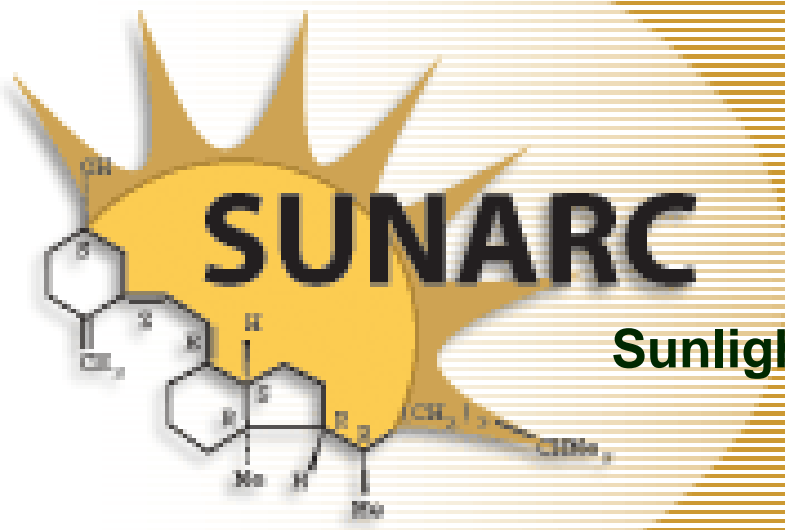


# The Role of Vitamin D in Reducing Risk of Cardiovascular Disease

Abu Dhabi

March 23, 2012

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Sunlight, Nutrition, and Health Research Center  
San Francisco, California

[www.sunarc.org](http://www.sunarc.org)

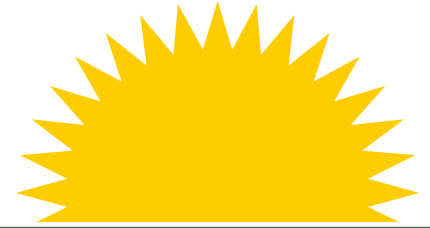
# Disclosure



I am pleased to acknowledge funding from these organizations:

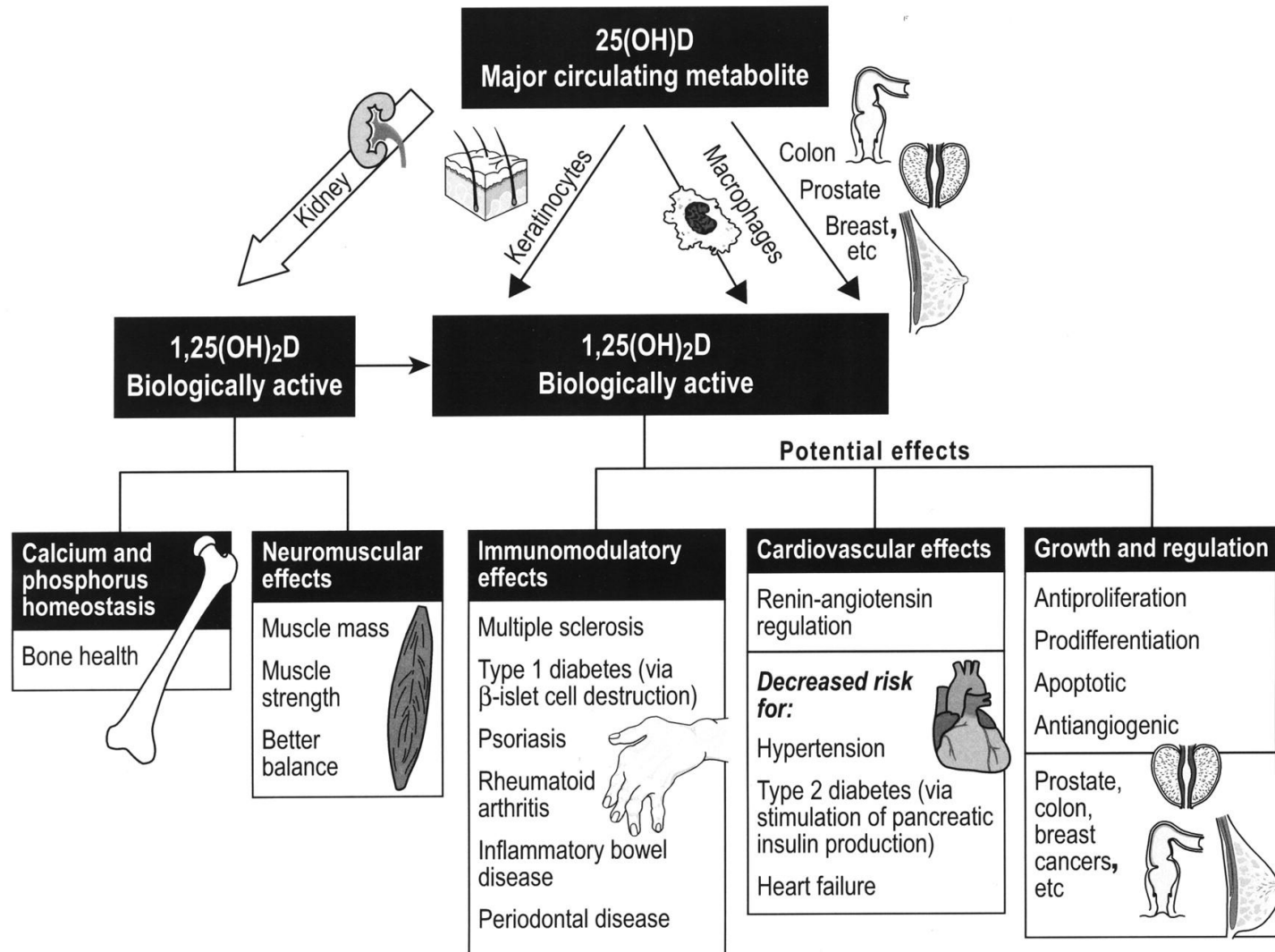
- ★ UV Foundation (McLean, Virginia)  
[www.uvfoundation.org](http://www.uvfoundation.org)
- ★ Bio-Tech-Pharmaceutical (www.Bio-Tech-Pharm.com)  
(Fayetteville, AR)
- ★ The Vitamin D Council (San Luis Obispo, CA)  
[www.vitaminDCouncil.org](http://www.vitaminDCouncil.org)
- ★ The Vitamin D Society (Canada)

