Vitamin D, Cancer and Health
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Holistic Health Research Foundation of Canada
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Vitamin D (Cholecalciferol)

- Generated when UV light (UVB) interacts with 7-dehydrocholesterol in skin
- Vitamin D cannot be made when the angle of the sun is low
  - October-March in Toronto and similar latitudes
- Exposure of significant amounts of skin (bathing suit) at noon in summer in Toronto will generate 10,000 IU in 15 minutes
  - The darker your skin the longer the exposure needed to generate vitamin D

Vitamin D synthesis and metabolism

- 7-dehydrocholesterol in skin
- 1,25-dihydroxy D (calcitriol) - active
- Binding to vitamin D receptors (VDR)
- Cholecalciferol (vitamin D3)
- 25-hydroxy D (stable storage form)
- 25-hydroxylase in liver (CYP 27B1)
- 1-alpha-hydroxylase in kidney (CYP 24) and other tissues
- Physiological actions in multiple tissues
**1,25-dihydroxy D (calcitriol)**

- Regulates calcium and phosphorous absorption and utilization
- Controls cell replication and differentiation
- Regulates the immune system
- Influences muscle strength, balance and gait

**Vitamin D deficiency**


Adult with rickets unable to give birth due to deformity of pelvis
Other conditions linked to vitamin D deficiency

- Autoimmune diseases
  - Diabetes
  - Rheumatoid arthritis
  - Multiple sclerosis
  - Inflammatory bowel disease (Crohn’s, ulcerative colitis)
- Lung problems: asthma, COPD
- Mental health: schizophrenia, SAD, dementia
- Cancer: breast, prostate, colon, lung

Physical Signs of Vitamin D Deficiency

- Osteomalacia and rickets
  - Sick Kids now seeing rickets in children again
- Osteoporosis and stress fractures
- Muscle and bone pain
  - Foot, hip, knee, back

Note: Fibromyalgia may be misdiagnosed vitamin D deficiency

- Minor signs
  - Stiffness
  - Difficulty climbing stairs
  - Muscle weakness
    - Grip strength
    - Difficulty getting out of a chair
  - Unsteady gait
Chronic Degenerative Diseases associated with vitamin D insufficiency

- Obesity and metabolic syndrome
- Type 1 and type 2 diabetes
- Osteopenia and osteoporosis
- Cardiovascular disease and stroke  
  - Note: blood pressure and cholesterol are higher in winter than in summer in both northern and southern hemispheres
- Alzheimer's and dementia
- Most cancers

Vitamin D Deficiency

- Everyone in Canada now considered at risk of deficiency (not enough sunlight)
- The use of sun block makes this worse – supplements needed (D3, the natural form)
- European Commission has set the NOAEL at 4000iu/day. In Canada and US it is 2000IU
  - Many vitamin D researchers suggest 10,000 IU per day is safe for unsupervised intake
- Individuals with certain genes (genetic polymorphisms) may need more

How widespread is vitamin D deficiency?
Vitamin D insufficiency in southern Arizona

- Analyzed serum 25-hydroxy D levels in residents of southern Arizona
- Results: mean serum 25(OH)D of study population was 26.1 ± 9.1 ng/mL (65.25 nmol/L)
  - 22.3% had 25(OH)D concentrations >30 ng/mL (75 nmol/L)
  - 25.4% had concentrations <20 ng/mL (50 nmol/L)
  - 2.0% had concentrations <10 ng/mL (25 nmol/L)

Vitamin D insufficiency in southern Arizona

- Conclusions: alarmingly high rate of hypovitaminosis D in Arizona
  - Blacks (55.5%) and Hispanics (37.6%) were more likely to be vitamin D deficient (<20 ng/mL or 50 nmol/L)
  - Obesity was a risk for low vitamin D levels in fair-skinned

Undiagnosed Vitamin D Deficiency in the Hospitalized Patient.

- Symptoms of severe vitamin D deficiency
  - Neuromuscular irritability
  - Numbness and tingling
  - Muscle cramps, spasm of the larynx
  - Seizures
- Symptoms of mild deficiency: Subtle
  - Usually muscle weakness and/or pain, unsteady gait
Undiagnosed Vitamin D Deficiency in the Hospitalized Patient.

