrophages?
Haug et al. 1998: No HAART:
- 54% 1α,25(OH)₂D₃ deficient
- Normal 25(OH)D

Seminari et al. 2005: HAART:
- 81.5% 25(OH)D <18ng/ml
- 1,25(OH)₂D₃ not analysed

Stephensen 2006: Comparing HIV pos and HIV neg subjects:
- No difference HIV + & -
- High prevalence VD deficiency
- Disadvantaged urban USA youth

Stephensen, Am J Clin Nutr 2006;83:1135-1141
Prevalence Study Nijmegen

Screening:
Parameters:
• 25(OH)D, 1,25(OH)D
• PTH, Ca, Fosf, alb, kreat,
• ALAT, ASAT, gamma-GT, AF
• CD4, CD8 en VL.
Questionaire: vitamin D intake, sunexposure

Included:
Nijmegen  n = 252,  73 deficiënt (29%)

Bout et al AIDS Research and Human retroviruses 2008: 24(11): 1375

Results prevalence study

White PI vs white NNRTI p = 0.007
White PI vs white no-treatment, p = 0.049
Results prevalence study

Univariate analysis: risk factors for 25(OH)VD deficiency

- **Sex**: female (58.1%) vs male (24.7%); p = 0.010
- **Skin pigment**: white (19%) vs Mediterranean (33%) vs Asian (44%) and Black patients (62%). $P_{\text{black vs blank}} = <0.001$
- **Treatment**: untreated 24.5% treated 30%; PI 23% en NNRTI 36.5%. PI vs NNRTI ($P_{\text{NNRTI vs PI}}=0.07$)
- Sunlight, supplements, diets were not different

• Vitamin D deficiency 29% HIV-1-patients
• Multivariate analysis: skin colour
• Inverse correlation PTH and 25(OH)VD ($r: -0.394$, $p< 0.001$)

PTH levels

- No HAART: 2.98 (2.15 - 3.68)
- PI: 4.27 (3.26 – 5.46)
- NNRTI: 4.61 (3.30 – 6.89)

• NNRTI’s additional effect?
Other studies:

**Rodriguez** AIDS Research and Human retroviruses 2009: 25(1): 9
10-20 nmol/L: 36%
<10 nmol/L: 10%
Role NNRTI??

**Lattuada** AIDS Research and Human retroviruses 2009: 25(8): 849

Longitudinal study: AZT+3TC+NEV

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First year</th>
<th>Second year</th>
<th>Third year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (T-score)</td>
<td>−0.5±1.3</td>
<td>−0.27±1.2</td>
<td>−0.26±1.2</td>
<td>−0.24±1.2</td>
<td>0.102</td>
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<tr>
<td>Femoral neck (T-score)</td>
<td>−0.6±0.8</td>
<td>−0.5±0.7</td>
<td>−0.5±0.7</td>
<td>−0.4±0.7</td>
<td>&lt;0.001</td>
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<tr>
<td>PTH (pmol/liter)</td>
<td>5.7±2.4</td>
<td>6.4±5.7</td>
<td>5.4±1.7</td>
<td>5.1±1.1</td>
<td>0.308</td>
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<tr>
<td>Vitamin D (nmol/liter)</td>
<td>52.0±28.1</td>
<td>66.9±17.8</td>
<td>69.4±13.9</td>
<td>66.1±21.0</td>
<td>0.230</td>
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</tbody>
</table>

Vitamin D deficiency is common in HIV infected subjects

- Relation HIV ?
- Relation medication ?
- Relation to skin, ethnicity etc !

**Consequences?**

- Bone:
  - Osteopenia (14-84% in HIV)
  - Osteoporosis (0-45% in HIV)
- Metabolism
- Immunity
Vitamin D supplementation

- More adipocyte differentiation
- Less lipolysis
- Stimulation insulin secretion
- Increases number Tregs

Intervention study

HIV positive (n=20),
Vitamin D deficient,
No hypercalcemia
No renal hepatic disorder
No drug alcohol abuse
Compliant
No pregnancy

Supplementation 2000 IU colecalciferol for 14 weeks, thereafter 1000 IU, if 25(OH)D level > 50 nmol/L. Follow up 48 weeks.
Intervention study

Week 0, 12, 24, 48:
- 25(OH)D en 1,25(OH)D
- PTH
- Cholesterol triglycerides
- Adipokines: adiponectin, leptin
- CD4, CD8

Week 0, 24, 48
- Dexa (bone mineral density and fat mass and distribution)
- HOMA: fasting insulin x fasting glucose/22.5
- Treg

Results intervention study (1)
Results intervention study (2)

No effect on:

• Bone: BMD hip / spine (30% osteopenia baseline)
• Fat: BMI
total bodyfat %
trunk/limb fat % ratio
leptine and adiponectine levels
cholesterol and triglyceride levels

Results intervention study (3)

Effect on glucose and insulin sensitivity:

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 wk</th>
<th>48wk</th>
<th>p 0vs24</th>
<th>p 0vs48</th>
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<tr>
<td>Glucose</td>
<td>5.1 (4.7-5.6)</td>
<td>5.2 (4.8-6.0)</td>
<td>5.3 (4.8-5.9)</td>
<td>0.023</td>
<td>0.088</td>
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<tr>
<td>Insuline</td>
<td>9 (7-14)</td>
<td>9 (6-14)</td>
<td>10 (7-13)</td>
<td>0.151</td>
<td>0.637</td>
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<tr>
<td>HOMA-index</td>
<td>1.70 (1.58-3.09)</td>
<td>2.38 (1.94-3.77)</td>
<td>2.13 (1.68-2.58)</td>
<td>0.013</td>
<td>0.435</td>
</tr>
</tbody>
</table>
Intervention studies: conclusions

• Dose response effects vit D
• 2000 IE colecaltiferol resulted in elevation 1,25(OH)D, and:
  • ↓ PTH
  • ↓ insuline sensitivity

• Larger trials are needed to define the metabolic and immunological role vitamin D in HIV infections

Questions?