Vitamin D and liver disease: Which role does it play?

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Vitamin D metabolism – potential interactions with hepatitis C or other liver diseases

Skin, Food → Cholecalciferol → Liver: 25-hydroxylase → 25-hydroxyvitamin D

Hepatitis C Virus:
- Cell proliferation
- Cell differentiation
- Apoptosis

Immune modulation

Kidney: 1α-hydroxylase (CYP27B1) → 1-25-dihydroxyvitamin D (Calcitriol) → Calcium homeostasis
Clinical evidence that vitamin D supplementation can be beneficial beyond bone metabolism

Vitamin D supplementation in addition to antibacterial chemotherapy reduces time to sputum conversion

Insufficient vitamin D status was associated with an increased incidence of inflammatory bowel diseases in a prospective observational trial (n>70,000, >20 years follow-up)

Ashwin et al, Gastroenterology 2012
Vitamin D and chronic hepatitis C
### Chronic hepatitis C is associated with severe vitamin D deficiency

<table>
<thead>
<tr>
<th>25(OH)D$_3$ (ng/mL)</th>
<th>All HCV Patients, n (%)</th>
<th>All, F0-1, n (%)</th>
<th>All, F2-4, n (%)</th>
<th>Control, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>115 (25)</td>
<td>57 (23)</td>
<td>42 (28)</td>
<td>1630 (12)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>310 (66)</td>
<td>159 (63)</td>
<td>107 (73)</td>
<td>5415 (41)</td>
</tr>
<tr>
<td>20-30</td>
<td>117 (25)</td>
<td>65 (25)</td>
<td>31 (21)</td>
<td>3968 (30)</td>
</tr>
<tr>
<td>30-100</td>
<td>37 (8)</td>
<td>27 (8)</td>
<td>8 (5)</td>
<td>3927 (29)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>23 (0.2)</td>
</tr>
</tbody>
</table>

Lange et al, J Hepatol 2011
Vitamin D deficiency is highly prevalent in patients with chronic hepatitis C even in summer.

Data from 468 patients with chronic hepatitis C enrolled in the Swiss Hepatitis C Cohort Study.

Vitamin D serum levels are not a reliable predictor of SVR

Petta et al, Hepatology 2010
Bitetto et al, Hepatology 2011
Baur K et al, Antivir Ther 2012
Mandorfer et al, AIDS 2012

Vitamin D Supplementation:
Abu-Mouch et al, World J Gastro 2011

Lange et al, J Hepatol 2011

Association bet. 25(OH)D3 and SVR
No association bet. 25(OH)D3 and SVR

Milazzo et al. Cur HIV Research 2011
Terrier et al. J Hepatol 2011
Grammatikos et al, EASL 2012
Stauber T, EASL 2011
Genetic association studies indicate a functional role for vitamin D in response to IFN-therapy.

CYP27B1 Genotyp

Studies on CYP27B1 and SVR
Lange et al, J Hepatol 2011
and unpublished data

Studies on VDR polymorphisms and SVR
Baur et al, Antivir Ther 2012
Synergistic effect of vitamin D and IFN-α on HCV replication

![Graph showing the synergistic effect of vitamin D and IFN-α on HCV replication for HCV gt 1b and HCV gt 2a.](image)
STAT1 constitutively interacts with VDR

Calcitriol - + + - | -Ag -Ab

VDR

STAT1

VDR

IP: STAT1

Input
Vitamin D and HCC
Vitamin D deficiency is partially inherited

**THE LANCET**
Wang et al., 2010; 376:180-88.

**GC** (vitamin D binding protein)
**DHCR7** (cholesterol metabolism)
**CYP2R1** (25-hydroxylase)

Genetic variations in these genes are associated with life-long risk of reduced vitamin D serum levels.

Associations between these variants and traits may provide better arguments for causal relationships than assessing punctual vitamin D serum levels.
Study design to investigate a possible relationship between vitamin D and HCV-related HCC

- Multicenter study including patients with chronic hepatitis C with or without HCC from the Swiss Hepatitis C Cohort Study (discovery cohort), as well as from three German and Japanese replication cohorts.

- Genotypes of CYP2R1, GC, and DHCR7 were determined and tested for associations between presence vs. absence of HCV-related HCC by logistic regression analyses.

- A total of 1279 and 4325 HCV-infected patients with or without progression to HCC was identified for these analyses.
Genetic analyses suggest a role for vitamin D insufficiency in HCV-induced HCC development

<table>
<thead>
<tr>
<th>Gene</th>
<th>Allele 1/2</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2R1</strong></td>
<td>A/G</td>
<td>0.64</td>
<td>0.63</td>
<td>0.07</td>
<td>1.13</td>
</tr>
<tr>
<td><strong>GC</strong></td>
<td>T/G</td>
<td>0.31</td>
<td>0.27</td>
<td>0.007</td>
<td>1.56</td>
</tr>
<tr>
<td><strong>DHCR7</strong></td>
<td>T/C</td>
<td>0.33</td>
<td>0.29</td>
<td>0.003</td>
<td>1.42</td>
</tr>
</tbody>
</table>
Vitamin D and liver fibrosis / steatosis
Vitamin D alters cytokine profiles which may translate in decelerated liver fibrosis progression

- Cholecalciferol supplementation decreases levels of IL-6, TNF-alpha, and TGF-beta, but not of IL-1, IL-8, or IL-10
- Supplementation prevents liver fibrosis progression in animal models
- However, no association between vitamin D serum levels and liver fibrosis progression has been observed in HALT-C

Vitamin D may ameliorate NAFLD

- Vitamin D serum levels are decreased in NAFLD patients, and inversely associated with insulin resistance and BMI
- VDR expression in liver specimens of NASH patients is inversely correlated with disease severity
- In an animal model, vitamin D deficiency exacerbated while phototherapy ameliorated NAFLD / insulin resistance

Conclusions

- Patients with liver diseases are at high risk of severe vitamin D deficiency.

- Clinical and *in vitro* data suggest a functional role of vitamin D in IFN-alfa-based therapy of chronic hepatitis C.

- Vitamin D deficiency may play a functional role in (HCV-induced) hepatocarcinogenesis.

- Vitamin D might be a therapeutic opportunity for NASH patients, data from clinical trials will be available shortly.

- Until data from controlled clinical trials for liver-specific endpoints are available, patients might be supplemented with vitamin D according to international guidelines for the prevention of bone disease (800-2000 IU/d, avoid high doses of calcium)