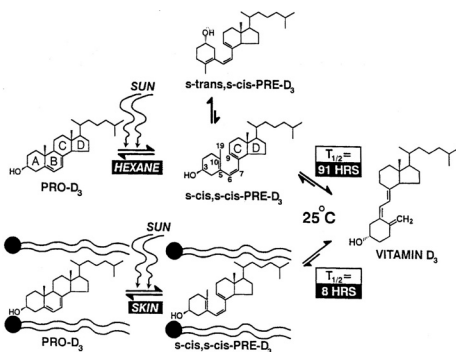


## 최근 각광받는 비타민 D 총정리

김도훈

고려대학교 안산병원 가정의학과

FIGURE 1. Photolysis of provitamin D3 (pro-D3) to previtamin D3 (pre-D3) and thermal isomerization of vitamin D3 in hexane and in lizard skin



Copyright ? 004 The American Society for Nutrition

Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

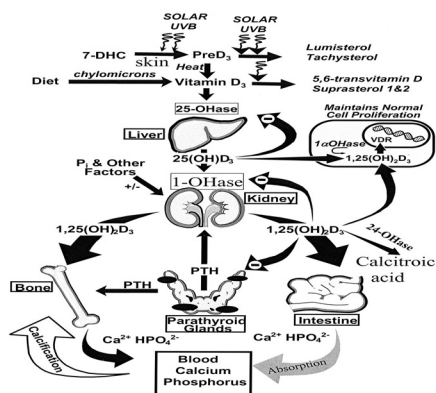
FIGURE 2. Typical presentation of 2 children with rickets



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Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

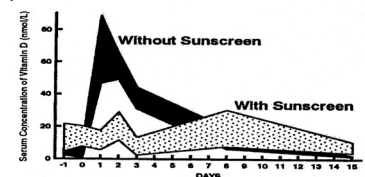
FIGURE 3. Schematic diagram of cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth



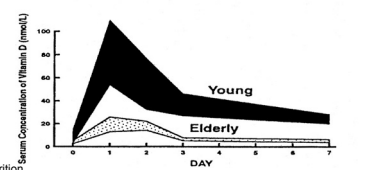
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Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

FIGURE 4. A: Circulating concentrations of vitamin D3 after a single exposure to 1 MED (minimal erythral dose) of simulated sunlight, with a sunscreen (SPF 8) or a topical placebo cream



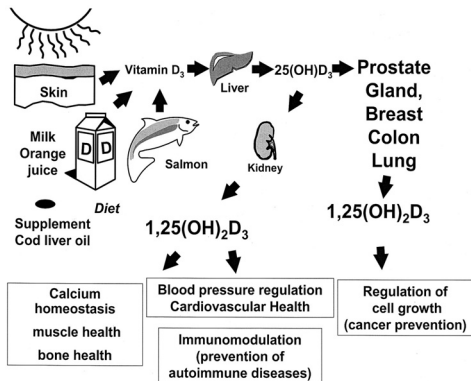
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Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

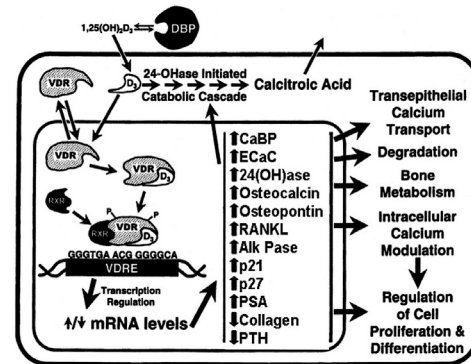
FIGURE 10. Metabolism of 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> in the kidney and other organs and the biological consequences



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Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

FIGURE 9. Schematic representation of the mechanism of action of 1,25(OH)<sub>2</sub>D in various target cells, resulting in a variety of biological responses



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Holick, M. F. Am J Clin Nutr 2004;80:1678S-1688S

## Overview

- **Effect of Vitamin D on Skeletal health**
  - Vitamin D & Osteoporosis
  - Vitamin D & Fall
- **Effect of Vitamin D on Extraskkeletal health**
  - Vitamin D & Immune function
  - Vitamin D & Cancer prevention
  - Vitamin D & Hypertension prevention
  - Vitamin D & Hyperlipidemia

## Part 1. Vitamin D & Fall

### Effect of Vitamin D on falls: a meta-analysis

- Based on 5 RCTs involving 1237 participants, vitamin D **reduced the corrected odds ratio (OR)** of falling by **22%** (corrected OR, **0.78**; 95% confidence interval [CI], **0.64-0.92**) compared with patients receiving calcium or placebo.
- The number needed to treat (NNT) was **15** (95% CI, 8-53)
- The inclusion of 5 additional studies, involving 10001 participants, in a sensitivity analysis resulted in a smaller but still significant effect size (corrected RR, 0.87; 95% CI, 0.80-0.96).

