**Vitamin D: Therapeutic Overview & Evaluation of Evidence for Current Claims**

### Vitamin D deficiency in Canada

(see table below for significance of level)

- ○ 4% of Canadians had levels < 27.5 nmol/L; ~10% had levels between 27.5 and 37.5 nmol/L; >60% had levels < 75 nmol/L (mean overall 67.7 nmol/L).

#### Symptoms
- ○ muscle weakness, bone pain

#### Risk factors
- ○ dark skin, lack of sunlight (northern latitude, atmospheric pollution), sunscreen use (SPF28), coexistent clothing, elderly, obese or institutionalized, malabsorption (e.g. inflammatory bowel disease, celiac disease), renal disease, medications (see list)

### Medication induced
- ○ anticonvulsants, corticosteroids, antiretrovirals (HIV), cholesterol, rifampin

### Types of vitamin D
- ○ vitamin D3 or cholecalciferol: (preferred form) synthesized normally in the skin via 7-dehydrocholesterol; no longer considered bioequivalent to vitamin D2
  - ○ vitamin D2 (or ergocalciferol) a plant based derivative; option for vegans
- ○ calcitriol: one of the active forms of Vit D in the body is calcitriol: used in patients with end-stage renal disease (ESRD) who are unable to convert vit D3 to calcitriol

### Supplements available in Canada

- ○ vitamin D3: OTC: 400 IU, 1,000 IU tabs
  - ○ vitamin D3: Rx: DOXERCALCIOL, D-TABS 10,000 IU, 50,000-75,000 IU manufactured cap from powder or gel (cumulative up to 500,000 IU/month) liquid; OTC: D-VI-SOL 400 IU/ml, DDROPS (600 or 1000 units/drop in 5ml-10drops)
- ○ vitamin D2 Rx: OSTO-D2 50,000 IU/cap; Peds OTC: DRISOL 8,288 IU/ml
- ○ calcitriol Rx: ROCALCITROL: 0.25ug, 0.5ug, 1ug/ml soln (expensive)
- ○ other options: Rx; alfalcacidol ONE-ALPHA; doxercalciferol HECTOROL; paricalcitol ZEMPLAR

### Dosage Guidelines/Considerations

#### Maintenance Range:
- ○ 400 IU - 2,000 IU daily
- ○ evidence supports efficacy & safety of 800 – 1,000 IU/day for most and possibly up to 2,000 IU, especially in high risk & in winter.

#### Unit Conversion:

- ○ 400 IU = 10 mcg
- ○ 800 IU = 20 mcg
- ○ 1000 IU = 25 mcg
- ○ 2000 IU = 50 mcg

### Vitamin D Bolus doses

#### for severe deficiency

- ○ may consider initial bolus if serum 25(OH)D level is <25-50 nmol/L followed by maintenance

#### Vitamin D adverse effects

- ○ hypercalcemia, hypercalciuria
- ○ GI symptoms (may be due to combination with Ca++ intake)
- ○ renal disease, nephrolithiasis (400 IU/days + Ca++ ~2,100mg/day total intake on average) HR: 1.1^11 - 7^39
- ○ increased fall & fracture rates with very high single yearly doses of 500,000 IU oral vitamin D3, & similar increases in fractures (not falls) with 300,000 IM yearly.

### Food sources

- ○ fish: salmon, sardines, tuna & mackerel (200-600 IU/3.5 oz serving) & fish oils
- ○ small amounts found in beef liver, cheese and egg yolks
- ○ some mushrooms may contain varying amounts of vitamin D2
- ○ fortified food sources such as fortified milk/orange juice (8oz glass = 100 IU)

### Extras: appropriate vitamin D levels may improve absorption of dietary calcium from 10-15% up to 30-40%.

### Table 1: Classification of 25-hydroxyvitamin D (25-OH-D) serum levels

<table>
<thead>
<tr>
<th>25(OH)D (nmol/L)</th>
<th>&lt;25</th>
<th>25-75 (especially &lt;50)</th>
<th>75-250</th>
<th>&gt;250</th>
<th>&gt;375-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomalacia/rickets</td>
<td>Poor bone health</td>
<td>Optimal health (75-110 for most)</td>
<td>Potential adverse effects</td>
<td>Toxic</td>
<td></td>
</tr>
</tbody>
</table>

*Levels • not routinely recommended; useful if high risk of vitamin D deficiency or toxicity concerns. 
  - Cost: $20-50
  - IOM 2010: ≥50 nmol/L adequate level •1000IU/day of D3 will increase 25(OH)D levels by ~15-25 nmol/L over 8 months

---

1.2.3.4
5.
6.
7.
8.
9.
10.
11.
12.
13.
14.
15.
16.
17.
18.
19.
20.
21.
Table 2: Claims and Evidence for Vitamin D

