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

- **Vitamin D deficiency in Canada**:
  - 32% of Canadians have levels < 50 nmol/L (40% in summer, 25% in winter), and 10% are < 30 nmol/L (mean overall 64 nmol/L).
  - **Symptoms**: muscle weakness, bone pain
  - **Risk factors**: dark skin, lack of sunlight (northern latitude, atmospheric pollution), sunscreen use (SPF ≥ 8), occlusive clothing, elderly, obese or institutionalized, malabsorption (e.g., inflammatory bowel disease, celiac disease), renal disease, medications (see list)

- **Medication induced**:
  - anticonvulsants, thiazides, corticosteroids, antiretrovirals (HIV), cholestyramine, rifampin

- **Types of vitamin D**:
  - **D3 (cholecalciferol)**
  - **D2 (ergocalciferol)**
  - Other (active vitamin D analogues)

- **Supplements available in Canada**:
  - D3 and D3 are most useful in primary care; other analogues used in specialized areas such as chronic kidney disease.

- **Dosage Guidelines/Considerations**:
  - **Osteoporosis Canada guidelines**: for deficiency: vitamin D3 400-1000 IU once daily
  - **adults ≥50 yrs at low risk**: if high fracture risk, strongly recommended, otherwise dep. on values/preferred sources

- **Maintenance Range**:
  - 400 IU - 2000 IU daily
  - Evidence supports efficacy & safety of 800 - 2000 IU/day for most and possibly up to the daily upper limit of 6000 IU, especially in high risk & in winter.

- **Unit Conversion**:
  - (some suggest Vit D3 10,000 IU weekly or Vit D2 50,000 IU monthly to 1 pill burden)

- **Vitamin D Bolus doses**
  - for severe deficiency
  - may consider bolus if serum 25(OH)D level is < 25-50 nmol/L

- **Vitamin D adverse effects**
  - hypercalcemia
  - GI symptoms (may be due to combination with Ca++ intake)
  - renal disease, nephrolithiasis
  - increased fall & fracture rates with very high single yearly doses of 500,000 IU oral vitamin D3

- **Food sources**
  - fish: salmon, sardines, tuna & mackerel (200–600 IU/3.5-oz serving)
  - small amounts found in beef liver, cheese and egg yolks
  - some mushrooms may contain varying amounts of vitamin D2
  - fortified food sources such as 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>
<thead>
<tr>
<th>25(OH)D (nmol/L)</th>
<th>&lt; 30</th>
<th>30-50</th>
<th>50-250</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 bone health</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.