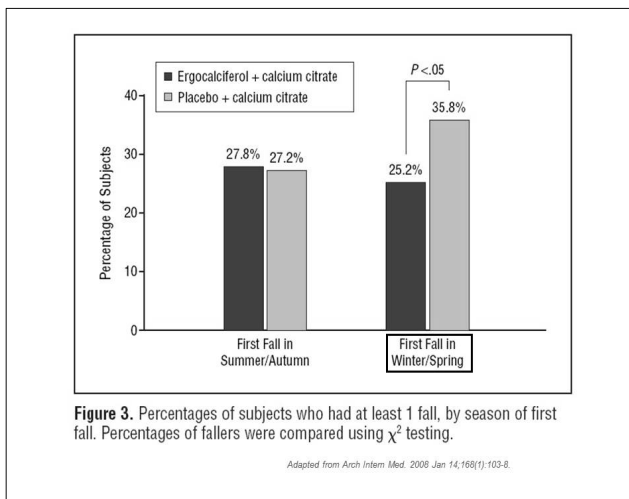
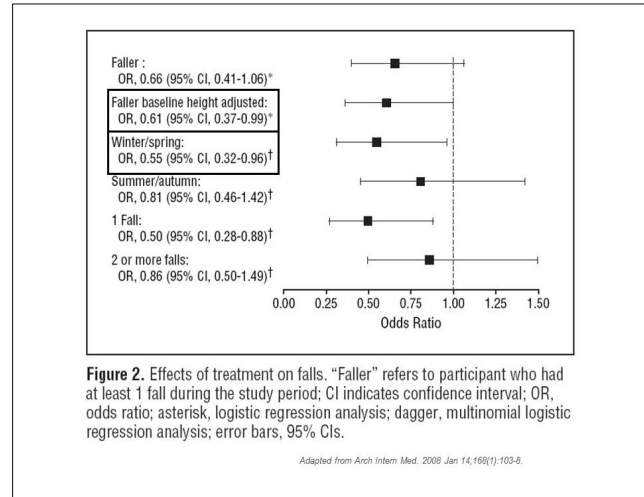
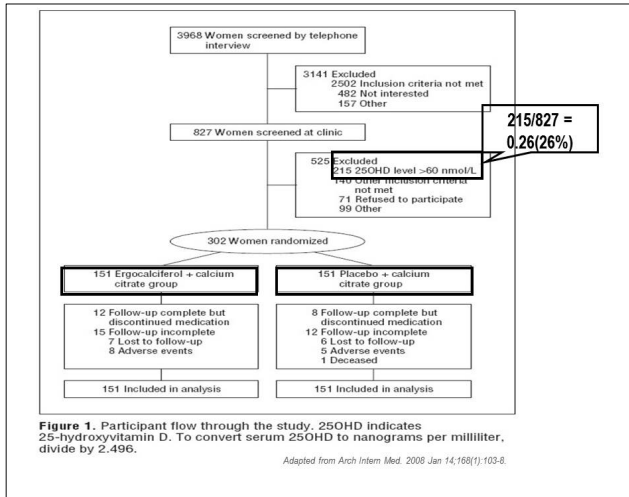
Adapted from JAMA, 2004;291:1999-2006.

### Effects of Ergocalciferol Added to Calcium on the Risk of Falls in Elderly High-Risk Women

#### Background :

- Ergocalciferol (vitamin D<sub>2</sub>) supplementation **plays a role in fall prevention**, but the effect in patients living in the community in sunny climates remains uncertain.
- We evaluated the effect of **ergocalciferol and calcium citrate supplementation** compared with **calcium alone** on the risk of falls in older women at high risk of falling.

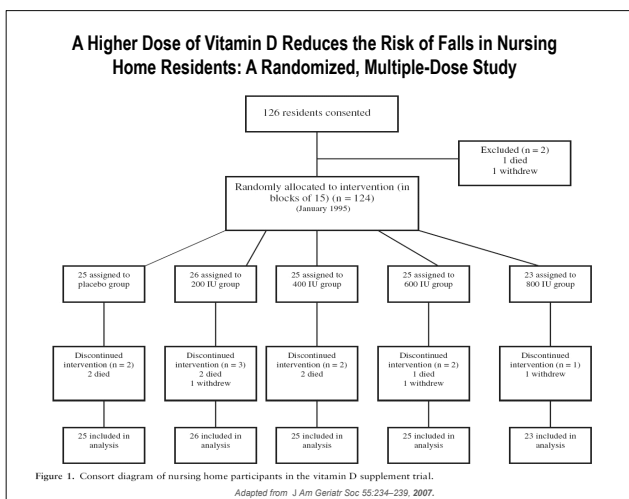
Adapted from Arch Intern Med. 2008 Jan 14;168(1):103-8.



## Conclusion

► Patients with a history of falling and vitamin D insufficiency living in sunny climates *benefit from ergocalciferol supplementation in addition to calcium*, which is associated with a *19% reduction* in the relative risk of falling, *mostly in winter*.

Adapted from Arch Intern Med. 2008 Jan 14;168(1):103-8.



**A Higher Dose of Vitamin D Reduces the Risk of Falls in Nursing Home Residents: A Randomized, Multiple-Dose Study**

Table 2. Vitamin D Supplement Intake and Fall Outcomes During 5-Month Clinical Trial by Supplement Group for 124 Nursing Home Residents

Outcome	Placebo (n=25)	200 IU (n=26)	400 IU (n=25)	600 IU (n=25)	800 IU (n=23)
Total vitamin D supplement intake, IU, mean (range) <sup>a</sup>	272.00 (0-400)	446.15 (200-600)	672.00 (400-800)	840.00 (600-1,000)	1,026.09 (800-1,200)
Serum 25-hydroxyvitamin D, ng/mL, mean $\pm$ SD <sup>b</sup>	24.12 $\pm$ 13.04	24.50 $\pm$ 8.29	21.89 $\pm$ 9.22	24.47 $\pm$ 8.78	29.82 $\pm$ 6.26
Faller, n (%)	11 (44)	15 (58)	15 (60)	15 (60)	5 (20)
Total falls, n	31	37	33	41	9
Hazard ratio (95% CI) of time to first fall <sup>c</sup>	1.00	1.79 (0.78-3.71)	1.70 (0.77-3.73)	1.68 (0.78-3.71)	0.44 (0.15-1.28)
Incidence rate ratio (95% CI) of falls during the study <sup>d</sup>	1.00	1.10 (0.49-2.50)	1.05 (0.48-2.28)	1.21 (0.55-2.61)	0.28 (0.10-0.75)

<sup>a</sup>Total vitamin D supplement intake = Vitamin D from the study pill + Hebrew Rehabilitation Center for Aged multivitamin (400 IU).  
<sup>b</sup>Valid follow-up serum concentrations available for some participants: placebo (n=20), 200 IU (n=22), 400 IU (n=23), 600 IU (n=19), 800 IU (n=17).  
<sup>c</sup>Adjusted for age and multivitamin use.  
<sup>d</sup>CI = confidence interval.

Adapted from J Am Geriatr Soc 55:234-239, 2007.

### A Higher Dose of Vitamin D Reduces the Risk of Falls in Nursing Home Residents: A Randomized, Multiple-Dose Study

- ▶ Nursing home residents in the *highest vitamin D group (800 IU)* had a lower number of fallers and a lower incidence rate of falls over 5 months than those taking lower doses.
- ▶ Adequate vitamin D supplementation in elderly nursing home residents could reduce the number of falls experienced by this high falls risk group.

