IS VITAMIN D IMPORTANT IN THE MANAGEMENT OF TUBERCULOSIS?

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Sources of Vitamin D

• **Diet:**
  Oily fish, egg yolk, liver, lard, dairy products; marge, soya milk, some breakfast cereals (fortified).

• **Sunshine:**
  London at 52° North – no radiation of appropriate wavelength (290-310nm) from end Oct to end March.
ON THE USE OF COD-LIVER OIL, IN DISEASES OF THE BONES AND JOINTS, IN CONSUMPTION AND IN OTHER MALADIES ATTENDED BY GREAT EMACIATION.

BY HENRY T. CHAPMAN, F.R.C.S., Late Senior Surgeon to the St. George's and St. James's Dispensary, Corresponding Member of the Hamburg Medical Society, &c. &c.

LONDON: PRINTED BY J. & I. TIREBUCK, MONKWELL STREET, FALCON SQUARE. 1849.
Cod liver oil supplements – did it protect children from TB?
Hospital for Consumption and Diseases of the Chest, Brompton, 1849

Green BMJ 2011;343:1305-7
### Results as shown in 1848 study

<table>
<thead>
<tr>
<th></th>
<th>Standard treatment</th>
<th>Standard treatment plus cod liver oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>542</td>
<td>535</td>
</tr>
<tr>
<td>Improved</td>
<td>60.8%</td>
<td>63.1%</td>
</tr>
<tr>
<td>Arrested</td>
<td>5.6%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Deteriorated or died</td>
<td>33.3%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>
Lupus vulgaris treated with calciferol: (a) Jan. 10, 1946, at start of treatment; (b) 14 days later.
## Vitamin D Deficiency & TB

*Sita-Lumsden et al., Thorax 2007*

<table>
<thead>
<tr>
<th></th>
<th>Culture +veTB (n=119)</th>
<th>Healthy Contacts (n=123)</th>
<th>(\chi^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean +/- SD</strong></td>
<td>18 [11.8]</td>
<td>29 [15.9]</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Normal levels</strong></td>
<td>3 (2.5%)</td>
<td>27 (22%)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>(&gt;39nmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe deficiency</strong></td>
<td>81 (68%)</td>
<td>46 (37%)</td>
<td>(p&lt;0.001)</td>
</tr>
<tr>
<td>(&lt;20nmol/l)</td>
<td></td>
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</table>
Biologically active

$1\alpha,25(OH)_2D_3$ (Calcitriol).
## Vitamin D Levels

<table>
<thead>
<tr>
<th></th>
<th>TB (178)</th>
<th>Contacts (128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean +/- SE</td>
<td>20.1 +/- 0.95</td>
<td>30.84 +/- 1.71**</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.14 to 14.34</td>
<td></td>
</tr>
<tr>
<td>Dark skinned</td>
<td>19.0 +/- 1.15</td>
<td>27.8 +/- 1.45**</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.19 to 12.41</td>
<td></td>
</tr>
<tr>
<td>Mid coloured</td>
<td>20.9 +/- 1.73</td>
<td>43.8 +/- 8.54**</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.53 to 34.27</td>
<td></td>
</tr>
<tr>
<td>Light skinned</td>
<td>24.4 +/- 3.63</td>
<td>36.7 +/- 4.89</td>
</tr>
<tr>
<td>95% CI</td>
<td>-6.69 to 17.97</td>
<td></td>
</tr>
</tbody>
</table>

**Numbers with Vitamin D levels**

- **<20 nmol/l**
  - 106 (60%)
  - 36 (28%)**
- **20-39 nmol/l**
  - 61 (34%)
  - 57 (45%)
- **40+ nmol/l**
  - 11 (6%)
  - 35 (27%)**

**p<0.001**

*(Sita-Lumsden et al., Thorax 2007)*
Summer sunlight exposure, daily dietary vitamin D intake and serum 25-OH-cholecalciferol levels.