# Outline



- ★ Vitamin D physiology
- ★ Vitamin D status in U.A.E.
- ★ Primary risk factors for cardiovascular disease:
  - ★ Hypertension
  - ★ Elevated LDL cholesterol level
  - ★ Smoking status
  - ★ Diabetes status
- ★ Secondary risk factors
  - ★ Arterial calcification, respiratory infections
- ★ Role of vitamin D for these risk factors
- ★ Epidemiology of vitamin D, cardiovascular disease
- ★ Vitamin D recommendations

# Endocrine and autocrine or paracrine functions of 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub>D).

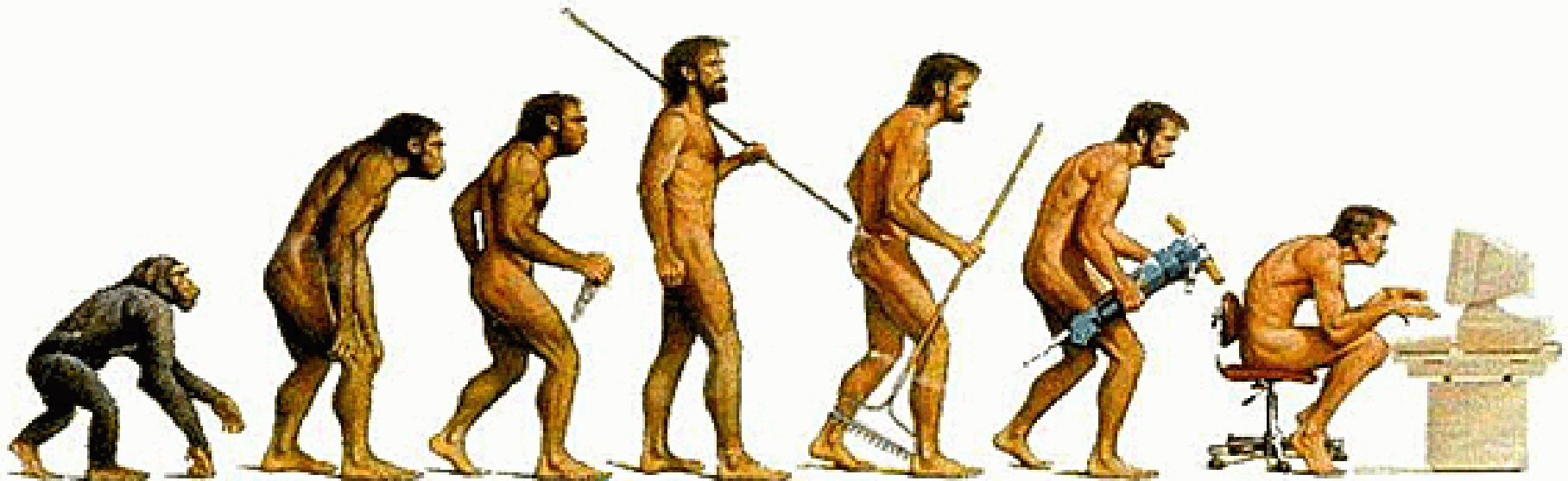


# Mechanism of Vitamin D Function



- ★ Vitamin D has been produced by plants and animals almost from the time life began.
- ★ The driving factor was the need to regulate calcium flux and storage within cells.
- ★ In complex animals, vitamin D receptors formed to affect gene expression, enhancing many of them, suppressing others..
- ★ The hormonal metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], can activate the vitamin D receptor (VDR).
- ★ VDRs control expression of >200 genes.

# Why vitamin D Concentrations Are Low



In the UAE, Staying indoors and wearing clothing that blocks the sun reduce serum 25(OH)D concentrations.

# Serum 25OHD in Emirati women



- ★ Serum 25OHD concentration in the 259 women volunteers was 25.3 +/- 10.8 nmol/l (mean +/- SD), and all had vitamin D deficiency (25OHD <80 nmol/l).
- ★ Mean serum 25OHD was highest in April (29.2 +/- 13.0 nmol/l), which marks the end of the short and cooler winter season, and lowest in August (18.2 +/- 5.9 nmol/l).
- ★ No significant difference in 25OHD concentration was noted among Emirati women wearing different dress styles, but the mean serum 25OHD was significantly lower in comparison with non-Arab Caucasian women volunteers who dressed in a Western style (P < 0.001)
- ★ Saadi et al., Bone. 2006 Nov;39(5):1136-43.

# Indications of CVD Risk in the UAE in 2000




Sex	Obesity	Diabetes mellitus	Metabolic syndrome	CVD
Male	25.6%	47.0%	35.1%	3%
Female	39.9%	32.4%	42.7%	1.7%

Fields et al., Curr Osteoporos Rep (2011) 9:243–250



# Diet and Prevention of Diabetes, Metabolic Syndrome, and CVD in Arab Countries



- ★ Golden rule: maintain body weight (energy balance) at young adult level with BMI of 20–22 kg/m<sup>2</sup>, i.e. ‘eat less, exercise more’.
- ★ Adults keep fat intake <30% of total energy (<33 g/1,000 kcal) and saturated fatty acids (SFA) <10%. Avoid trans fatty acid-rich foods and fats.
- ★ Derive the major portion of energy from complex carbohydrates in cereal grains, vegetables, and fruits.
- ★ Restrict visible fat consumption, especially animal fat sources of saturates and cholesterol (cheese, ice cream, whole milk, fatty meats).
- ★ Assure daily intake of 5% as 18:2 fatty acids; best accomplished with soybean oil- or canola oil-based salad dressing (1 tsp/1,000 kcal/day).
- ★ Eat fish at least once per week.
- ★ Musaiger AO. Med Princ Pract. 2002;11 Suppl 2:9-16.

# Lifetime risks of cardiovascular disease



- ★ Blood pressure,
  - ★ LDL cholesterol level,
  - ★ Smoking status, and
  - ★ Diabetes status were used to stratify participants according to risk factors into five mutually exclusive categories.
- 
- ★ Berry JD, et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012 Jan 26;366(4):321-9.

# Risk Factors for CVD in Oman



Risk factor	Odds ratio	95% CI
Hypertension	7.3	3.1-17.2
Diabetes mellitus	3.3	1.3-8.4
Sedentary occupation	3.1	1.5-6.6

Ganguly SS, Sultan Qaboos University Medical Journal, 2008;8:45-51.

