Vitamin D deficiency and hepatitis C

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

Skin, Food

Cholecalciferol

Liver: 25-hydroxylase

Liver: 25-hydroxyvitamin D

Kidney: 1α-hydroxylase (CYP27B1)

1-25-dihydroxyvitamin D = Calcitriol

Hepatitis C Virus

Cell proliferation
Cell differentiation
Apoptosis

Immune modulation

Calcium homeostasis
Clinical evidence that vitamin D can be beneficial beyond bone metabolism

Vitamin D metabolism was associated with:

- Autoimmune diseases (diabetes, multiple sclerosis, …)
- Cancer (colon, breast, ….)
- Infectious diseases (sepsis, tuberculosis, flue, ….)
- Death (>4000 persons, > 11 years follow-up)

Levin GP et al, JAMA 2012; Rosen CJ, NEJM 2011
25(OH)D3 in addition to standard therapy reduces time till sputum conversion in lung tuberculosis

Paricalcitol in addition to ACE-inhibitor reduces albuminuria in diabetic nephropathy
Does viral hepatitis impact on vitamin D metabolism?
Stage of liver disease correlates inversely with vitamin D serum levels

Petta S et al, Hepatology 2010
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
Seasonal variation of vitamin D serum levels

Data from 468 random Swiss patients with chronic hepatitis C

Vitamin D deficiency in patients with chronic hepatitis B

203 patients with treatment-naïve hepatitis B
(majority low replicative, HBe-Ag negative)

- 34%: 25(OH)D3 < 10ng/mL
- 47%: 25(OH)D3 ≥ 10 and < 20 ng/mL
- 19%: 25(OH)D3 ≥ 20ng/mL

Vitamin D serum levels according to HBV DNA serum concentration:

- <2,000 IU/mL: mean 25(OH)D3 = 17 ng/mL
- ≥2,000 IU/mL: mean 25(OH)D3 = 11 ng/mL (P<0.0001)
Determinants of low vitamin D serum levels in patients with chronic hepatitis B

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ Value, Univariate</th>
<th>$P$ Value, Multivariate</th>
<th>Standard Beta, Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (years, continuous)</td>
<td>0.3600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.1300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (Caucasian versus non-Caucasian)</td>
<td>0.6000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis (F1-F2 versus F3-F4)</td>
<td>0.1100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (U/L, continuous)</td>
<td>0.1900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT (U/L, continuous)</td>
<td>0.6300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$, continuous)</td>
<td>0.5100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (count/nL, continuous)</td>
<td>0.2900</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (presence versus absence)</td>
<td>0.7000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBeAg (positive versus negative)</td>
<td>0.0040</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA ($\log_{10}$ IU/mL, continuous)</td>
<td>0.0007</td>
<td>0.000048</td>
<td>−0.31</td>
</tr>
<tr>
<td>HBsAg ($\log_{10}$ IU/mL, continuous)</td>
<td>0.5800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Farnik H et al, Hepatology 2013
Seasonal fluctuations of vitamin D and HBV DNA serum levels in patients with chronic hepatitis B

P = 0.010 for HBV DNA
P < 0.000001 for 25(OH)D$_3$

Farnik H et al, Hepatology 2013
Does vitamin D impact on treatment outcome of hepatitis C?
Vitamin D serum levels are not a reliable predictor of SVR

Association bet. 25(OH)D3 and 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

No association bet. 25(OH)D3 and SVR

- 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

Studies on CYP27B1 and SVR
Lange et al, J Hepatol 2011
Grammatikos et al, Hepatology 2012
D´Avolio et al, Hepatology 2012

Studies on VDR / GC SNPs and SVR
Baur et al, Antivir Ther 2012
Falleti et al, Hepatology 2012
25(OH)D3 inhibits HCV RNA replication in vitro

Gal-Tanamy et al, Hepatology 2011

25(OH)D3 exposure selects resistant mutants in NS3!

Matsumara et al, Hepatology 2012
Calcitriol enhances IFN-α induces suppression of HCV replication \textit{in vitro}

\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{HCV_repli_stack.png}
\end{center}
\end{figure}

\textsuperscript{Lange et al, unpublished data}
Does vitamin D impact on the natural course of viral hepatitis?
Vitamin D supplementation alters cytokine profiles

Kinetics of serum cytokines during vitamin D supplementation (solid line) vs. placebo (dotted line)

Implications for prevention of steatosis / fibrosis?
Vitamin D prevents experimental liver fibrosis

- Vitamin D inhibits hepatic stellate cell activation / fibrosis
- \( Vdr \) ko mice spontaneously develop liver fibrosis
- TGF\( \beta \)1 signaling shifts the genome-wide binding locations of VDR
- VDR antagonizes SMAD3/TGF\( \beta \)1 activation of profibrotic gene

Ding et al, Cell 2013
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.
Inherited variations of vitamin D serum and risk of HCV-related HCC

- Genotyping of 1279 and 4325 HCV patients with or without HCC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk allele freq.</th>
<th>Allele 1/2</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2R1</td>
<td></td>
<td>rs1993116</td>
<td>A/G</td>
<td>0.64</td>
<td>0.63</td>
<td>0.07</td>
</tr>
<tr>
<td>GC</td>
<td></td>
<td>rs2282679</td>
<td>T/G</td>
<td>0.31</td>
<td>0.27</td>
<td>0.007</td>
</tr>
<tr>
<td>DHCR7</td>
<td></td>
<td>rs7944926</td>
<td>T/C</td>
<td>0.33</td>
<td>0.29</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Lange et al, in press
Conclusions

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

- However, prerequisites of a beneficial usage of vitamin D during treatment remain unclear.

- Patients with viral hepatitis are at high risk of severe vitamin D deficiency.

- Vitamin D supplementation in these patients appears mandatory to maintain bone health.

- This may have beneficial effects on prevention of hepatocarcinogenesis, steatosis, fibrosis progression.
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