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

- **RxFiles Q&A Summary**
- **Extras**

---

**Revised T Rawn Oct'17 – Originally Prepared by S Stone, L Regier - www.RxFiles.ca**
<table>
<thead>
<tr>
<th>Category</th>
<th>Claims</th>
<th>Evidence</th>
</tr>
</thead>
</table>
| Skeletal          | Prevents hip fractures and mortality                                    | Falls/fractures (per 1,000 treated)*:  
  - 5 fewer hip # (95% CI 2-8)  
  - No change in fall risk*  
  - 7 fewer deaths (95% CI 1-14)  
  CADTH umbrella review of 5 meta-analyses (elderly long-term care population): fall risk only reduced in 1 meta-analysis; others showed no benefit.  
* Benefits only seen when used with Ca++. Subgroups with more benefit: low vitamin D levels, community-dwelling elderly under 80 with no cognitive impairment, no Hx of fall/fracture.  |
|                   | Does not prevent falls* 23, 24, 48-53                                    |                                                                           |
|                   |                                                                         | Toxocities for every 1,000 patients:*  
  - 8 more GI AEs  
  - 5 more hypercalcemia  
  - 3 more renal insufficiency or calculi  
  - 23 more MI  
* Most harms related to Ca++ component. Limit Ca++ to max 500 mg/day (elemental).  |
|                   |                                                                         |                                                                           |
|                   | Slightly increases femoral neck mineral density* 54                      | 0.8% increase at femoral neck (95% CI 0.2-1.4%, with heterogeneity among trials)  |
|                   |                                                                         |                                                                         |
|                   | Steroid induced osteoporosis: Increases lumbar spine and forearm BMD* 55 | 2 years of Vit D + Ca++ increased lumbar spine and forearm BMD* 55       |
|                   |                                                                         |                                                                         |
|                   | Low levels related to RA disease activity 25, 56                         | Low vit D levels increase disease activity and bone loss. 26             |
|                   |                                                                         |                                                                         |
|                   | Osteoarthritis: No benefit for pain, stiffness, or function* 57          | Vit D3 (800-60,000 IU) does not improve pain, stiffness, or function (2/3 studies showed improvement in knee pain on visual analogue scale)* 57 |
| Cancer            | Conflicting findings on cancer risk 26, 58                               | Cancer risk:  
  - 1,000 IU / day vitamin D + Ca++ 1400-1500 mg/day in postmenopausal women (>55yo) had decreased rates of cancer (NNT=25/4 years), baseline 25(OH)D=71.8 nmol/L  
  - 2,000 IU / day vitamin D + Ca++ 1500 mg/day postmenopausal women (>55yo) did not sig. ↓ cancer risk 58 HR 0.70 (95% CI 0.47-1.02) pts were Vit D replete; mean baseline levels 32.8ng/mL (81.9 nmol/L), unknown whether Vit D would ↓ cancer risk if given to deficient pts  |
|                   | Reduces cancer mortality 59                                              | Cancer mortality:  
  - 400-1100 IU vitamin D/day (+/- Ca++) for 2-7 years sig. ↓ cancer mortality (RR 0.88) 95% CI 0.78-0.98  
  Risk likely related to 25(OH)D levels: In this meta-analysis, baseline 25(OH)D was 38-74.4 nmol/L; NHANES III cohort did not find cancer mortality benefit with higher 25(OH)D levels 27  |