# How Vitamin D Reduces Risk of Cardiovascular Disease (CVD)



- ★ The mechanisms include:
  - ★ Reduced risk of hypertension;
  - ★ Reduced risk of chronic kidney disease, diabetes, and respiratory infectious diseases, which are risk factors for CVD;
  - ★ Reduced risk of calcification of arteries;
  - ★ Reduced risk of inflammation;
  - ★ Reduced levels of matrix metalloproteinase 9, which can destroy tissue.

# Hypertension Rates vs. 25(OH)D



- ★ A cross-sectional study of 2722 individuals in Los Angeles:

25(OH)D Concentration:	<38 nmol/l	38-75 nmol/l	75-99 nmol/l	>100 nmol/l
Hypertension rate	52%	41%	27%	20%
Odds ratio	2.7 (1.4-5.2)	2.0 (1.5-2.6)	1.3 (1.2-1.6)	1.00

Bhandari et al., J Clin Hypertens (Greenwich), 2011;13(3):170-7.

# Blood Pressure Reduction with Vitamin D Supplementation?

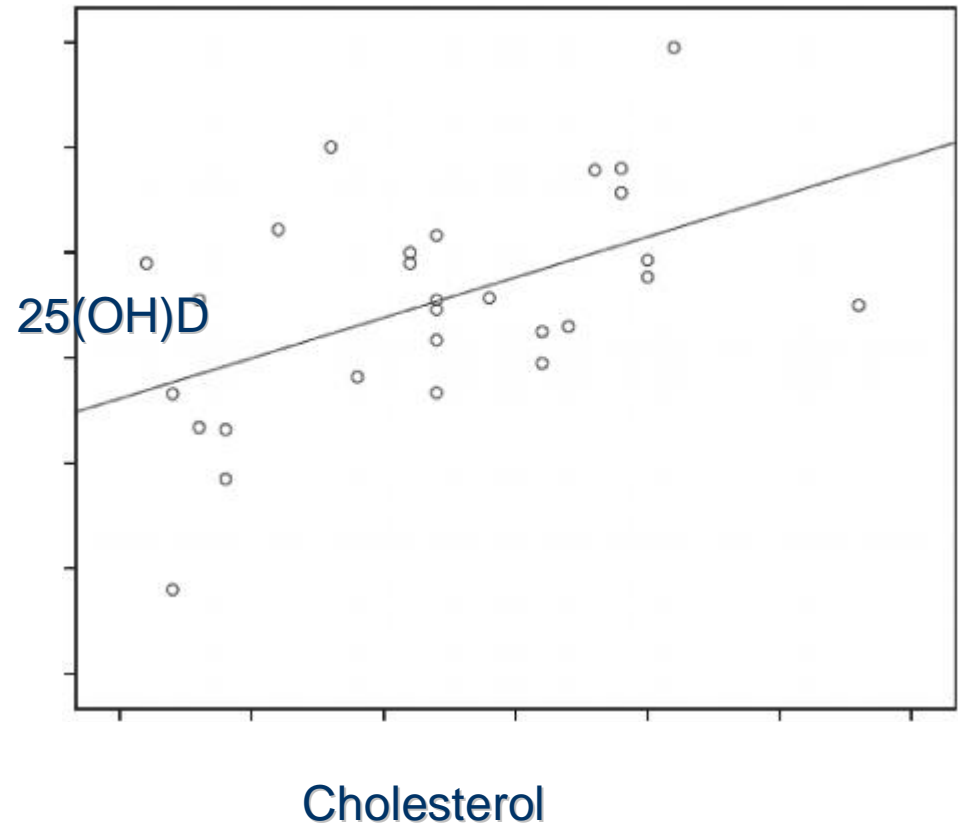


- ★ There is limited evidence that vitamin D supplementation affects blood pressure.
- ★ This suggests that vitamin D deficiency affects blood pressure early in life.
- ★ A rat study found “early life vitamin D deficiency is associated with endothelial vasodilator dysfunction, and this is likely to contribute to the accompanying elevation in blood pressure and an increased cardiovascular disease risk.”
- ★ Tare et al. J Physiol. 2011;589(Pt 19):4777-86.

# Cholesterol and Vitamin D



- ★ There is little evidence that vitamin D affects cholesterol.
- ★ However, total cholesterol affects vitamin D production from UVB.
- ★ Bogh, J Invest Dermatol. 2010 Feb;130(2):546-53.



# Vitamin D Supplementation Effects on CVD Risk Factors – 1-yr Study

Factor	Month 0	Month 12	P treatment
25(OH)D	33.0 +/- 17.5	85.5 +/- 57.5	<0.001
1,25(OH)2D	87.0 +/- 33.8	127.0 +/- 87.5	<0.001
PTH	4.69 +/- 3.25	3.39 +/- 2.03	0.03
Tumour necrosis factor	7.84 +/- 3.15	7.04 +/- 2.25	0.09

Unchanged: blood pressure, calcium, triglycerides, LDL, HDL, CRP

Reduced in both treatment and control groups: interleukin-6, glucose, Hb A1c, proinsulin

Zittermann et al., Am J Clin Nutr. 2009;89:1321




# The Effect of Smoking on 25(OH)D



- ★ Smokers had significantly reduced concentrations of serum 25OHD ( $P=0.02$ ), 1,25(OH)<sub>2</sub>D ( $P=0.001$ ), and PTH ( $P<0.001$ ). There was no difference in serum ionized calcium between smokers and non-smokers.
- ★ Smokers had small but significant reductions in bone mineral density.
- ★ Brot C, Jorgensen NR, Sorensen OH. The influence of smoking on vitamin D status and calcium metabolism. *Eur J Clin Nutr.* 1999 Dec;53(12):920-6.

# Obesity and serum 25(OH)D; Cross-Sectional Study of Unsupplemented Adults



- ★ The fit to a hyperbolic model of 25(OH)D against body weight completely removed the obesity-related component of inter-individual variability in serum 25(OH)D concentration.
- ★ Dilution of ingested or cutaneously synthesized vitamin D in the large fat mass of obese patients fully explains their typically low vitamin D status.
- ★ Vitamin D replacement therapy needs to be adjusted for body size if desired serum 25(OH)D concentrations are to be achieved.
- ★ Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric Dilution, Rather Than Sequestration Best Explains the Low Vitamin D Status of Obesity. *Obesity* (Silver Spring). 2012 Jan 19. doi: 10.1038/oby.2011.