- Test all patients for vitamin D status on admission to hospital
- If vitamin D deficiency or insufficiency is confirmed (25-hydroxy D < 50nmol/L) treatment should be initiated immediately in hospital
- Treatment with high doses of vitamin D is safe and well tolerated

Low maternal vitamin D status and fetal bone development: Cohort study.

- **Research question:** Does maternal vitamin D insufficiency affect fetal bone development?
- **Methods:** Maternal 25-(OH)D checked in 424 British pregnant women
  - High resolution 3D ultrasound of femur looked for splaying or flaring at the end of the femur – a classical sign of rickets
- **Results:** 3 groups of women identified
  - Sufficient or borderline: 25-(OH)D >50 nmol/L (63.4%)
  - Insufficient: 25 to 50 nmol/L (30.7%)
  - Deficient: < 25 nmol/L (5.9%)

- **Conclusion:** Maternal vitamin D insufficiency influences fetal bone development as early as 19 weeks' gestation. Must start supplementation early in pregnancy
One Third of Canadian Toddlers Are Vitamin D Deficient


- Measured 25-hydroxy D between Nov 2007 and June 2008 in 92 children (24-30 m) attending well children clinic
  - 82% had levels < 75 nmol/L
  - 32% had levels < 50 nmol/L
- Low milk consumption associated with low vitamin D levels
- High body mass index (BMI) also associated with low blood levels

Aging and Vitamin D

Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women

Semba RD et al, Nutr Metab, 2009; 29(8): 525-530

- **Study:** Prospective study in older community dwelling women
  - 714 women 70-79 years, followed for 72 months after Vitamin D status checked (25-hydroxy D)
- **Results:** During follow up 14% (n=100) died
  - Compared to women in the highest quartile of 25-hydroxy D, women in the lowest quartile had the highest risk of mortality
    - <38.25 nmol/L vs >67.5 nmol/L (p=0.02)
Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women

Semba RD et al, Nutr Metab, 2009; 29(8): 525-530

- Conclusion: Older women with very low vitamin D status have an increased risk of death
  - Additional research is needed to assess the effects of supplementation with vitamin D on mortality
- Note: all women in the study had vitamin D levels below the lower limit of the normal range

Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women


- Background: Telomere length (LTL) is a predictor of aging-related disease
  - LTL decreases with each cell cycle, increasing inflammation
  - Vitamin D diminishes turnover of leukocytes and is a potent inhibitor of inflammation
- Research question: Do vitamin D concentrations modify telomere attrition in leukocytes and are higher vitamin D concentrations therefore associated with longer LTLs?

Methods: Serum 25-hydroxy D measured in 2160 women aged 18-79 y (mean age: 49.4) from a large population-based cohort of twins
  - LTL measured by Southern blot analysis
  - Serum C-reactive protein measured as a marker for inflammation
- Results: Age correlated negatively with LTL (P<0.0001) and serum 25-(OH) D associated with LTL (P = 0.001)
  - Relationships persisted after adjustment for age (r = 0.09, P < 0.0001), season of 25-(OH)D testing, menopausal status and HRT use, physical activity (P for trend across tertiles = 0.003)

- **Results (cont.):** The difference in LTL between the highest and lowest tertiles of vitamin D was equivalent to 5.0 y of telomeric aging
  - Difference further accentuated by ↑ CRP, a measure of systemic inflammation
- **Conclusions:** Higher vitamin D concentrations are associated with longer LTL
  - Results underscore the potentially beneficial effects of vitamin D status on aging and age-related diseases, which is easily modifiable through supplementation

Many drugs affect vitamin D needs

- **H2 receptor antagonists** (cimetidine, ranitidine) – impair liver metabolism
- **Anticonvulsants** – induce liver enzymes that destroy vitamin D
- **Steroids** (prednisone, etc) – interfere with the conversion of 25(OH)D to 125(OH)2D
- **Alcohol** – reduces absorption and interferes with conversion in the liver
- **Heparin** – interferes with kidney activation

Cancer and Vitamin D
Vitamin D and Cancer
– proposed mechanisms of action

1,25-dihydroxy D (calcitriol)
- Suppresses tumour cell proliferation
- Promotes cell differentiation
- Required for malignant cell apoptosis
- Inhibits angiogenesis (blood-vessel formation)
- Inhibits protease enzymes involved in tumour invasion (metastasis)