|                   | Does not reduce colon cancer risk 28, 60-62                              | Prevention RCT: Vit D 1000 IU/day + Ca++ 1200 mg/day for 3-5 years did not sig. ↓ colorectal cancer risk, 60 but genotype affects risk (AA genotype ↓ risk 64% ; 1 or 2 G alleles ↑ risk 41%)  |
|                   | Colon cancer mortality inversely related to levels                       | Mortality: inverse to 25(OH) D levels (observational studies) 62          |
|                   | Reduces breast cancer mortality 29, 30, 31, 62, 63                       | Observational studies: 25(OH)D levels correlated with lower progression/mortality exp. in pre-menopausal women 62, 63  
  Meta-analysis of observational studies: Higher 25(OH)D correlated with lower case-fatality rate (highest vs. lowest quintile pooled HR 0.56, 95% CI 0.40-0.71) 64  
  RCT suggests safety with 10,000 IU vitamin D3 dose daily x 4 months  
Consider Vit D dose, Ca++ intake!  |
<p>|                   | May reduce prostate cancer progression 33, 62                            | Low 25(OH)D levels related to aggressive cancer (&lt;30ng/mL associated with adverse pathology; OR 2.64 95% CI 1.25-5.59) 65  |</p>
<table>
<thead>
<tr>
<th>Category</th>
<th>Claims</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>Does not reduce cardiovascular risk</td>
<td>• Inconsistent data for progression and mortality; open-label trial suggests 4,000 IU/day may ↓ progression[^62]</td>
</tr>
<tr>
<td></td>
<td>Does not reduce blood pressure</td>
<td>• 100,000 IU q3 months x 1yr did not improve blood pressure[^VIDISH]</td>
</tr>
<tr>
<td>Diabetes Mellitus (DM)</td>
<td>May reduce T1DM risk[^22]</td>
<td>• RCT: 200,000 IU once, then 100,000 IU monthly for 3.3 years did not reduce CV disease risk (both groups were vitamin D replete and only half were at high CV risk; unknown if deficient or higher CV risk patients might benefit)[^66]</td>
</tr>
<tr>
<td></td>
<td>Does not reduce T2DM risk[^68,69]</td>
<td>• Type 2 DM prevention: No benefit on insulin sensitivity, glucose control, or cardiometabolic risk[^68,69]</td>
</tr>
<tr>
<td></td>
<td>Low levels associated with CV morbidity/mortality (T2DM)</td>
<td>• Low 25(OH)D associated with higher risk of CV morbidity/mortality in T2DM[^74]</td>
</tr>
<tr>
<td></td>
<td>No benefit for non-alcoholic fatty liver disease (T2DM)[^67]</td>
<td>• No benefit on non-alcoholic fatty liver disease in T2DM[^67]</td>
</tr>
</tbody>
</table>
| Renal                     | Kidney disease: reduces PTH, controls mineral and bone disorders[^22,70,71] | Chronic kidney disease:  
• Effective for decreasing parathyroid hormone (PTH) in patients with chronic kidney disease (but can increase calcium and phosphate)  
• Vitamin D3 raises 25 (OH)D levels more than D2 in non-dialysis dependent CKD patients (but levels ↓ rapidly after Tx stopped); D2 and D3 equally effective in lowering PTH.[^70]  
• D2 and calcitriol equally effective to control mineral & bone disorders in stage 3-5 CKD.[^71]  
Toxicity (data from Women’s Health Initiative (WHI):[^34] nephrolithiasis: Vit D 400 IU/day + Ca++ (~2,100mg/day total intake on average)  
HR=1.17 95% CI 1.03-1.34 Wks - ~ 7yr  
May prevent UTI[^99]  
UTI: Vit D (20,000 IU/wk x 5 years) ↓ UTI risk (7% Vit D vs. 13% placebo, p<0.02)[^99]  
Inverse relationship between vitamin D intake and Alzheimer’s risk[^74-76]  
• Alzheimer’s dementia: Proposed benefit but data lacking (inverse relationship between levels/intake and risk)[^4-76]  
May slow Parkinson’s disease progression[^77]  
• Parkinson’s: RCT showing potential benefit (1,200 IU/day may slow progression)[^77]  
Not effective for treating depression[^78,79]  
• Depression treatment: 2 meta-analyses showed no benefit.[^78,79]  
May reduce MS relapse rate[^80-83]  
• MS: association between low neonatal and childhood Vit D and MS[^80,83], placebo-controlled trial found no changes in inflammatory markers[^82], but prospective cohort study found ↓ in relapse rate (in pts on natalizumab)  