Adapted from J Am Geriatr Soc 55:234-239, 2007.

### Effect of Cholecalciferol Plus Calcium on Falling in Ambulatory Older Men and Women

- little is known about whether supplemental cholecalciferol plus calcium citrate malate will lower the long-term risk of falling in men, active older individuals, and older individuals with higher 25-hydroxyvitamin D levels.

Adapted from Arch Intern Med. 2006;166:424-430.

### Effect of Cholecalciferol-Calcium on the Number of Persons Who Fell During the 3-Year Follow-up

Table 3. Effect of Cholecalciferol-Calcium on the Number of Persons Who Fell During the 3-Year Follow-up

Patients	OR (95% CI)*	
	Intent-to-Treat Analysis (n = 445)	Per Protocol Analysis (n = 318)
Total sample	0.77 (0.51-1.15) (n = 416)	0.68 (0.43-1.08) (n = 318)
Less active	0.60 (0.33-1.07) (n = 204)	0.42 (0.20-0.87) (n = 146)
More active	0.98 (0.54-1.77) (n = 212)	0.88 (0.46-1.68) (n = 172)
Women	0.54 (0.30-0.97) (n = 228)	0.44 (0.21-0.90) (n = 170)
Less active	0.35 (0.15-0.81) (n = 130)	0.26 (0.09-0.83) (n = 91)
More active	1.06 (0.42-2.65) (n = 99)	0.88 (0.31-2.55) (n = 79)
Men	0.93 (0.50-1.72) (n = 187)	0.84 (0.42-1.66) (n = 148)
Less active	0.96 (0.34-2.67) (n = 74)	0.65 (0.18-2.29) (n = 55)
More active	1.01 (0.43-2.40) (n = 113)	0.94 (0.37-2.38) (n = 93)

Abbreviations: CI, confidence interval; OR, odds ratio.

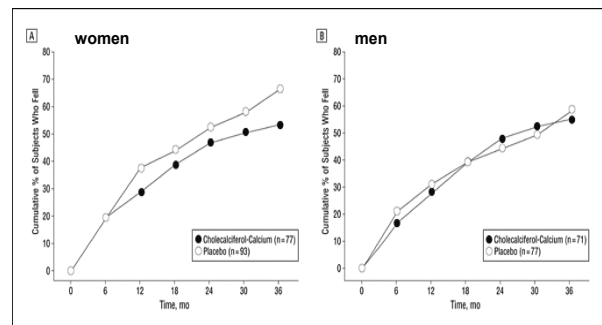
\*Controlling for age, sex, body mass index, average dietary calcium intake, baseline 25-hydroxyvitamin D levels, baseline intact parathyroid hormone level, activity level, smoking status, use of alcoholic beverages, number of comorbid conditions, creatinine clearance, and length of follow-up.

Bischoff-Ferrari, H. A. et al. Arch Intern Med 2006;166:424-430.

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### Cumulative percentage of falls by treatment group and sex

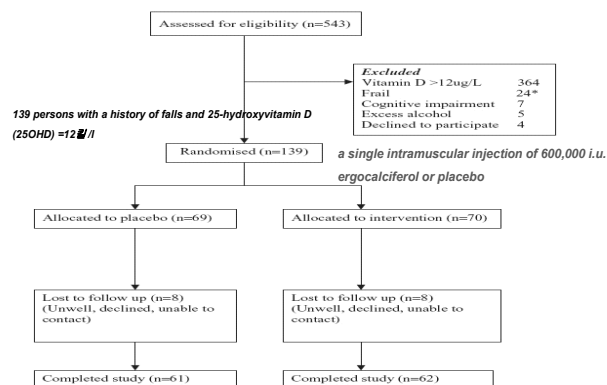


Bischoff-Ferrari, H. A. et al. Arch Intern Med 2006;166:424-430.

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### Vitamin D supplementation improves neuromuscular function in older people who fall



Adapted from Age and Ageing 2004; 33: 589-595

### Vitamin D supplementation improves neuromuscular function in older people who fall

Table 2. Biochemistry and neuromuscular function of placebo (P) and intervention (I) groups at baseline and at 6 months

		Baseline	6 months	Change over 6 months
25OHD (µg/l)	P	10.0 (9.5-10.5)	12.6 (11.4-13.8)	2.7 (1.6-3.8)
	I	10.7 (10.2-11.2)	17.5 (16.3-18.5)	6.9 (5.9-8.0)
PTH (pg/L)	P	59.1 (51.7-66.5)	60.1 (50.0-70.3)	1.2 (-8.6-11.1)
	I	52.1 (44.8-59.5)	49.8 (44.0-55.7)	-2.1 (-7.8-3.6)
AFPT (s)	P	72.9 (63.0-82.8)	76.8 (65.4-88.1)	+6.6 (0.8-12.4)
	I	65.8 (55.6-76.0)	65.5 (54.9-76.1)	-2.0 (-4.4-0.3)
<b>P value &lt; 0.01</b>				
CRT (s)	P	7.20 (7.02-7.38)	7.37 (7.18-7.56)	+0.06 (-0.35-0.47)
	I	7.67 (7.13-8.21)	7.30 (7.02-7.58)	-0.41 (-0.72-0.66)
<b>P value = 0.01</b>				
Postural sway	P	0.0978 (0.0850-0.1105)	0.0999 (0.0857-0.1140)	+0.0025 (-0.0089-0.0139)
	I	0.1044 (0.090-0.1178)	0.0899 (0.0784-0.1015)	-0.0138 (-0.0218-0.0050)
<b>P value = 0.02</b>				
MVC (Newtons)	P	205 (187-223)	198 (178-218)	-10 (-19-2)
	I	203 (182-225)	204 (181-227)	-7 (-11-2)
<b>Not significant</b>				

AFPT ? Aggregate Functional Performance Time, Functional Performance 확인

CRT ? Choice reaction time, Psychomotor function 확인

MVC ? Maximum voluntary contraction, Quadriceps contraction을 확인

Adapted from Age and Ageing 2004; 33: 589-595

### Vitamin D supplementation improves neuromuscular function in older people who fall

#### Key points

- Vitamin D supplementation has beneficial effects on **functional performance, balance and reaction time** but not on muscle strength.
- Vitamin D supplementation improves **neuromuscular coordination, rather than muscle strength**

Adapted from Age and Ageing 2004; 33: 589-595

## Part 2. Vitamin D & Cancer prevention

### Vitamin D and cancer

- Vitamin D may reduce the risk of cancer through **regulation of cellular proliferation and differentiation** as well as **inhibition of angiogenesis**
- Cells, including cancer cells, express specific receptors (**VDR**) for 1,25-dihydroxyvitamin D

Adapted from J Cancer Res Ther. 2007 Oct-Dec;3(4):225-30.