<table>
<thead>
<tr>
<th></th>
<th>TB n=35</th>
<th>Contacts n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sun exposure:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Inadequate</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td><strong>Dietary vitamin D</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>micrograms</td>
<td>6.09(5.39)</td>
<td>6.06(8.2)</td>
</tr>
<tr>
<td><strong>Serum vitamin D</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nmol/l</td>
<td>21.1(2.52)</td>
<td>33.77(3.04)*</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.79 to 20.55</td>
<td></td>
</tr>
<tr>
<td>*p&lt;0.01</td>
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</table>
Seasonal variation in serum 25-OH-cholecalciferol concentrations in TB patients and contacts.

Contacts show an expected increase to normal concentrations in the summer months but this response was absent in patients with TB.

\[*p=0.013 \quad **p=0.027\]
Vitamin D as an Immunoregulatory Molecule

Mycobacterial ligand

TLR

CYP27R1

25(OH)D₃

1,25(OH)₂D₃

VDR
Vitamin D as an immuno-regulatory molecule

• TH1 mediated immune response important for host immunity to TB

• But in vitro, vit D suppresses IFNγ & IL12 production, & induces T regs

How can vit D then be beneficial in TB?
Vitamin D as an Immunoregulatory Molecule

- **1,25(OH)_2D_3** (calcitriol)
  - Upregulates NO Synthase
  - Inhibits supranoxides
  - Enhances lysosome fusion
  - Expression Cathelicidin
    - Inhibits replication MTB
  - Reduces inflammation
  - Inhibits IL12
    - IFNγ
    - TNFα
Vitamin D as an immuno-regulatory molecule

From *in vitro* studies, Vit D has two complimentary actions:

- Stimulates protective innate response in APCs
  - suppression growth MTB
- Damps down over-responsiveness in adaptive response to invading Ag.
<table>
<thead>
<tr>
<th>Ref; study design</th>
<th>Patients</th>
<th>Mean Baseline Serum Vit D Level</th>
<th>Dose of Vit D</th>
<th>Mean Final Serum Vit D Level</th>
<th>Outcome Measures</th>
<th>Therapeutic Response</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martineau 2007(^{39}) DBRCT</td>
<td>192 adult healthy contacts</td>
<td>35.2nmol/L</td>
<td>Single dose of 2.5mg</td>
<td>67.4nmol/L at 6 weeks</td>
<td>1. Ability of whole blood to restrict growth of reporter mycobacteria \textit{in vitro}; 2. IFN-(\gamma) responses to ESAT-6 &amp; CFP10</td>
<td>1. Significant enhancement of mycobacterial immunity; 2. Not affected</td>
<td>None</td>
</tr>
<tr>
<td>Nursyam 2006(^{40}) DBRCT</td>
<td>67 new cases of PTB &amp;15yrs</td>
<td>Not given</td>
<td>0.25mg/day for 6 weeks</td>
<td>Not given</td>
<td>1. 6 week sputum conversion; 2. 6 week radiological change</td>
<td>1. 100% in vitamin D group, 76.7% in placebo group (p=0.002); 2. Improvement in 87.5% vitamin D group, 65% placebo group</td>
<td>None reported</td>
</tr>
<tr>
<td>Wejse 2009(^{41}) DBRCT</td>
<td>365 adults with TB</td>
<td>77.5nmol/L (vitamin D), 79.1nmol/L (placebo)</td>
<td>3 doses of 100,000IU at inclusion, 5 and 8 months</td>
<td>105 &amp; 102nmol/L (vitamin D), 103 &amp; 95nmol/L (placebo) at 2 &amp; 8 months</td>
<td>1. Clinical improvement in clinical severity score; 2. All-cause mortality at 12 months; 3. Sputum conversion in smear +ve patients, weight gain and changes in CD4+ count.</td>
<td>1. Trend to improvement in HIV- vitamin D group; 2. Similar in both groups; 3. No difference</td>
<td>6% in vitamin D group, 9% in placebo group (usually thirst); Serum calcium above reference range in 1 vitamin D and 2 placebo patients.</td>
</tr>
</tbody>
</table>
Vitamin D supplementation regimens compared