Does not prevent ALS or slow progression[^84-86]  
• ALS: Prospective cohort study found no protective effects[^84], non-randomized comparative study found no change in prognosis (100,000IU/wk x 4 wks),[^85] and vitamin D levels do not predict survival.[^86]  
Small decrease in non-specific pain[^35,87-90]  
• Chronic pain[^88]; small ↓ in non-specific pain 6 wks post 150,000 IU PO x1or2  
• Low vit D levels found in fibromyalgia,[^87] carpal tunnel,[^88] and chronic widespread pain,[^89] but not low back pain.[^90]  
Pulmonary                  | Reduces asthma attacks and hospitalization[^91,96]                      | • Asthma: Cochrane review - Low Vit D levels linked to asthma severity, attacks; vitamin D ↓ avg. attacks/yr (from 0.48 to 0.22, RR 0.63, 95% CI 0.45-0.88), risk of |
<table>
<thead>
<tr>
<th>Category</th>
<th>Claims</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>attending hospital due to attack (from 6% to 3%, OR 0.39 95% CI 0.19-0.78). No effect on lung function or day to day symptoms. Data mostly in mild-mod asthma. Vit D did not influence time to exacerbation or infections in asthmatics. There was no sig ( \downarrow ) wheeze/asthma in kids when prenatal supplement given. Low Vit D levels were not found to increase the risk of atopic disease (e.g., asthma, atopic dermatitis).</td>
<td></td>
</tr>
<tr>
<td>COPD: reduces mod-severe exacerbation risk (only if vit D deficient)</td>
<td>COPD: Correcting Vit D deficiency (120,000 IU q2mo x 6) ( \downarrow ) mod-severe exacerbation risk (HR 0.57, 95% CI 0.35-0.92, p=0.021) ONLY in Vit D deficient pts (&lt;50nmol/L) but did not affect time to 1st mod-severe exacerbation or time to 1st URTI ( \uparrow ) (ViDiCo)</td>
<td></td>
</tr>
<tr>
<td>Small decrease in URTI risk (mainly in vit D deficient and LTC residents)</td>
<td>URTI: Vit D (300-2,000 IU daily or boluses of 100,000 IU monthly) ( \downarrow ) acute URTI risk (OR 0.88, 95% CI 0.81-0.96) but ARR only 2% (most benefit in very deficient pts and those not receiving boluses) ( \downarrow ) and definitions of URTI varied between studies (included many different conditions) ( \uparrow ); reduced acute URTI in older LTC residents but more falls Ginde'16</td>
<td></td>
</tr>
<tr>
<td>Reduces influenza A risk (and risk of flu-related asthma attacks) in children</td>
<td>Influenza: Vit D ( \downarrow ) influenza A risk in schoolchildren (RR 0.58, 95% CI 0.34-0.99, p=0.04); ( \downarrow ) risk of flu-related asthma attacks (RR 0.17, 95% CI 0.04-0.73, p=0.006) ( \uparrow )</td>
<td></td>
</tr>
<tr>
<td>Does not help with sputum culture conversion in tuberculosis</td>
<td>TB: Vit D deficiency increases TB risk (OR 2.57, 95% CI 1.74-3.80) ( \uparrow ); Vit D did not have any significant benefits on sputum culture conversion in active tuberculosis ( \downarrow )</td>
<td></td>
</tr>
<tr>
<td>Skin ( \uparrow ), ( \uparrow )</td>
<td>Psoriasis: topical vitamin D application may be useful in psoriasis but has more adverse effects when compared to corticosteroids; (ie eczema, psoriasis)</td>
<td></td>
</tr>
<tr>
<td>Improves winter atopic dermatitis in children</td>
<td>Atopic dermatitis: improved winter related atopic dermatitis in children ( \uparrow )</td>
<td></td>
</tr>
<tr>
<td>May reduce inflammatory acne lesions</td>
<td>Acne: Low Vit D levels correlate with acne incidence/severity; 1,000 IU daily x 2 mo ( \downarrow ) inflammatory lesions 34.6% ( p&lt;0.05 ) ( \uparrow )</td>
<td></td>
</tr>
<tr>
<td>Low levels may be linked to skin aging (conflicting findings) ( \uparrow ), ( \downarrow )</td>
<td>Skin aging: Conflicting findings (some studies suggest a link, others do not; ethnic group may play a role) ( \uparrow ), ( \downarrow )</td>
<td></td>
</tr>
</tbody>
</table>