### Vitamin D and cancer

- VDR regulates > 60 genes that exert prodifferentiating, antiproliferative and antimetastatic effects
- The amount of exposure to the sun has been found to correlate inversely with cancer mortality and survival in numerous epidemiological studies

Adapted from J Cancer Res Ther. 2007 Oct-Dec;3(4):225-30.

### Vitamin D and cancer

- ▶ Several ecological studies suggest that sunlight may protect against prostate, colon, rectal, female breast and ovarian cancer, all diseases that contribute to a substantially higher proportion of cancer mortality in the western industrialized world.
- ▶ Some analytical studies also suggest a protective association between circulating vitamin D in blood, which is largely derived from sunlight, or dietary vitamin D.

Adapted from J Cancer Res Ther. 2007 Oct-Dec;3(4):225-30.

http://www.hsph.harvard.edu/hpfs/

#### HEALTH PROFESSIONALS FOLLOW-UP STUDY

Harvard School of Public Health

- About the Study
- Researchers and Staff
- Publications
- Newsletters
- Contact
- Questionnaires
- Change Address Form
- Questions And Answers

#### About the Study

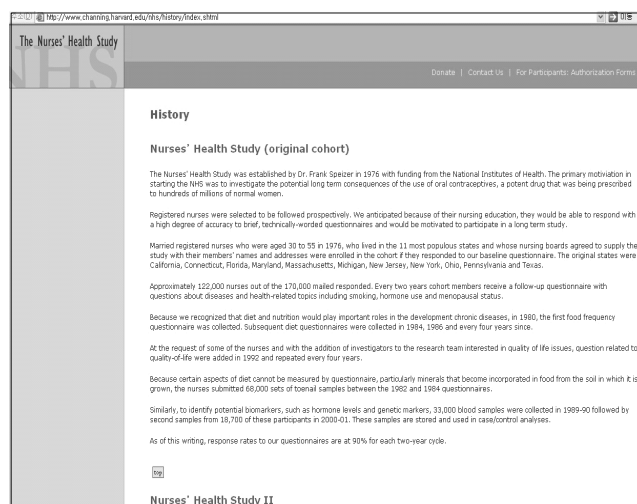
The Health Professionals Follow-Up Study (HPFS) began in 1986. The purpose of the study is to evaluate a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease, and other vascular diseases. This all-male study is designed to complement the all-female Nurses' Health Study, which examines similar hypotheses. The HPFS is sponsored by the Harvard School of Public Health and is funded by the National Heart, Lung, and Blood Institute and National Cancer Institute.

In the beginning, Walter Willett, Principal Investigator, Meir Stampfer, and colleagues enlisted 64,426 men in health professions to participate in the study. This group is composed of 29,683 dentists, 4,185 pharmacists, 3,745 optometrists, 2,220 osteopath physicians, 1,600 podiatrists, and 10,098 veterinarians. Among the study participants are 531 African-Americans and 877 Asian-Americans.

The researchers selected health professionals in the belief that men who chose these types of careers would be motivated and committed to participating in a long-term project and would appreciate the necessity of answering the survey questions accurately.

Every two years, members of the study receive questionnaires with questions about diseases and health-related topics like smoking, physical activity, and medications taken. The questionnaires that ask detailed dietary information are administered in four-year intervals.

Since its inception, more than 100 published research articles have been produced by scientists working with data from the study.



### Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

- Consider multiple determinants of vitamin D exposure (*dietary and supplementary vitamin D, skin pigmentation, adiposity, geographic residence, and leisure-time physical activity*)—to estimate sunlight exposure) in relation to cancer risk in the Health Professionals Follow-Up Study
- Among 1095 men of this cohort, we quantified *the relation of these six determinants to plasma 25-hydroxy-vitamin D level* by use of a *multiple linear regression model*.

Adapted from J Natl Cancer Inst 2006;98:451 – 9

### Prospective Study of Predictors of Vitamin D Status and Cancer Incidence and Mortality in Men

- We used results from the model to compute a *predicted 25(OH)D level* for each of **47800 men** in the cohort based on these characteristics.
- We then prospectively examined *this predicted 25(OH)D level* in relation to cancer risk with multivariable Cox proportional hazards models
- **From 1986 through January 31, 2000**

Adapted from J Natl Cancer Inst 2006;98:451 – 9

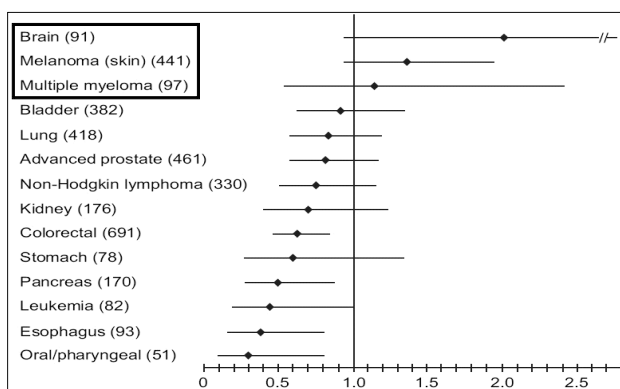


Fig. 1. Multivariable relative risks and 95% confidence intervals for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). Number in parentheses = number of cases. Covariables included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

**Table 3.** Relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D [25(OH)D] level for total cancer incidence and mortality in the Health Professionals Follow-Up Study (1986–2000)

Endpoint	RR (95% CI)
Total cancer incidence (N = 4286)	
Age-adjusted	0.78 (0.70 to 0.86)
Multivariable-adjusted*	0.83 (0.74 to 0.92)
Multivariable + BMI†	0.83 (0.73 to 0.94)
Multivariable + physical activity	0.84 (0.72 to 0.98)
Total cancer mortality (N = 2025)	
Age-adjusted	0.65 (0.56 to 0.76)
Multivariable-adjusted*	0.71 (0.60 to 0.83)
Multivariable + BMI†	0.71 (0.59 to 0.84)
Multivariable + physical activity	0.69 (0.55 to 0.86)

\*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

†BMI = body mass index.