# Type 2 Diabetes Mellitus

- ★ Vitamin D and calcium have been found inversely correlated with incidence and prevalence of type 2 diabetes mellitus.
- ★ 20-year study, vitamin D from diet, supplements assessed every 2-4 years.
- ★ 33% reduced risk for >800 IU/d vitamin D3 and >1200 mg/d calcium.
- ★ Pittas, Diabetes Care. 2006 Mar;29(3):650-6

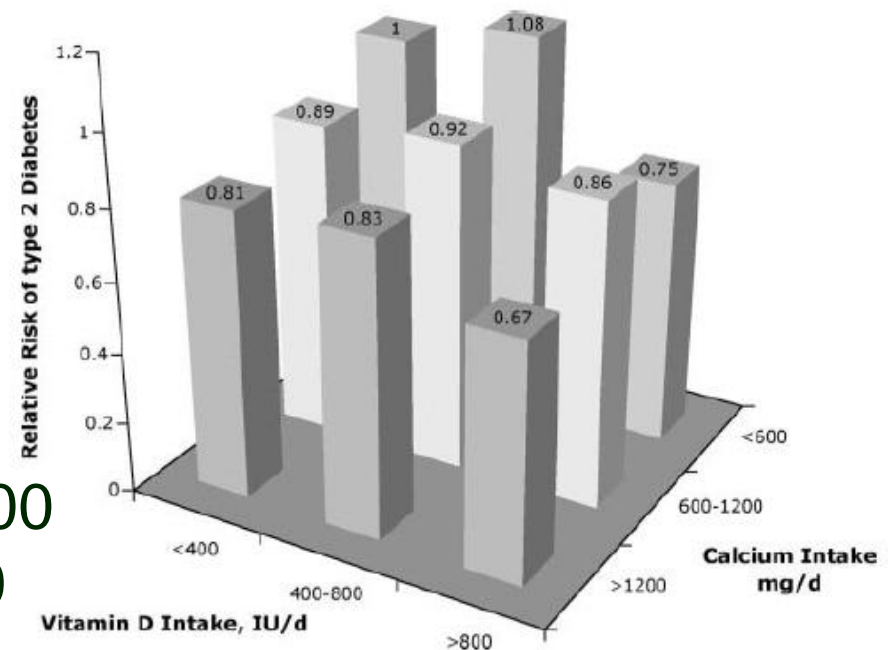


FIG. 1. Adjusted relative risk of incident type 2 DM in the Nurses Health Study by calcium and vitamin D intake (52).

# 25(OH)D and Insulin Resistance in Adolescents



- ★ A study in Poland examined the role of 25(OH)D concentration related to CVD risk factors.
- ★ In the multivariable model, older age, puberty, higher value of percentage of body fat, and the presence of acanthosis nigricans (dark skin areas) were all negatively associated with 25(OH)D.
- ★ Lower 25(OH)D concentrations were also associated with higher blood glucose, insulin, and insulin resistance after adjustment for puberty and a measure of BMI.
- ★ Garanty-Bogacka et al., Serum 25-hydroxyvitamin D (25-OH-D) in obese adolescents. *Endokrynol Pol.* 2011;62(6):506-11.

# Sunlight, Risk of Diabetes Mellitus



- ★ A South Swedish cohort study comprising 1000 women from each age group between 25 and 64 (n=40,000) drawn from the Southern Swedish population registry 1990-1992.
- ★ **RESULTS:** Women with active sun exposure habits were at a 30% lower risk of having DM, as compared to those with non-active habits.
- ★ **CONCLUSION:** Our investigation gives possible epidemiological explanation to ethnic and seasonal differences in type 2 DM and metabolic control. The study supports that sunlight is involved in the glucose metabolism.
- ★ Lindqvist PG, Olsson H, Landin-Olsson M. Are active sun exposure habits related to lowering risk of type 2 diabetes mellitus in women, a prospective cohort study? *Diabetes Res Clin Pract.* 2010 Oct;90(1):109-14.

# Mechanisms for Reduced Risk of Type 2 Diabetes by Vitamin D – Beta-cell Function, Insulin Sensitivity



- ★ **METHODS:** We enrolled 150 healthy, glucose-tolerant subjects for the assessment of  $\beta$ -cell function (acute insulin response) and insulin sensitivity index (ISI) using a hyperglycemic clamp. Adjusted  $\beta$ -cell function (ABCF) was defined as the product of acute insulin response and ISI.
- ★ **RESULTS:** Plasma 25(OH)D concentrations were positively associated with ABCF ( $P = 0.00004$ ) and ISI ( $P < 0.00001$ ). The associations remained significant after adjustment for age, sex, body mass index, physical activity, ethnicity, and season of study.
- ★ **CONCLUSIONS:** Plasma 25(OH)D concentrations are positively associated with both  $\beta$ -cell function and insulin sensitivity. Our observations suggest the roles of vitamin D deficiency in the dual defect of type 2 diabetes.
- ★ Karnchanasorn R, Ou HY, Chiu KC. Plasma 25-Hydroxyvitamin D Levels Are Favorably Associated With  $\beta$ -Cell Function. *Pancreas*. 2012 Jan 17. [Epub ahead of print]

# Arterial Calcification



- ★ Calcification of vessels reduces their elasticity, affecting hemodynamic parameters of the cardiovascular system. The development of arterial hypertension, cardiac hypertrophy, ischemic heart disease or peripheral arterial disease significantly increases mortality in patients over 60 years of age. Stage of advancement and the extent of accumulation of calcium deposits in vessel walls are key risk factors of ischemic events.
- ★ Vascular calcification is an active and complex process that involves numerous mechanisms responsible for calcium depositions in arterial walls. They lead to increase in arterial stiffness and in pulse wave velocity, which in turn increases cardiovascular disease morbidity and mortality.
- ★ **Karwowski W, et al. The mechanism of vascular calcification - a systematic review. Med Sci Monit. 2011 Dec 22;18(1):RA1-11.**