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

Green = consistent evidence from high quality meta-analysis or RCTs; Yellow = evidence from RCTs or lower-quality meta-analyses; Orange = evidence from observational studies, or RCT evidence with limitations or inconsistency; Pink = lack data
**Figure 1: Vitamin D Supplementation Evidence - The Bottom Line**

This figure summarizes the findings of vitamin D supplementation studies for various health conditions (for details, see Table 2). It does not include health conditions where a correlation has been identified with vitamin D levels but not tested with vitamin D supplementation (these are outlined in Table 2).

<table>
<thead>
<tr>
<th>Body system</th>
<th>Where to put it</th>
<th>Text</th>
</tr>
</thead>
</table>
| Skeletal    | Hip bone       | ↓ hip fractures (NNT 200) with Ca<sup>48-53</sup>  
|             |                | ↓ mortality (NNT 143) with Ca<sup>48-53</sup>  
|             |                | ↔ falls<sup>48-53,111</sup>  
|             |                | ↔ osteoarthritis<sup>57</sup>  
|             |                | Slight ↑ BMD<sub>lumbar spine, forearm</sub>, with Ca in steroid-induced osteoporosis<sup>59</sup>  
| Overall cancer risk | Have a circle around the body with an arrow pointing to the circle. | ↓ mortality (NNT 290<sup>59</sup>)  
|             |                | ↔ risk (conflicting results)  
| Colon cancer | Gut (colon)    | ↔ risk<sup>60</sup>  
| Breast cancer | Breast        | ↓ breast cancer mortality<sup>59</sup>  
| Cardiovascular | Heart         | ↔ CV disease risk<sub>pts were Vit D replete</sub><sup>66</sup>  
|             |                | ↔ BP<sup>72</sup>  
| Diabetes    | Gut (pancreas) | ↔ T2DM prevention<sup>68,69</sup>  
|             |                | ↔ Non-alcoholic fatty liver disease<sup>67</sup>  
|             |                | May ↓ T1DM risk<sub>in infants</sub><sup>22</sup>  
| Renal       | Kidney         | ✓ Control mineral/bone disorders  
| Mortality   | Circle         | Inverse relationship with levels and mortality: threshold is 20-30ng/mL (50-75 nmol/L) for overall mortality, 30ng/mL (75 nmol/L) for CV mortality<sup>72,94</sup>  
|             |                | ↔ ICU mortality, length of stay<sup>34</sup>  
| Nervous System | Head          | ↔ Depression treatment<sup>68,79</sup>  
|             |                | May ↓ Parkinson’s progression<sup>77</sup>  
|             |                | May ↓ MS relapse rate<sub>pts on natalizumab</sub><sup>83</sup>  
|             |                | ↔ ALS prevention or prognosis<sup>84-86</sup>  
|             |                | Small ↓ in non-specific chronic pain<sup>36</sup>  
| Pulmonary   | Lungs          | ↓ Asthma attacks/hospital visits<sub>in mild-moderate asthma</sub><sup>91</sup>  
|             |                | ↔ Asthma symptoms/lung function<sup>91</sup>  
|             |                | ↓ TB sputum culture conversion<sup>38</sup>  
|             |                | ↓ COPD mod-severe exacerbation risk<sub>ONLY in Vit D deficient pts (ViDiCo)</sub><sup>92</sup>  
|             |                | ↔ time to 1<sup>st</sup> mod-severe exacerbation or time to 1<sup>st</sup> URTI<sup>92 (ViDiCo)</sup>  
|             |                | Small ↓ acute URTI risk<sub>most benefit in very deficient pts and those not receiving boluses</sub><sup>94</sup>  
|             |                | ↓ influenza A risk/flu-related asthma attacks<sub>in children</sub><sup>95</sup>  
| Skin        | Arm or leg (in the skin area) | ↓ plaque psoriasis (but more AE vs steroids) – topical vit D<sup>59</sup>  
|             |                | ↓ winter-related atopic dermatitis<sub>in children</sub><sup>103</sup>  
|             |                | May ↓ inflammatory acne lesions<sup>109</sup>  
|             |                | **Conflicting findings re: skin aging**<sup>109,102</sup> |
This figure does not include health conditions where a correlation has been observed with Vitamin D levels but not yet tested with Vitamin D supplementation (these are outlined in Table 2).
Vitamin D: What we know, what’s coming next

What do we know (bottom line)?
1. Although it is suggested that there may be multiple benefits for vitamin D, the evidence for vitamin D (when used with calcium) is strongest in preventing fractures (NNT 200).
2. Cut-off points for 25(OH)D have not been well established.
3. There may be an association between low 25(OH)D and mortality, but it is unknown whether treatment will be of benefit.

What’s new since the last update (Jan 2013)?
- Concept of a threshold for the association between lower 25(OH)D levels and mortality (50-75 nmol/L)72,94
- New Osteoporosis Canada guidelines on preventing fracture in long-term care46
- New evidence (see Table 2 and Figure 1)

What are the headlines saying?