**Table 4.** Relative risks (RRs) and 95% confidence intervals (CIs) for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D [25(OH)D] level for digestive system cancer incidence and mortality in the Health Professionals Follow-Up Study (1986–2000)

Endpoint	RR (95% CI)
Digestive cancer incidence (n = 1123)	
Age-adjusted	0.54 (0.44 to 0.66)
Multivariable-adjusted*	0.57 (0.46 to 0.71)
Multivariable + BMI†	0.59 (0.47 to 0.75)
Multivariable + physical activity	0.52 (0.38 to 0.71)
Digestive cancer mortality (n = 594)	
Age-adjusted	0.51 (0.39 to 0.67)
Multivariable-adjusted*	0.55 (0.41 to 0.74)
Multivariable + BMI†	0.54 (0.39 to 0.75)
Multivariable + physical activity	0.45 (0.30 to 0.68)

\*The following covariables were included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables.

†BMI = body mass index.

### Prospective Study of Serum Vitamin D and Cancer mortality in the United States

- ▶ A total of 16 818 participants in the 3rd NHNES who were 17 years or older at enrollment were followed from 1988 – 1994 through 2000.
- ▶ Levels of serum 25(OH)D were measured at baseline by radioimmunoassay.
- ▶ Our results do not support an association between 25(OH)D and total cancer mortality, although there was an inverse relationship between 25(OH)D levels and colorectal cancer mortality

Adapted from J Natl Cancer Inst 2007;99: 1594 – 602

**Table 4.** Relative risks (RRs) and 95% confidence intervals (CIs) for site-specific cancer mortality according to baseline serum 25-hydroxyvitamin D [25(OH)D] levels (nmol/L) in the Third National Health and Nutrition Examination Survey (NHANES III Study), 1988–2000\*

Cancer site	25(OH)D (nmol/L)				P <sub>trend</sub>
	<50	50 to <80	80 to <100	≥100	
Lung cancer					
No. of deaths	57	51	23	22	
RR	1.0	0.78	0.65	1.14	
95% CI		0.50 to 1.22	0.36 to 1.18	0.60 to 2.18	.41
Digestive cancers other than colorectal cancer†					
No. of deaths	34	37			
RR	1.0	1.42			
95% CI		0.73 to 1.76			.18
Breast cancer					
No. of deaths	20	8			
RR	1.0	0.28			
95% CI		0.08 to 0.93			.76
Prostate cancer					
No. of deaths	22	25			
RR	1.00	0.91			
95% CI		0.39 to 2.14			.95
Non-Hodgkin lymphoma/leukemia					
No. of deaths	16	24			
RR	1.0	1.34			
95% CI		0.62 to 2.91			.96
Colorectal cancer†					
No. of deaths	28	24	14		
RR	1.0	0.44	0.28		
95% CI		0.20 to 0.95	0.11 to 0.68		.02
Other cancer sites‡					
No. of deaths	38	60	32		
RR	1.0	1.83	1.86		
95% CI		0.93 to 3.61	0.75 to 4.63		.84

## Part 3. Vitamin D & Cardiovascular risk

### Vitamin D & Cardiovascular risk

- Results of several epidemiologic and clinical studies have suggested that there is **an excess risk of hypertension and diabetes mellitus** in persons with suboptimal intake of vitamin D
- The association between serum levels of **25-hydroxyvitamin D** and **cardiovascular disease risk factors** in US adults.

Adapted from Arch Intern Med. 2007;167:1159-1165

### Vitamin D & Cardiovascular risk

- **7186 male and 7902 female** adults 20 years and older with available data in the Third NHNES

Adapted from Arch Intern Med. 2007;167:1159-1165

**Age-, Sex-, and Race-Adjusted Prevalence and ORs of Select Cardiovascular Disease Risk Factors between the First and Fourth Quartiles of Serum 25(OH)D Levels**

**Table 3. Age-, Sex-, and Race-Adjusted Prevalence and ORs of Select Cardiovascular Disease Risk Factors between the First and Fourth Quartiles of Serum 25(OH)D Levels**

Risk Factor	Prevalence of Cardiovascular Risk Factor		OR (95% CI)	P Value
	1st Quartile (<21 ng/mL)	4th Quartile (≥37 ng/mL)		
Blood pressure ≥140/≥90 mm Hg	20.46	15.10	1.30 (1.13-1.49)	
Fasting blood glucose level, mg/dL				
110-125	6.96	3.25	2.15 (1.69-2.74)	<.001
≥126	6.95	3.38	1.98 (1.57-2.51)	<.001
History of diabetes mellitus	6.96	3.28	1.73 (1.38-2.16)	<.001
Body mass index ≥30*	24.69	11.50	2.29 (1.99-2.63)	<.001
Triglyceride level ≥150 mg/dL	32.86	23.84	1.47 (1.30-1.65)	<.001
Total cholesterol level ≥240 mg/dL	19.98	15.92	0.97 (0.85-1.11)	.65
Non-HDL cholesterol level ≥150 mg/dL	48.99	41.49	1.04 (0.93-1.16)	.50
Serum albumin level <3.5 g/dL	2.77	1.57	2.90 (1.89-4.46)	<.001
eGFR <60 mL/min per 1.73 m <sup>2</sup>	5.12	4.27	1.08 (0.87-1.35)	.47
ACR ≥200 for males/≥300 for females	1.59	0.76	2.54 (1.65-3.46)	<.001

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.  
SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; 25(OH)D to nanomoles per liter, multiply by 2.496; triglycerides to millimoles per liter, multiply by 0.0113.  
\*Calculated as weight in kilograms divided by the square of height in meters.

Martins, D. et al. Arch Intern Med 2007;167:1159-1165.