# Low 25(OH)D and Increased Aortic Stiffness



- ★ Arterial stiffness was measured as aortic pulse-wave velocity (PWV) using Sphygmocor device. We found a clear negative trend in aortic PWV among 25(OH)D quartiles. Subjects in the bottom 25(OH)D quartile (<50 nmol/l) showed the highest aortic PWV (9.04 m s<sup>-1</sup>), compared with 2nd-4th quartile (8.07 m s<sup>-1</sup>, 7.93 m s<sup>-1</sup>) and 7.70 m s<sup>-1</sup>, respectively; P for trend <0.0001).
- ★ The association between 25(OH)D and aortic PWV remained significant after adjustment for age, gender and other potential confounders; subjects in the first 25(OH)D quartile had adjusted odds ratio 2.04 (1.26-3.30) for having aortic PWV >9 m s<sup>-1</sup> (top quartile) in multiple regression.
- ★ Mayer O Jr, Filipovský J, Seidlerová J, Vaněk J, Dolejšová M, Vrzalová J, Cífková R. The association between low 25-hydroxyvitamin D and increased aortic stiffness. J Hum Hypertens. 2011 Oct 20.



# Vitamin D and Inflammation



- ★ On univariate linear regression analysis, C-reactive protein (CRP) decreased [geometric mean CRP change 0.285 mg/dl for each 10-ng/ml change in 25(OH)D, 95% confidence interval [CI] -0.33 to -0.23] as 25(OH)D increased  $\leq 53$  nmol/l.
- ★ The inverse relation between 25(OH)D below its median and CRP remained significant [geometric mean CRP change 0.11 mg/dl for each 25-nmol/l change in 25(OH)D, 95% CI 0.16 to -0.04] on multivariate linear regression analysis.
- ★ Additionally, we observed a positive relation between 25(OH)D above its median and CRP [geometric mean CRP change 0.06 mg/dl for each 25-nmol/l change in 25(OH)D, 95% CI 0.02 to 0.11) after adjusting for traditional cardiovascular risk factors.
- ★ Amer M, Qayyum R. Am J Cardiol. 2012 Jan 15;109(2):226-30.

# Matrix Metalloproteinase (MMP)



- ★ Proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis.

# MMP and Abdominal Aortic Pathology

- ★ After adjustment for traditional cardiac risk factors and body size, higher MMP-9 quartiles were independently associated with higher aortic wall thickness and larger luminal diameter ( $p < 0.0001$  for each), but not abdominal aortic plaque ( $p = 0.08$ ), coronary artery calcium ( $p = 0.20$ ) or the aortic luminal diameter/aortic wall thickness ratio ( $p = 0.37$ ), supporting the hypothesis that therapies targeting MMP-9 may affect the abdominal aortic wall and modify aortic pathology.
- ★ Grodin JL, et al. Vasc Med. 2011 Oct;16(5):339-45.

## MMP-9, Myocardial Infarction, 25(OH)D

- ★ **RESULTS:** 25(OH)D deficiency was present in 72.7% of the patients. Hypertension and positive history of cardiovascular drug use were risk factors for the presence of low vitamin D concentrations (OR = 2.92; CI = 1.34-6.37,  $P < 0.05$ ) and (OR = 2.36; CI = 1.05-5.29,  $P < 0.05$ ), respectively.
- ★ Moreover, a significant positive relationship between the inpatients' survival and the concentration of vitamin D was present ( $P < 0.001$ ). By performing a multivariate analysis, we found that there was a significant inverse relationship between the concentration of 25 (OH) D and the concentration of MMP-9 after 72 h ( $P = 0.01$ ).
- ★ Khalili H, Talasaz AH, Salarifar M. Clin Res Cardiol. 2011 Dec 11.

# Respiratory Infections and Risk of Cardiovascular Disease, e.g., Influenza

- ★ There were  $\geq 1.2$  million myocardial infarction (MI)-associated hospitalizations and 410,204 MI-associated deaths in England and Wales, with a marked peak in the winter season.
- ★ In Hong Kong, the incidence of MI had a large winter and smaller summer peak, mirroring patterns of influenza activity.
- ★ There was strong evidence for a link between influenza and MI both in England and Wales, where 3.1%-3.4% of MI-associated deaths ( $P < 0.001$ ) and 0.7%-1.2% of MI-associated hospitalizations ( $P < 0.001$ ) were attributable to influenza, and in Hong Kong, where the corresponding figures were 3.9%-5.6% ( $P = 0.02$ ) and 3.0%-3.3% ( $P = 0.002$ ).
- ★ Warren-Gash C, et al. J Infect Dis. 2011 Jun 15;203(12):1710-8.