<table>
<thead>
<tr>
<th>The headline</th>
<th>The facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a vitamin D deficiency “pandemic”, and most of us aren’t getting enough. Nearly everyone needs a supplement.</td>
<td>This “hype” stems from misinterpretation of the Institute of Medicine (IOM) vitamin D recommended 25(OH)D levels of 50 nmol/L (20 ng/mL) as a “cut point” for good bone health. But this is actually the upper end of the spectrum of human need; 97.5% of people need this amount or less, and 50% need 40 nmol/L (16 ng/mL) or less. This means that many people whose requirement is being met are being misclassified as “deficient”. Guidelines vary on who needs a supplement (generally those at high risk of deficiency or fracture; see Dosage Guidelines above).106</td>
</tr>
</tbody>
</table>

On one hand... Vitamin D is a “cure-all” that can prevent and treat a wide variety of diseases. | Correlation is not causation. Many observational studies have found relationships between low 25(OH)D levels and various diseases. But for many of these conditions, vitamin D supplementation does not result in a significant improvement.109 |

And on the other hand... Vitamin D does not live up to the “hype” – it’s not as effective as we hoped. | Some news stories tout vitamin D as a cure-all, while others say it’s useless and possibly harmful. The truth is somewhere in between. There is a lot of low-quality evidence linking lower levels of vitamin D to various conditions, but not much convincing evidence for supplementation except for a few key areas (see Table 2 and Figure 1). Supplementation trials may have disappointing results because vitamin D benefits are greatest in those with the lowest vitamin D levels, but many studies used patients who were vitamin D replete. Vitamin D may exhibit a “threshold effect” (only patients with levels below a certain threshold will benefit from supplementation) rather than a linear “dose response” relationship.110 New studies are underway to help clarify the role of vitamin D supplementation (see below).108,109,110 |

What’s still unclear?
1. What is the appropriate 25(OH)D level definition for vitamin D deficiency?106
2. Do low 25(OH)D levels increase the risk of death?72
3. What is the best 25(OH)D level range for optimal health, and is it the same for all populations and disease states?104,110
4. Do dietary recommendations for vitamin D need to be updated?105,110
5. Do vitamin D dosage guidelines need to be updated (guidelines have not been recently updated and recommendations differ)?105,110
6. How safe are large doses of vitamin D, and what is the maximum daily (or weekly, monthly or yearly) dose?110
7. What is the optimal dosing regimen: would daily or weekly supplementation be more effective than monthly (which can cause fluctuations in levels) for reducing cardiovascular risk? What other conditions are sensitive to 25(OH)D level fluctuations?107
8. Does vitamin D supplementation reduce all-cause mortality, cancer or cardiovascular risk in people who are vitamin D deficient (most studies were in replete patients)?72,94
9. What are the indications for vitamin D levels?108,109,110

What upcoming studies will help us answer these questions?

<table>
<thead>
<tr>
<th>Study</th>
<th>Expected publication date</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-HEALTH 5-year RCT</td>
<td>2019/early 2020’s (5-year study that launched in Jan 2014)</td>
<td>Population: N=25,000 Australian adults aged 60-84 (no Hx of sarcoidosis, hyperparathyroidism, hypercalcemia, or kidney stones) Intervention: Vit D 60,000 IU monthly x 5 years Control: Placebo Outcomes: All-cause mortality (primary), total cancer incidence (secondary), colorectal cancer incidence (secondary) Type of question: Prevention trial Type of trial: Randomized <a href="https://dhealth.qimrberghofer.edu.au/">https://dhealth.qimrberghofer.edu.au/</a></td>
</tr>
<tr>
<td>VITAL RCT</td>
<td>Enrollment will complete at end of 2017; Publication likely in 2018</td>
<td>Population: N=25,874 adults (Women 55 and over, men 50 and over, no Hx of cancer, heart attack or stroke) in Boston MA Intervention: Vit D 2,000 IU daily and/or omega-3 fatty acids 1 gram daily (Vit D alone, omega-3 alone, or both) Control: Placebo Outcomes: Risk of cancer, heart disease and stroke Type of question: Prevention trial</td>
</tr>
</tbody>
</table>