400-800 IU vitamin D$_3$
daily

Single oral dose
100,000 IU
vitamin D$_2$

4 x oral
dose 100,000 IU
vitamin D$_3$
AdjuVIT Trial – 100,000Ux3

Patients with smear positive pulmonary TB

Randomise

Vitamin D + antibiotics  Placebo + antibiotics

Follow-up

Compare time to sputum culture conversion

Serum – vit D; FBC; Antigen stimulated cytokine release
Baseline vitamin D status

Serum 25(OH)D, nmol/L

131/135 < 75 nmol/L
Serum 25-hydroxyvitamin D

![Graph showing the increase in serum 25(OH)D levels over days of treatment. The graph compares Vitamin D and Placebo groups.](image-url)
Time to sputum culture conversion

Time to sputum culture conversion

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Influence of allocation by *TaqI* genotype of VDR

- TT: p = 0.67
- Tt: p = 0.63
- tt: p = 0.02

p for alloc* *TaqI* = 0.03

Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment.

*Coussens et al., PNAS 2012*

- Detailed analysis of longitudinal changes in inflammatory responses in trial participants
- 8 week intensive phase
- Circulating and antigen stimulated responses
- Effects of antibiotics vs effects antibiotics + vitamin D
Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment.

*Coussens et al., PNAS 2012*

**Effect of antibiotics:**
- Platelets and N down
- ESR and CRP down
- Hb, RBC parameters, albumin up

PCA Network Analysis:
- Ns linked to monos and CRP which are linked to IL6 and ESR
- PIs & CCL5 grouped
- Other IFNγ stimulated chemokines CXCL9 & CXCL10 linked to each other
  & IFNγ which linked to IL6
Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment.

Coussens et al., PNAS 2012;109:15449-54
Coussens et al. PNAS 2012
Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment.

- In all cases, vit D accel effect of anti-TB therapy
- N counts not signif affected but N assoc AMP, MMP-9 fell more quickly;
- Accelerated resolution of acute phase response (ESR, CRP)
- Vit D modulated immune responses in TT & Tt patients aswell as tt.

PCA Network Analysis – effect of vit D:
- Accelerated reduction in monos linked to inc Ly & reduction ESR & CRP;
- IFNγ inducible chemokines – CXCL9 & CXCL10 linked to IFNγ, IL2-R, IL10 & CCL3 reduced faster.

(Coussens et al., PNAS 2012;109:15440-54)
Conclusions of AdjuVit Study

• Vitamin D associated with reduced time to sputum conversion, especially in \textit{tt} genotype of \textit{Taq1} polymorphism of VDR;

• But immunomodulating properties not confined to individuals with \textit{tt} genotype of \textit{Taq1} polymorphism of VDR;

• Vit D accelerated resolution of inflammatory responses.
Vitamin D Binding Protein

- Transports vit D metabolites in blood
- Increased in mycobacterial infections
- ? Marker of acute inflammatory response or role in pathogenesis

- Assoc between Gc2/2 genotype and susceptibility to TB in Gujeratis with vit D <20;
- Not preserved with higher vit D levels, in Brazilian adults or SA children.

Is vitamin D important in the management of TB?

• Although time to sputum conversion only reduced in some patients, enhances anti-inflammatory effects of antibiotics;
• Country of birth and ethnic differences in serum vitamin D
• Ethnic differences in VDBP and inflammatory markers in TB; *(Coussens et al., PLoS Pathol 2013)*
• Role of higher doses?
• Role in MDR/XDR TB?
Acknowledgements

• Dr Adrian Martineau, Queen Mary University of London
• Dr Anna Coussens
• British Lung Foundation