## Summary, Effects of Vitamin D for CVD

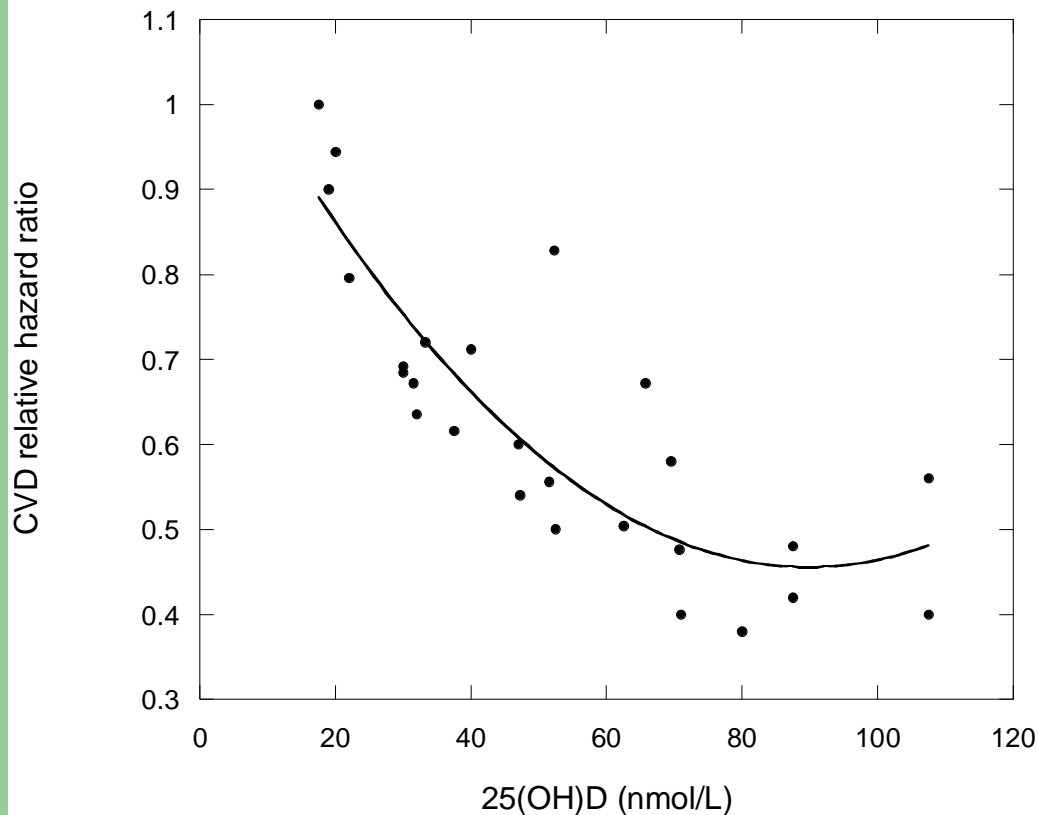


- ★ Higher serum 25(OH)D concentrations are associated with lower risk of hypertension, diabetes mellitus, arterial calcification, inflammation, MMP-9, and respiratory infections.
- ★ Smoking and obesity lower serum 25(OH)D concentrations.
- ★ Therefore, higher serum 25(OH)D concentrations should be associated with lower risk of CVD.
- ★ The next slides will examine the evidence that it does.

## Relation of Vitamin D Deficiency to Cardiovascular Risk in a General Healthcare Population in Utah

- ★ The database contained 41,504 patient records with at least one measured vitamin D level. The prevalence of vitamin D deficiency ( $\leq 75$  nmol/l) was 63.6%, with only minor differences by gender or age.
- ★ Vitamin D deficiency was associated with highly significant ( $p < 0.0001$ ) increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease.
- ★ Also, those without risk factors but with severe vitamin D deficiency had an increased likelihood of developing diabetes, hypertension, and hyperlipidemia.
- ★ The vitamin D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke (all  $p < 0.0001$ ), as well as with incident death, heart failure, coronary artery disease/myocardial infarction (all  $p < 0.0001$ ), stroke ( $p = 0.003$ ), and their composite ( $p < 0.0001$ ).
- ★ Anderson JL, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol.* 2010 Oct 1;106(7):963-8.

# Meta-analysis of CVD Relative Risk vs. Serum 25(OH)D Concentration from Prospective Studies



The effect is nonlinear, with more rapid change at lower 25(OH)D concentrations

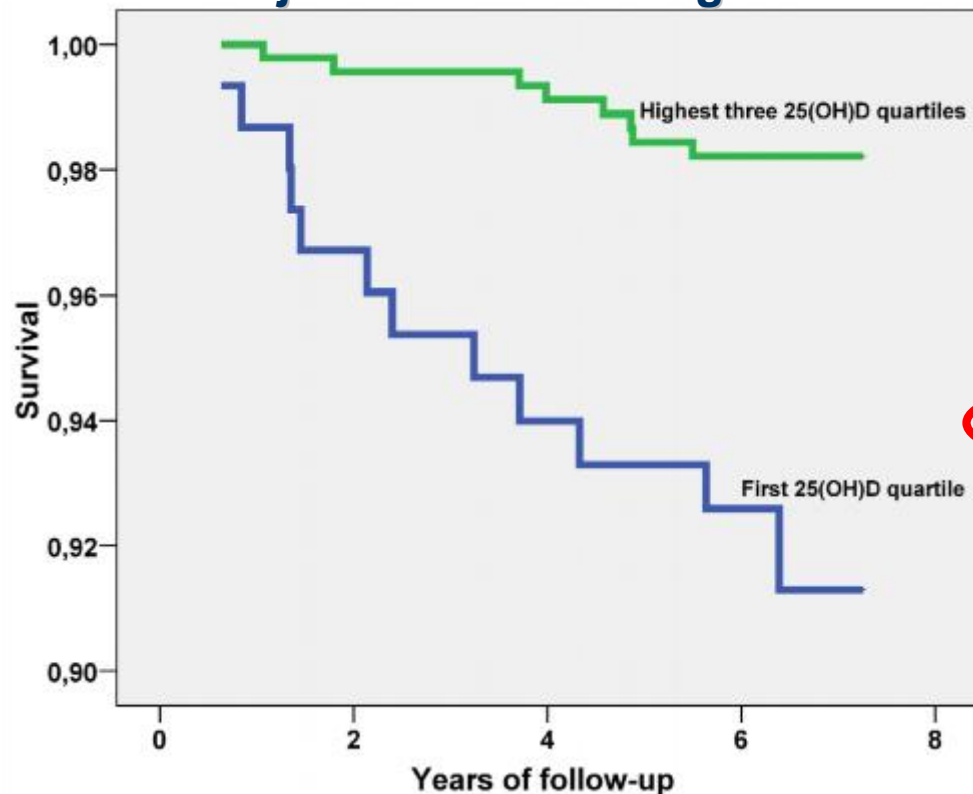
Grant, Eur J Clin Nutr, 2011 Sep;65(9):1016-26.



# Vitamin D and Cardiovascular Mortality

Follow-up period of 6.2 years:

51 subjects died including 20 deaths due to cardiovascular causes



Hazard ratio for CVD mortality in the first vs. the upper three 25(OH)D quartiles:

**5.38 (95% CI, 1.28-14.34, p<0.001)**

Adjusted for age, sex, diabetes mellitus, Smoking status, hypertension, HDL-C, GFR and WHR

Pilz S, Dobnig H, Nijpels G, et al. Vitamin D and mortality in older men and women. Clin Endocrinol (Oxf). 2009 Nov;71(5):666-72.