<table>
<thead>
<tr>
<th>Claims</th>
<th>Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone &amp; Joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture</td>
<td>✓</td>
<td>• evidence for benefit in higher risk groups such as elderly, frail, institutionalized, etc., consistent with doses 700-800 IU/day</td>
</tr>
<tr>
<td>Fall prevention</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>?</td>
<td>• lack of benefit with doses ≤400 IU/day</td>
</tr>
<tr>
<td>Steroid induced OP</td>
<td>?</td>
<td>• most trials also use a concomitant calcium supplement</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>26</td>
<td>• evidence equivocal for studies including lower risk groups (Cochrane)16</td>
</tr>
<tr>
<td>OA - Knee Pain</td>
<td>X</td>
<td>• RCT n=146; 3 yr, Vit D 2000 IU/day; no ↓ in knee pain or cartilage volume McAlindon</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cancer risk</td>
<td>?</td>
<td>• 1,000 IU / day vitamin D + Ca++ 1400-1500mg/day in postmenopausal women (&gt;55yo) had decreased rates of cancer (NNT=25/4years) (NHANES III cohort did not find cancer mortality benefit with higher 25(OH)D levels)29</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>29</td>
<td>• epidemiologic evidence shows a ↓ cancer risk with higher serum levels, however lack data for treatment (colorctal adenomas-no benefit 29)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>30, 31, 32</td>
<td>• epidemiologic data has conflicting results of vitamin D status and risk of prostate cancer; recent trials → show little or no association</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td>• some benefit on surrogate markers but lack clinical data</td>
</tr>
<tr>
<td>Cardiovascular risk</td>
<td>22</td>
<td>• 100,000 units q3 months x 1yr did not improve blood pressure</td>
</tr>
<tr>
<td>Blood pressure: VITDISH</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td></td>
<td>• type 1 DM prevention: some benefit suggested in large cohort trial</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>• type 2 DM: limited benefit on surrogate markers; lacks clinical data</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>• meta-analysis looking at all-cause mortality in RCTs, suggests a statistically significant benefit with supplements of vitamin D (D2 or D3)</td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td>• VITdAL-ICU: among critically ill pts with vit D deficiency giving 540,000 IU x1 then 90,000 IU monthly x 5 months did not reduce hospital length of stay, hospital mortality or 6 month mortality</td>
</tr>
<tr>
<td>Neurology</td>
<td>22</td>
<td>• proposed benefit but data lacking: dementia, Parkinson’s, depression 35, MS; chronic pain, small ↓ in non-specific pain 6 wks post 150,000 IU PO x1or2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22</td>
<td>• proposed benefit, but limited data: asthma/COPD, URTI, influenza</td>
</tr>
<tr>
<td>CV</td>
<td></td>
<td>• RCT n=182; RCT 100,000 IU q-4-wks x1yr, no ↓ in AECOPD (except ? in those with level &lt;25 nmol/L)</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td>• not influence time to spumon culture conversion in active tuberculosis</td>
</tr>
<tr>
<td>Skin</td>
<td>37, 38</td>
<td>• not influence time to exacerbation or upper respiratory infections in asthmatics</td>
</tr>
<tr>
<td>Topical skin issues</td>
<td>39</td>
<td>• not influence risk of acute respiratory infection in older adults &amp; their carers</td>
</tr>
<tr>
<td>Breathing, memory, lung function</td>
<td>40</td>
<td>• Vitamin D dose + Ca++) x1 in patients with chronic kidney disease but also can increase calcium and phosphate</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td>• some benefit on surrogate markers but lack clinical data</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>• proposed benefit, but limited data: asthma/COPD, URTI, influenza</td>
</tr>
</tbody>
</table>

Acknowledgements: We would like to thank those who contributed to the development and review of various components of this newsletter & accompanying chart. Dr. W. Olszynski (Rheumatology, Saskatoon), Dr. Susan Whiting (C. of Pharmacy & Nutrition, U of S), Dr. R Geerts (Rheumatology, Saskatoon), Dr. T. Laubscher (Family Medicine, U of S, Saskatoon), Dr. J. Richardson (SHR Pharmacy), Dr. Y. Shevchuk (C. of Pharmacy & Nutrition, U of S), Dr. J. Taylor (C. of Pharmacy & Nutrition, U of S), K. Jensen (CDS-C. of Pharmacy & Nutrition, U of S), M. Dr. Shanes, I. Painting (Dalhousie Academics, Dalhousie Nova Scotia), B. & the RxFiles Advisory Committee. Prepared by: Shannon Stone BSN, Lorne Reger BSN BA, Brent Jensen BSN RN CMA, CMAJ.

Disclaimer: The content of this newsletter represents the research, experiences and opinions of the authors and is not those of the Board or Administration of Saskatchewan Health Region (SHR). Neither the SHR nor Saskatchewan Health Region is responsible for any errors or omissions or for the result of use of this newsletter. Any user of this newsletter is expected to verify the accuracy and relevance of the information contained herein as well as the potentials for useful or side effects. Readers are encouraged to check the information contained herein with other sources.

Copyright 2010, 2014 – RxFiles, Saskatchewan Health Region (SHR) www.RxFiles.ca

7 Canadian Cancer Society http://www.cancer.ca/Canada-wide/Prevention/Vitamin%20D.aspx?sc_lang=en

AECOPD=acute exacerbation of COPD, COPD=chronic obstructive pulmonary disease, MS=multiple sclerosis, OA=osteoarthritis, OP=osteoporosis, RA=rheumatoid arthritis, RCT=randomized controlled trial, URI=upper respiratory tract infection.


Kumar Geeta Trilok, Sachdev Harshpal Singh, Chellani Harish, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. BMJ 2011;342:d2975 (Published 31 May 2011)


Manson JE. Vitamin D and the heart: Why we need large-scale clinical trials (VITAL). Cleveland Clinic Journal of Medicine 2010; 77(12):903-910; doi:10.3949/ccjm.77gr.10004


Strabe S, Derry S, Strabe C, et al. Vitamin D for the treatment of chronic painful conditions in adults. Cochrane Database Syst Rev. 2015 May 6;5:CD007771. 'The evidence addressing the use of vitamin D for chronic pain now contains more than twice as many studies and participants than were included in the original version of this review. Based on this evidence, a large beneficial effect of vitamin D across different chronic painful conditions is unlikely. Whether vitamin D can have beneficial effects in specific chronic painful conditions needs further investigation.'


Theodorou E, Tzoulaki I, Lima J, Ioannidou JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014;348:g3035.