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### Vitamin D & Cardiovascular risk

- Serum 25(OH)D levels are associated with **important cardiovascular disease risk factors** in US adults.
- **Prospective studies** to assess a direct benefit of cholecalciferol(vitamin D) supplementation on cardiovascular disease risk factors are warranted.

Adapted from Arch Intern Med. 2007;167:1159-1165

### Vitamin D & Blood Pressure

- Recent clinical trials and animal studies have suggested that **vitamin D insufficiency** may be associated with **elevated blood pressure**
- VitaminD is one important nutrient that has been postulated as **a contributing factor to the development of hypertension**, possibly through **inhibition of the renin angiotensin system**

Adapted from Am J Clin Nutr 2008;87:136-41.

### Vitamin D & Blood Pressure

- ▶ Li et al showed that 1, 25-hydroxyvitaminD [**1,25(OH)2D**], the active steroid hormone form of vitamin D, **inhibits renin gene expression** in vitamin D receptor knockout mice.
- ▶ These mice develop **hypertension** that can be reversed with treatment with **captopril**, an angiotensin-converting enzyme inhibitor as well as treatment with **1,25(OH)2D**.

Adapted from J Clin Invest 2002;110:229-38

### Vitamin D & Blood Pressure

- **The concentration of 25(OH)D** needed for cardiovascular benefits may be **even higher than that needed for skeletal benefits** and **may differ by race**

Adapted from Am J Clin Nutr 2008;87:136-41.

**TABLE 1**  
Demographic characteristics of white and black adults without a diagnosis of hypertension who had a serum vitamin D measurement 25(OH)D available in the third National Health and Nutrition Examination Survey NHANES (1988-1994)<sup>1</sup>

	Total (n = 7699)	White (n = 4663)	Black (n = 3036)
<b>Sex</b>			
Men	3613 (47)	2198 (47)	1415 (47)
Women	4086 (53)	2465 (53)	1621 (53)
<b>Age (yr)</b>			
18-49	4818 (63)	2413 (52)	2405 (79)
≥50	2881 (37)	2250 (48)	631 (21)
<b>BMI (kg/m<sup>2</sup>)<sup>2</sup></b>			
Normal and underweight (<25)	3692 (48)	2362 (51)	1330 (44)
Overweight (25-29.9)	2514 (33)	1572 (34)	942 (31)
Obese (≥30)	1493 (19)	729 (16)	764 (25)
<b>Season of measurement<sup>2</sup></b>			
January-March	1167 (15)	724 (16)	443 (15)
April-June	1987 (26)	1386 (30)	601 (20)
July-September	2485 (32)	1535 (33)	950 (31)
October-December	2060 (27)	1018 (22)	1042 (34)
<b>Systolic blood pressure (mm Hg)<sup>2</sup></b>			
<110 (normotensive)	1957 (25)	1123 (24)	834 (27)
110-119 (high normal)	2133 (28)	1218 (26)	915 (30)
120-129 (prehypertensive)	1654 (21)	983 (21)	671 (22)
130-139 (borderline)	919 (12)	595 (13)	324 (11)
140-159 (stage 1 hypertension)	793 (10)	568 (12)	225 (7)
≥160 (stage 2 hypertension)	243 (3)	176 (4)	67 (2)

<sup>1</sup> All values are n; weighted percentage in parentheses.

<sup>2</sup> P value comparing number of whites and blacks in each category was <0.01 (Mantel-Haenszel chi-square test).

Adapted from Am J Clin Nutr 2008;87:136-41.

**FIGURE 1.** Concentrations of 25-hydroxyvitamin D [25(OH)D] by systolic blood pressure with the use of the Joint National Committee 7 (JNC 7) hypertension classifications among adults in the third National Health and Nutrition Examination Survey (NHANES III; 1988-1994)

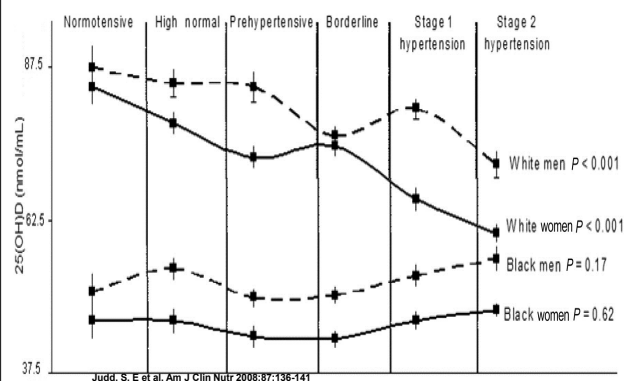
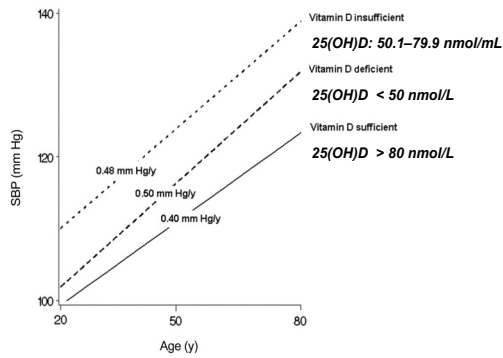




FIGURE 2. Age-related increase in systolic blood pressure (SBP) is shown in white participants not currently using medication to lower blood pressure, stratified by 3 concentrations of 25-hydroxyvitamin D [25(OH)D]



Judd, S. E et al. Am J Clin Nutr 2008;87:136-141  
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## Part 4. Vitamin D & Immune system

### D-Hormone and the Immune System

- ▶ important immune system regulator that has been shown to inhibit development of autoimmune diseases including experimental inflammatory bowel disease (IBD), rheumatoid arthritis (RA), multiple sclerosis (MS), and type 1 diabetes.
- ▶ Paradoxically, other immune mediated diseases (experimental asthma) and immunity to infectious organisms were not found to be affected by D-hormone treatment.

Adapted from J Rheumatol 2005;32 Suppl 76:11-20

### D-Hormone and the Immune System

- The effectiveness of D-hormone treatment of autoimmune diseases is due to inhibition of the development and function of Th1 cells and the induction of other Th cells including Th2 cells.
- The Results of microarray analysis of colons from D-hormone treated mice with experimental IBD.