# Serum 25OHD and CVD Mortality



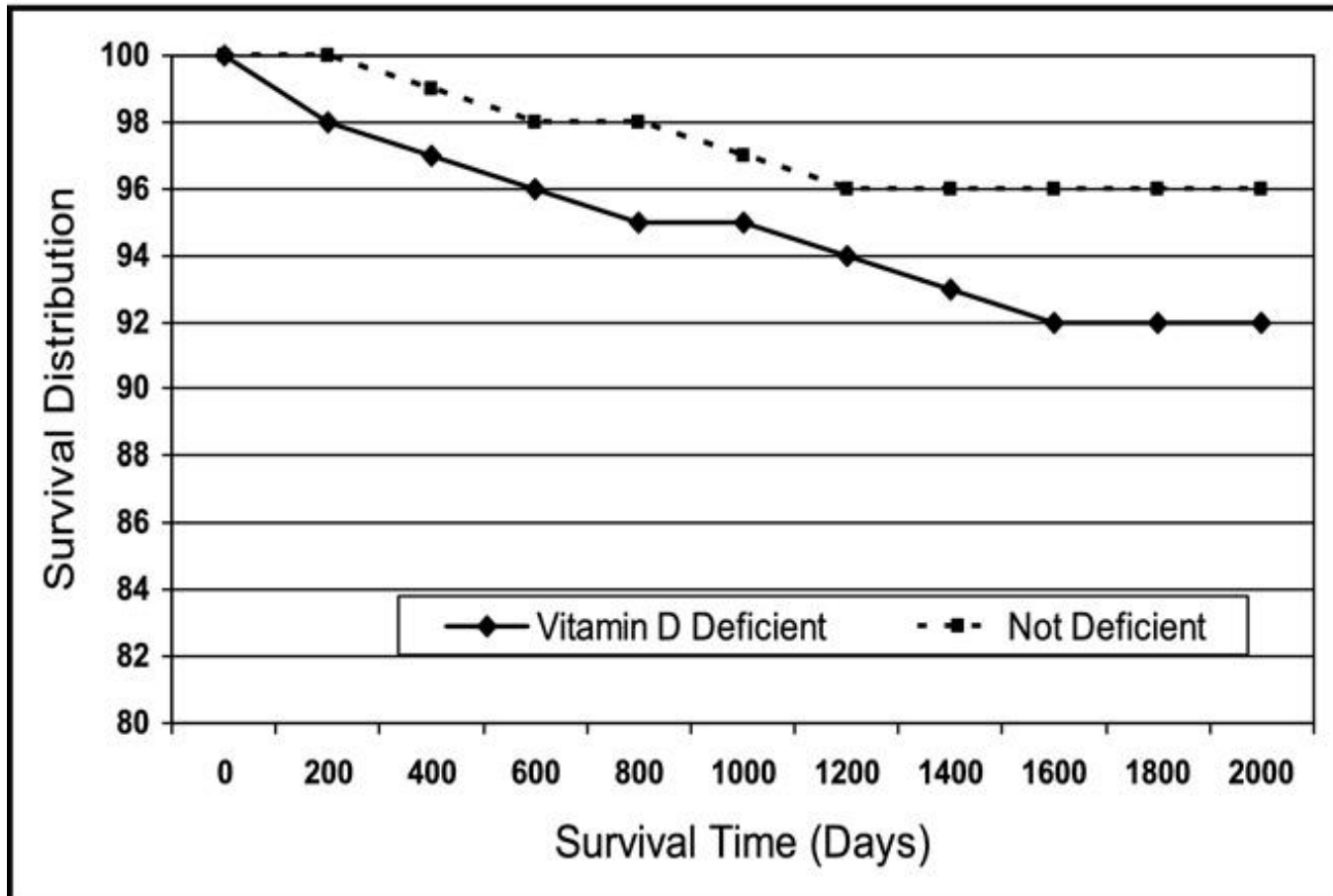
- ★ Of 2609 participants with hypertension, 191 died (including 68 CVD deaths) during an average of 3.7-year follow-up. Compared with participants with 25(OH)D concentrations in the highest quartile ( $\geq 72$  nmol/l), the hazard ratios for CVD mortality were 3.2 (95% CI 1.1-9.0), 2.4 (0.9-6.9), and 2.3 (0.9-6.1), respectively (P for trend  $< 0.05$ ), in the first ( $< 43$  nmol/l), second (43- $< 58$  nmol/l) and third (58- $< 72$  nmol/l) quartiles of 25(OH)D after adjustment for potential confounding variables.
- ★ Zhao G, et al. Serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: the NHANES linked mortality study. *J Hypertens*. 2012 Feb;30(2):284-9.