Cancers now known to be associated with vitamin D deficiency
- Pre- and post-menopausal breast cancer
- Ovarian, cervical and endometrial cancer
- Prostate cancer
- Lung cancer
- Colorectal cancer
- Leukemia, lymphoma
- Brain cancers

Association between pre-diagnostic circulating vitamin D concentrations and risk of colorectal cancer in European populations: a nested case-control study. BMJ 2010;340:b5500

- **Study:** Case-control study
  - Prospective study: 520,000 subjects from 10 countries
  - Cases and matched controls n = 1248
  - Male n = 620; Female n = 628. Mean age 58.8 yrs (30-77)
- **Outcome measures:** Incidence of colorectal cancer by 25-(OH)D concentrations and vitamin D intake
  - adjusted for dietary confounders and other variables (age, BMI, smoking, alcohol, etc)
- **Results:** Association between ↓ circulating 25-(OH)D and ↑ risk of colon but not rectal cancer
Association between pre-diagnostic circulating vitamin D concentrations and risk of colorectal cancer in European populations: a nested case-control study. BMJ 2010;340:b5500

- Results (cont): patients in highest quintile 25-(OH)D had 40% risk compared to lowest quintile (P<0.001)
  - Cutoff points Q1 < 25nmol/L; Q5 ≥ 100 nmol/L
- Dietary vitamin D intake was not associated with disease risk
  - average intake similar (166 IU) for cases and controls
- Conclusion: strong inverse association between pre-diagnostic serum 25-(OH)D and risk of colon cancer, but not with dietary vitamin D

Sun exposure and vitamin D - what about skin cancer?

- UV radiation damages DNA
- Major risk for basal and squamous cell carcinoma
  - treatable cancers
  - don’t easily metastasize
- Weaker association between UV and melanoma
  - the most aggressive skin cancer

Sun exposure and skin cancer
New Cases of Cancer in Canada
2007 estimates*

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Estimated Cases</th>
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<tbody>
<tr>
<td>Lung</td>
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<tr>
<td>Breast</td>
<td>22,500</td>
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<tr>
<td>Prostate</td>
<td>22,300</td>
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<tr>
<td>Colorectal</td>
<td>20,800</td>
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<tr>
<td>Melanoma</td>
<td>4,600</td>
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</table>

*Source: Canadian Cancer Society/ Globe and Mail Nov. 1, 2007

Inverse association between serum 25-hydroxy D levels and non-melanoma skin cancer in elderly men.

- **Study**: Nested case-control study. Examined link between vitamin D and calcium intake, 25-hydroxy D levels and risk of non-melanoma skin cancer (NMSK) in older men (age 73 yr +/- 5)
- **Results**: BMI, daily D and calcium intake similar men with (n = 178) and without NMSC (n = 930)
  - Men in the highest quintile of 25(OH)D (>75 ng/mL) had 47% lower risk of NMSC compared to those in the lowest quintile
- **Conclusion**: It's not how much vitamin D you take, but the serum levels that protect against NMSK

Vitamin D status and safe sun practices – the role of supplements

- Adequate 25-hydroxy D in mothers during pregnancy and in infants has lifetime implications
  - Prevents childhood and adult diseases such as type 1 diabetes, leukemia
- Emphasis should no longer be on rickets alone
  - Prevented by a relatively tiny vitamin D intake
- Supplements of 2000 IU per day required during pregnancy/breast-feeding

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Supplementing with vitamin D: How much is enough? How much is too much?

- The intake required for optimal serum levels varies from one individual to another
  - Depends on season, sun exposure, genes, age, BMI
- Canadian Cancer Society recommends 1000 IU/d for all Canadians in the winter months
- However, clinical experience demonstrates little correlation between serum level achieved and the amount of supplementation
  - Daily supplementation with 1000 IU to 10,000 IU needed to raise serum levels into the cancer protective range

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- **Study**: 98 adults genotyped for vitamin D binding protein (DBP)
  - 25-hydroxy D checked before and after taking 600 or 4000 IU/d vitamin D(3) for 1 yr
- **Results**: genetic variants of the DBP gene predicted starting 25-hydroxy D (no supplements)
- Starting 25-hydroxy D predicted the amount of supplemental vitamin D required to get into the normal range
  - Subjects with lower 25-hydrox D at baseline required higher amounts of vitamin D
Vitamin D and cancer mini-symposium: the risk of additional vitamin D. Veith R. Am Epidemiol. 2009;19(7):441-5

