

Vitamin D: Therapeutic Overview & Evaluation of Evidence for Current Claims ^{1,2,3,4}

Vitamin D deficiency in Canada ⁵ (see table below for significance of level) ○ ~4% of Canadians had levels < 27.5nmol/L; ~10% had levels < 37.5nmol/L; >60% had levels < 75nmol/L (mean overall 67.7nmol/L). OHTAC report: ~10-25% have level < 50nmol/L ²⁰

⇒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, corticosteroids, antiretrovirals(HIV), cholestyramine, rifampin

Types of vitamin D

- D3 (cholecalciferol)
- D2 (ergocalciferol)
- Other (active vitamin D analogues)

○ **vitamin D3 or cholecalciferol: (preferred form)** synthesized normally in the skin via 7-dehydrocholesterol; no longer considered bioequivalent to vitamin D2 {1000IU of D3 daily will increase 25(OH)D levels by ~15-25nmol/L ⁶ over 8 months}

○ **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 D2 and D3 most useful in primary care; other analogues used in specialized areas such as chronic kidney disease.

○ vitamin D3: **OTC**: 400IU, 1,000 IU **tabs**
 Rx: **D-TABS** 10,000 IU; 50,000-75,000 IU manufactured cap from powder 5ml=180drops

○ vitamin D3: **OTC**: **D-VI-SOL** 400 IU/ml, **DDROPS** (600 or 1000 units/drop 5ml=180drops) **liquid**;
OTC Peds: **BABY DDROPS** : 400 units/drop -520 / 2.5ml bottle (- 90 drops)

○ vitamin D2 Rx: **OSTO-D2** 50,000 IU/cap; Peds **OTC**: **DRISDOL 8,288 IU/ml** -200 IU/drop; D/C Jan 2011

○ calcitriol Rx: **ROCALTROL**: 0.25ug, 0.5ug, 1ug/ml soln (expensive)

○ other expensive Rx: alfacalcidol **ONE-ALPHA**; doxercalciferol **HECTOROL**; paricalcitol **ZEMPLAR**

Dosage Guidelines/Considerations

○ Osteoporosis Canada guidelines ⁶:

- **adults <50 yrs at low risk** for deficiency: vitamin D3 **400-1,000 IU once daily**
- **adults ≥ 50yrs & moderate-high risk**: vitamin D3 **800-2,000 IU once daily**
 - **up to 2,000 IU/day** considered safe without requiring medical supervision
 Max: Upper level for safe intake ≤10,000 IU/day with medical supervision; {≤4,000IU/day ^{IOM 2010}}

○ Canadian Cancer Society ⁷

- adult, high risk (during fall & winter): 1,000 IU/day
- older adults, dark skin or little sun exposure: 1,000 IU/day all year

○ North American Menopause Society ⁸:

- adult, ♀ at risk of vitamin D deficiency: 700-800 IU/day

○ Canadian Pediatric Society ⁹:

- **pregnancy** & lactation: consider 2,000 IU daily especially during the **winter**
- breastfed infants: 400 IU/day; 800 IU/day for northern Native communities (especially in winter)
- formula fed: no supplement needed; except Northern communities 400 IU/day from Oct-Apr

○ **IOM 2010**: Recommended dietary allowance ≥1yr = 600IU/day, if ≥71yr = 800IU/day

Vitamin D Bolus doses

◆ for severe deficiency

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

○ lack of evidence and highly variable in literature and clinical practice

○ approaches vary: {D3 used more than D2; **daily** ^{10,11} e.g. 2,000 – 4,000 IU daily x 8-20 weeks; **weekly** ^{12,13} e.g. 50,000 weekly x 8 wks (Vit D2 trials); **monthly** e.g. 50,000 monthly x 9; or **single bolus** 10,000 - 150,000 IU x1 }
 may depend on starting 25(OH)D level, BMI, effective sun exposure & other factors e.g. malabsorption

○ **single yearly high doses** (500,000 IU orally or 300,000 IU IM) are **not** recommended due to increased risk of fracture +/- fall esp. in the first few months post dose ^{14,15}

Vitamin D adverse effects

○ hypercalcemia ¹⁶, hypercalciuria

○ GI symptoms (may be due to combination with Ca++ intake) ¹⁷

○ renal disease, **nephrolithiasis** [400 IU/day + Ca++ (~2,100mg/day total intake on average) HR=1.17 ^{WHI - ~7yrs} ³⁹

○ increased fall & fracture rates with very high single yearly doses of 500,000 IU oral vitamin D3 ¹⁴, & similar increases in fractures (not falls) with 300,000 IM yearly. ¹⁵