Adapted from J Rheumatol 2005;32 Suppl 76:11-20

### D-Hormone and the Immune System

Table 4. D-hormone targets 3 TNF- $\alpha$  related genes in the colon of mice with experimental IBD.

Gene	Experiment 1		Experiment 2	
	Intensity*	Ratio**	Intensity	Ratio
TNF- $\alpha$	414	-2.1	309	-2.7
LPS-induced TNF- $\alpha$ factor <sup>#</sup>	4267	-1.7	4516	-1.9
TNF receptor	3494	-1.7	163	-3.1
VDR	745	2.6	422	1.9
Calmodulin	4663	1.7	11878	3.6
Calcium Binding Protein A6	97601	2.3	39160	4.7

\* Combined median red and green intensities.

\*\* The ratio is either the ratio of green fluorescence over red fluorescence (positive values) or the inverse (negative values). Positive ratios represent genes that are activated in the presence of D-hormone and negative ratios represent genes that are repressed in the presence of D-hormone.

<sup>#</sup> LPS-induced TNF- $\alpha$  factor was reanalyzed using quantitative real-time PCR. The expression of this gene was 4 to 461 times lower in colons of D-hormone treated IL-10 KO mice (n=4) compared to the D-control (n=4) colons. The microarray underestimated the efficacy of D-hormone to inhibit LPS-induced TNF- $\alpha$ .

Adapted from J Rheumatol 2005;32 Suppl 76:11-20

### D-Hormone and the Immune System

- ▶ The most evident effects of the D-hormone on the immune system seem to be in the control (down-regulation) of Th1-driven autoimmunity
- ▶ Latitude-related ecological features (i.e. different sun exposure), support a gradient of increasing prevalence of RA (Finland nearly 0.8% and 0.3% in Italy) with higher latitude, such as for other autoimmune diseases (i.e. multiple sclerosis)
- ▶ 25(OH)D3 plasma levels have been found inversely correlated with the RA disease activity showing a circannual rhythm (more severe in winter)

Adapted from Autoimmunity Reviews 2007;7:59-64

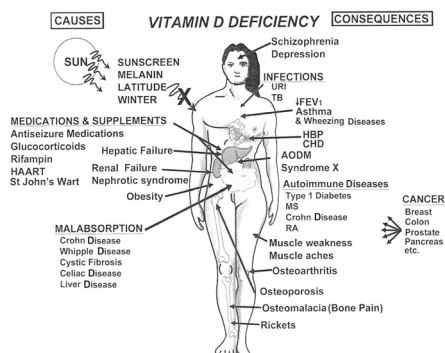
## D-Hormone and the Immune System

- Recently, greater intake of vitamin D was associated with a lower risk of RA
- Recent reviews suggest that the optimal plasma 25(OH)D3 concentration lies between 50-80 nmoles/L, other experts suggesting between 75-125 nmol/L

Adapted from Autoimmunity Reviews 2007;7:59-64

## Part 5. Vitamin D daily requirement

FIGURE 3. A schematic representation of the major causes of vitamin D deficiency and potential health consequences



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Holick, M. F et al. Am J Clin Nutr 2008;87:1080S-1086S

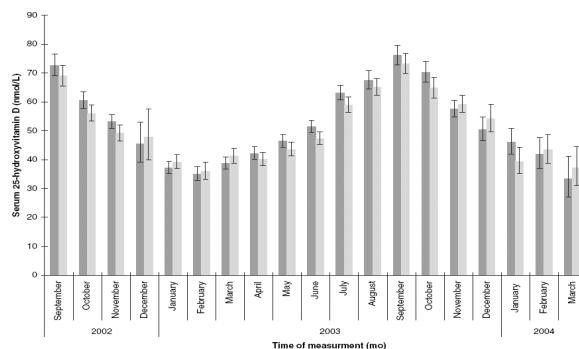


FIGURE 1. Geometric mean (95% CI) monthly variation in serum 25-hydroxyvitamin D (25(OH)D) concentrations in men (■, n = 3725) and women (□, n = 3712) in the 1958 British birth cohort at age 45 y. The interaction between sex and month was significant (P = 0.02, linear regression analyses on log 25(OH)D). n per sex and month ranged from 17 to 140; 98 in December 2003 for women and <100 for both sexes in December 2002 (n = 40 M, 37 F), January 2004 (n = 95 M, 75 F), February 2004 (n = 58 M, 70 F), and March 2004 (n = 22 M, 17 F).

Adapted from Am J Clin Nutr. 2007 Mar;85(3):860-8

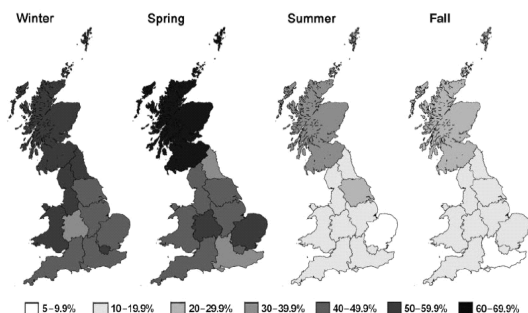


FIGURE 3. Seasonal and geographical variation in the prevalence of hypovitaminosis D (25-hydroxyvitamin D <40 nmol/L) in Great Britain.

Adapted from Am J Clin Nutr. 2007 Mar;85(3):860-8

Table 1

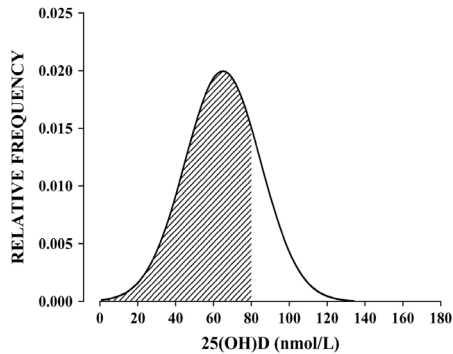
The daily requirements of 1,25(OH)2D3 change during the life and physiological conditions

Age	Children (µg/day)	Men (µg/day)	Women (µg/day)	Pregnancy (µg/day)	Lactation (µg/day)
Birth to 13 years	5 (=200 IU)				
14 to 18 years		5 (=200 IU)	5 (=200 IU)	5 (=200 IU)	5 (=200 IU)
19 to 50 years		5 (=200 IU)	5 (=200 IU)	5 (=200 IU)	5 (=200 IU)
51 to 70 years		10 (=400 IU)	10 (=400 IU)		
71+ years		15 (=600 IU)	15 (=600 IU)		

Dietary or exogenous 1,25(OH)2D3 integrations (in IU) might be required in order to keep the optimal 25(OH)D3 plasma concentrations between 50-125 nmol/L.