- Review: Are there risks attached to supplementing with vitamin D to reduce the risk of cancer?
- Background: Depending on climate, daily suberythemal exposure of large areas of skin to UVB for 20 mins. provides adults with about 10,000 IU vitamin D(3) per day
  - Plasma 25-hydroxy D can reach 220 nmol/L (88 ng/mL)
- Conclusion: Clinical trials show prolonged intake of 10,000 IU/d of vitamin D(3) poses no risk of adverse effects (hypercalcemia) – even when added to high physiologic levels of vitamin D

“The unpredictable relationship between vitamin D intake and blood levels makes it difficult to recommend a standard supplement dose and supports incorporating measurements of blood levels into recommendations.”

Goodwin PJ. J Clin Oncol 27(13):2117-9, 2009

Checking vitamin D status
– serum 25-hydroxy D
Laboratory reference range for 25-hydroxy D

- Normal ranges reflect what is common in an apparently healthy population
  - i.e. no obvious signs of diseases linked to vitamin D deficiency
- Until recently, reference range for 25-hydroxy D in most Toronto labs was 25-100 nmol/L
- Reference range currently 75-250 nmol/L
- Toxicity (hypercalcemia) usually assumed above 250 nmol/L

Laboratory “normal” range for vitamin D - is it normal?

Recent research shows that

- 25-50 nmol/L can be associated with serious musculoskeletal pain and dysfunction
- 75 nmol/L now considered to be the lowest level required for bone health
- Prevention of osteoporosis or stress fractures
- >100 nmol/L required to protect against multiple sclerosis
- 100-130 nmol/L associated with 50% reduction of risk of many cancers – breast, prostate, lung, colon

Pharmacokinetics of vitamin D toxicity


- Review article: Changing perspectives on vitamin D toxicity and its mechanisms

“Although current data support the viewpoint that plasma 25 (OH)D must rise above 750 nmol/L to produce toxicity (hypercalcemia), the more prudent upper limit of 250 nmol/L might be retained to ensure a wide safety margin.”
Where do we want to be within the normal range?

Serum 25(OH)D continuum and disease protection

<table>
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<tr>
<th>Rickets</th>
<th>Multiple sclerosis</th>
<th>Breast cancer</th>
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<tbody>
<tr>
<td>25</td>
<td>50</td>
<td>100</td>
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<tr>
<td>75</td>
<td>125</td>
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<td>175</td>
<td>200</td>
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Serum 25-hydroxy D (nmol/L)

Osteoporosis     Type 1 diabetes

Note: to convert values to ng/ml divide by 2.5

What should 25-hydroxy D levels be?

Physiological adult intake – 4000 IU
Aileen Burford-Mason

**Human Serum 25(OH)D in Sun-Rich Environments**

- Puerto Rico hospital personnel
- Puerto Rico farmers
- St. Louis USA lifeguards
- Israel lifeguards


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**Risk assessment for vitamin D**


- **Objective:** to derive a safe Tolerable Upper Intake Level (UL) for daily vitamin D supplementation
- **Method:** used existing risk assessment methodology of the US Food and Nutrition Board (FNB)
- **Conclusions:**
  - Well-designed human clinical trials in healthy adults show no toxicity at doses of vitamin D = 250 mcg/d (10,000 IU vitamin D3) per day
  - Therefore 10,000 IU/day can confidently be selected as the safe UL for unsupervised daily intake

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**Can higher blood levels of vitamin D reduce risk of cancer recurrence?**

- **Preliminary evidence suggests yes:**
  - Prostate cancer (slowed the rise in PSA) Nutr Cancer. 2005;51(1):32-6
Vitamin D does not work alone to prevent cancer or cancer recurrence

- Other vitamins and minerals involved in the metabolism of vitamin D include:
  - Magnesium, zinc, vitamin K, boron, vitamin A
- Dietary factors involved in the development of cancer and prevention of recurrence:
  - Lack of vegetables and fruit
  - High glycemic diet (sugar and starches)

Note: US and Canadian units used to express 25-hydroxy D are different…
Most US papers use ng/ml
Canada and the rest of the world use nmol/L
......to convert from US to Canadian values
multiply by 2.5
www.vitamindcouncil.org
www.aileenburfordmason.ca