Food sources ¹⁸

{Difficult to get adequate Vit D from dietary sources alone; whereas is possible with calcium from diet alone.}

○ fish: salmon, sardines, tuna & mackerel (200–600 IU/3.5-oz serving) ³ & 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% ^{3,19}

Table 1: Classification of 25-hydroxyvitamin D (25-OH-D) serum levels * (ng/ml x 2.496 = nmol/L)

25(OH)D (nmol/L)	< 25	25-75 (especially <50)	75 - 250	>250	> 375 – 500
	Osteomalacia/rickets deficiency	Poor bone health insufficiency/suboptimal	Optimal health (75-110 for most)	Potential adverse effects	Toxic

*Levels ◆ **not** routinely recommended; useful if high risk of vitamin D deficiency or toxicity concerns. ^{6,20} Cost: \$20-50
 ◆ IOM 2010: ≥50 nmol/L adequate level ◆1000IU/day of D3 will increase 25(OH)D levels by ~15-25nmol/L ²¹ over 8 months

Table 2: Claims and Evidence for Vitamin D (Abridged; for discussion, see reference link to detailed trials summary table)

	Claims	Evidence	Comments
Bone & Joint	Fracture ^{16,23}	✓	<ul style="list-style-type: none"> ♦ evidence for benefit in higher risk groups such as elderly, frail, institutionalized, etc., consistent with doses 700-800 IU/day ♦ lack of benefit with doses ≤400 IU/day ♦ most trials also use a concomitant calcium supplement ♦ evidence equivocal for studies including lower risk groups (Cochrane)¹⁶
	Fall prevention ^{24, 25}	✓✓	
	Bone mineral density	?	
	Steroid induced OP	?	
	Rheumatoid Arthritis ²⁶	?	
Cancer	All cancer risk ²⁷	✓?	<ul style="list-style-type: none"> ♦ 1,000 IU / day vitamin D + Ca⁺⁺ 1400-1500mg/day in postmenopausal women (>55yo) had decreased rates of cancer (NNT=25/4years) {NHANES III cohort did <u>not</u> find cancer mortality benefit with higher 25(OH)D levels}²⁸ ♦ epidemiologic evidence shows a decreased cancer risk with higher serum levels, however lack data for treatment ♦ epidemiologic data has conflicting results of vitamin D status and risk of prostate cancer; recent trials show little or no association
	Colon cancer ²⁹	✓?	
	Breast cancer ^{30, 31, 32}	?	
	Prostate cancer ³³	?	
CV	Cardiovascular risk ²¹	?	♦ some benefit on surrogate markers but lack clinical data
Diabetes Mellitus (DM)	Diabetes prevention ²¹	?	<ul style="list-style-type: none"> ♦ type 1 DM prevention: some benefit suggested in large cohort trial ♦ type 2 DM: limited benefit on surrogate markers; lacks clinical data
	Kidney	Kidney disease ²¹	✓?
Mortality	All cause death ³⁴	✓?	♦ meta-analysis looking at all-cause mortality in RCTs, suggests a statistically significant benefit with supplements of vitamin D (D2 or D3)
Neurology	Various ²¹	?	♦ proposed benefit, but data lacking: dementia, Parkinson's disease, depression ³⁵ , multiple sclerosis, chronic pain ³⁶
Respiratory	Various	?	♦ proposed benefit, but limited data: asthma/COPD, URTI, influenza
Skin ^{37, 38}	Topical skin issues ³⁹	✓?	♦ topical vitamin D application may be useful in psoriasis but has more adverse effects when compared to corticosteroids; (ie eczema, psoriasis)
Toxicity	Breast Ca trial	✓?	<ul style="list-style-type: none"> ♦ RCT suggests safety with 10,000 IU vitamin D3 dose daily x 4 months⁴⁰ ♦ nephrolithiasis: Vit D3 400 IU/day + Ca⁺⁺ (~2,100mg/day total intake on average) HR=1.17 95% CI 1.02-1.34 WHI - ~ 7yr ♦ Single dose resulted in an increase in fracture +/- or fall within the first 3 months after initial dose
	WHI ⁴¹ WHI=Women's Health Initiative	Consider Vit D dose, Ca ⁺⁺ intake!	
	Single yearly high dose ¹⁴ 500,000 IU po or 300,000IU IM ¹⁵		

COPD=chronic obstructive pulmonary disease, MS=multiple sclerosis, OP=osteoporosis, RA=rheumatoid arthritis, RCT=randomized controlled trial, URTI=upper respiratory tract infection
 ✓✓ = consistent evidence for benefit from high quality meta-analysis or RCTs; ✓ evidence for benefit from RCTs; ✓? Some evidence but limitations or inconsistency; ?= lack data

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