Adapted from Intern Med J 2007;37:377-82.

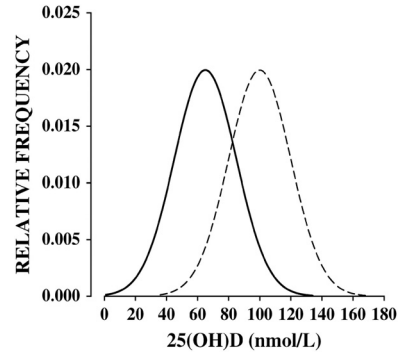
FIGURE-1. Approximation of the NHANES distribution of serum 25(OH)D values in women aged 60-79 y



Heaney, R. P. J. Nutr. 2006;136:1123-1125

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FIGURE-2. Data from Figure 1 plus a second distribution augmented by 35 nmol/L (the approximate difference predicted to be produced by an extra 2000 IU of cholecalciferol per day)



Heaney, R. P. J. Nutr. 2006;136:1123-1125

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**Table 1.**  
**Oral Vitamin D Formulations**

Ergocalciferol  
Vitamin D<sub>2</sub>  
Cholecalciferol  
Vitamin D<sub>3</sub>  
Calcitriol (Rocaltrol)  
Activated vitamin D<sub>3</sub>  
1,25(OH)<sub>2</sub> vitamin D<sub>3</sub>  
Doxercalciferol (Hectorol)  
Activated vitamin D<sub>2</sub> analog  
Paricalcitol (Zemlar)  
Activated vitamin D<sub>2</sub> analog

**Table 2.**  
**Oral Vitamin D<sub>3</sub> (Cholecalciferol) Dosing Guide**

Indication	Dosage Regimen	Maximum Daily Dose or Equivalent
RDA up to age 50	200 IU daily	2000 IU daily
RDA 50-70 years of age	400 IU daily	2000 IU daily
RDA >70 years of age	600 IU daily	2000 IU daily
Vitamin D deficiency, prophylaxis	400-800 IU daily	2000 IU daily
Fall and fracture prevention	700-800 IU daily	2000 IU daily*
	10,000 IU weekly	2000 IU daily
	50,000 IU monthly	60,000 IU monthly
	100,000 IU every 4 months (120 days)	60,000 IU monthly
Cancer prevention	1000-2000 IU daily	2000 IU daily

RDA = recommended daily allowance.

\*Vitamin D<sub>3</sub> (cholecalciferol) doses >2000 IU daily may be necessary for adults with nutritional osteomalacia, renal osteodystrophy, or familial X-linked hypophosphatemic vitamin D-refractory rickets. Use should be guided by serum calcium, phosphorus, and parathyroid concentration monitoring. Activated forms of vitamin D, as vitamin D analogs (calcitriol, paricalcitol, and doxercalciferol), are recommended in Stages 4 and 5 chronic kidney disease patients who are unlikely to have intact renal mechanisms for interconversion of 25-OH vitamin D to 1,25-OH vitamin D.

## Part 6. Vitamin D & Statin

- Vitamin D levels and statin effectiveness
- Vitamin D deficiency and statin myopathy
- Vitamin D as an inducer of CYP enzymes

- Vitamin D is known to activate CYP3A4.
- The fully active dihydroxylated vitamin D<sub>3</sub> induces the expression of not only CYP3A4, but also CYP2B6 and CYP2C9 in primary human hepatocytes.
- Hydroxylated vitamin D derivatives also possess 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase activity.

Q J Med 2012; 105:487-491 doi:10.1093/qjmed/hcs001

Table 2

Vitamin D supplementation in 64 (30 women, 34 men) hypercholesterolemic, vitamin D deficient patients previously statin-intolerant because of myalgia, myositis, myopathy, or myonecrosis. Prospective followup at 6 months, 12 months, and 24 months [mean (SD), median exhibited]. The 64 patients had all three follow-up visits at 6 months, 12 months, and 24 months

Measure	Study entry	6-month follow-up	12-month follow-up	24-month follow-up
Vitamin D (ng/mL)	21 (7), 22	57 (19), 54 <sup>***</sup>	54 (15), 55 <sup>***</sup>	58 (20), 56 <sup>***</sup>
LDLC (mg/dL)	161 (62), 158	90 (33), 90 <sup>***</sup>	89 (32), 88 <sup>***</sup>	91 (38), 82 <sup>***</sup>
HDLc (mg/dL)	48 (17), 45	51 (17), 48 <sup>***</sup>	52 (17), 49 <sup>*</sup>	52 (18), 48 <sup>*</sup>
TG (mg/dL)	235 (147), 201	133 (60), 123 <sup>***</sup>	132 (56), 120 <sup>***</sup>	137 (57), 131 <sup>***</sup>
Vitamin D normalized (dated cut point)	0	58 (91%)	58 (91%)	59 (92%)
Myositis-Myalgia-free	0	55 (86%)	59 (94%), 1 unknown	57 (95%), 4 unknown

Significance of change: \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .0001$  by paired Wilcoxon test. LDLC = Low-density lipoprotein cholesterol, HDLC = High-density lipoprotein cholesterol, TG = Triglyceride

PMC full text: [N Am J Med Sci. 2015 Mar; 7\(3\): 86-93. doi: 10.4103/1947-2714.153919](https://doi.org/10.4103/1947-2714.153919)

### Future of Vitamin D treatments

Further studies examining the effect of ***alternative types of vitamin D*** and their ***doses***, ***the role of calcium supplementation***, and ***effects in men*** should be considered.

Adapted from JAMA. 2004;291:1999-2006.