# Vitamin D Deficiency and Supplementation and Relation to Cardiovascular Health

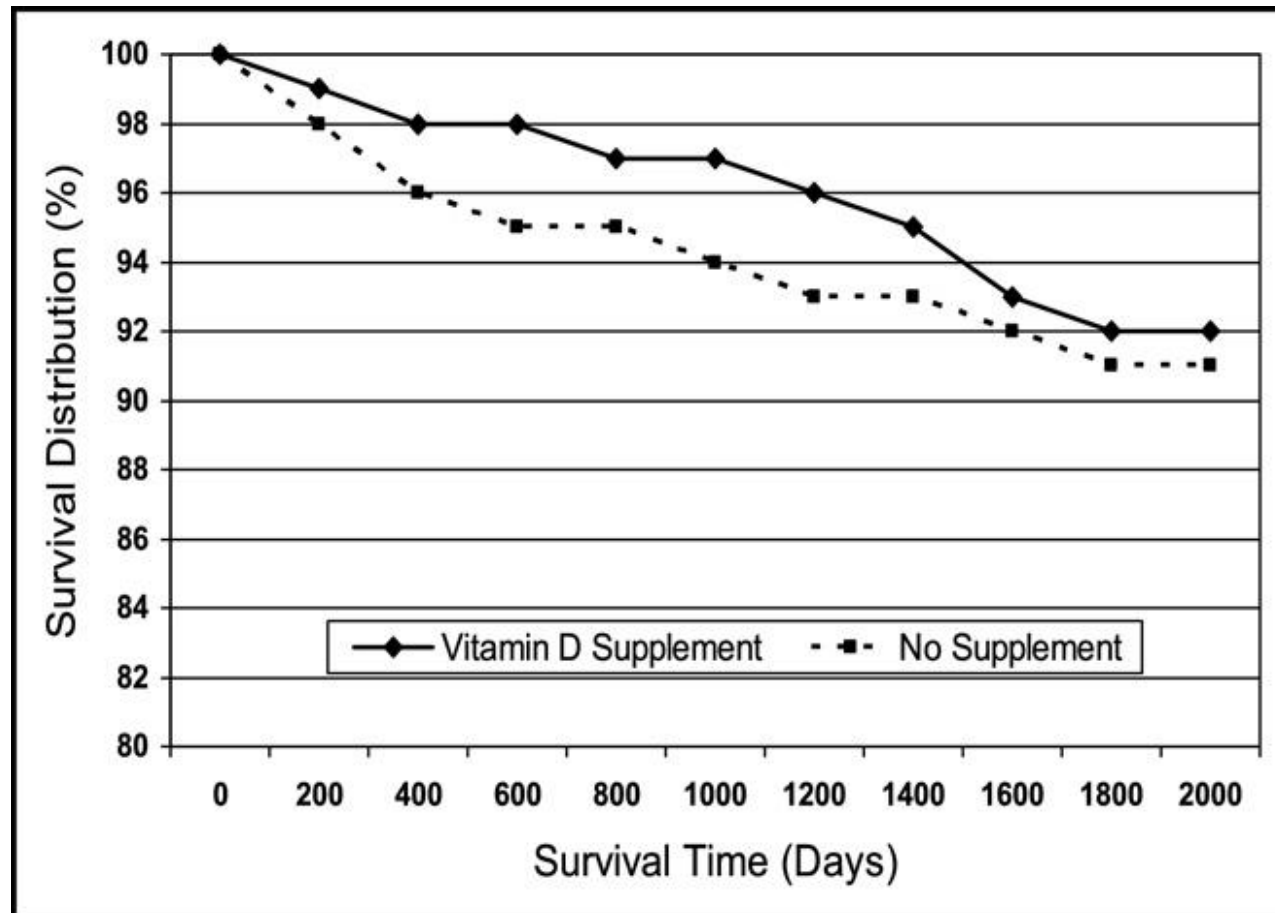


- ★ Serum vitamin D measurements for 5 years and 8 months from a large academic institution (University of Kansas Medical Center and Hospital) were matched to patient demographic, physiologic, and disease variables. The vitamin D levels were analyzed as a continuous variable and as normal ( $\geq 75$  nmol/l) or deficient ( $< 30$  nmol/l). Descriptive statistics, univariate analysis, multivariate analysis, survival analysis, and Cox proportional hazard modeling were performed. Of 10,899 patients, the mean age was  $58 \pm 15$  years, 71% were women, and the average body mass index was  $30 \pm 8$  kg/m<sup>2</sup>. The mean serum vitamin D concentration was  $60.3 \pm 34.0$  nmol/l.
- ★ Vacek JL, et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. *Am J Cardiol.* 2012 Feb 1;109(3):359-63.

Figure 1. Survival in vitamin D deficient (<30 nmol/l) versus not deficient subjects.  
[Vacek, 2012]



# Survival stratified by vitamin D supplementation in deficient subjects [Vacek, 2012]



# Logistic regression analysis for death as dependent variable with vitamin D supplementation added (Vacek, 2012)

- ★ Predictor OR (95% CI):
- ★ Coronary artery disease 2.5 (1.9–3.2)
- ★ Diabetes mellitus 1.7 (1.3–2.2)
- ★ Cardiomyopathy 3.1 (2.2–4.4)
- ★ Hypertension 1.6 (1.3–2.1)
- ★ Vitamin D supplement 0.44 (0.34–0.59)
- ★ Atrial fibrillation 2.1 (1.5–2.9)

# Vitamin D, Parathyroid Hormone (PTH), and Sudden Cardiac Death (SCD)

- ★ Multivariate adjustment attenuated associations of 25OHD and PTH with SCD. Finally, 267 participants (11.7% of the cohort) had high PTH and low 25OHD concentrations. This combination was associated with a >2-fold risk of SCD after adjustment (hazard ratio: 2.2 [95% CI: 1.2-4.1]; P=0.02) compared with participants with normal levels of PTH and 25OHD. The combination of lower 25OHD and higher PTH concentrations appears to be associated independently with SCD risk among older adults without cardiovascular disease.
- ★ Deo R, et al. Vitamin D, parathyroid hormone, and sudden cardiac death: results from the Cardiovascular Health Study. Hypertension. 2011 Dec;58(6):1021-8.

# Seasonality of CVD in Kuwait



- ★ Data were collected from North-East Scotland (Grampian region) and Kuwait. Seasonal differences were similar, in both timing and degree, for total mortality and deaths from circulatory disease, but were greater in Kuwait for respiratory disease.
- ★ The reasons why mortality peaks in warm climates in pleasant winter conditions is not known.
- ★ Douglas AS, et al. Lancet. 1991;337(8754):1393-7.



# Seasonality of CVD Mortality and the Possible Protective Effect of UV



- ★ Previous studies suggested that CVD seasonality is due to variations in temperature or respiratory disease prevalence. Another mechanism might be that the seasonal variation in UV radiation is responsible for the seasonality of CVD. An hypothesis is put forward that UV radiation, by increasing body levels of vitamin D, protects against CVD. This hypothesis might explain the seasonal variations in CVD mortality and morbidity which decrease in summer, the higher CVD mortality in higher latitudes, and the inverse relationship between altitude and CVD mortality.
- ★ Scragg R. Int J Epidemiol. 1981 Dec;10(4):337-41.

# Myocardial Infarction is Inversely Associated with Plasma 25(OH)D



- ★ The relation between the plasma level of 25(OH)D<sub>3</sub> and myocardial infarction (MI) was investigated in a community-based case-control study. Some 179 MI patients presenting to hospital within 12 hours of the onset of symptoms were individually matched with controls by age, sex and date of blood collection.
- ★ MI patients had significantly lower mean 25(OH)D<sub>3</sub> levels than controls (32.0 versus 35.5 nmol/L;  $p = 0.017$ ), with the case-control differences being greatest in winter and spring. The relative risk of MI for subjects with 25(OH)D<sub>3</sub> levels equal to or above the median was 0.43 (95% CI = 0.27, 0.69) compared to subjects below the median. The decrease in MI risk associated with raised vitamin D<sub>3</sub> levels was observed in all seasons.
- ★ Scragg R, et al. *Int J Epidemiol.* 1990 Sep;19(3):559-63.

## Statins Can Increase Serum 25(OH)D



- ★ The study group consisted of 91 hyperlipidemic patients who had not been treated with lipid lowering medications.
- ★ There was a significant increase in 25(OH)D, from mean 14.0 (range 3.7- 67) to mean 36.3 (range 3.8 -117) ng/ml ( $p < 0.001$ ), and also an increase of 1,25-(OH)<sub>2</sub>D from mean 22.9 +/- 11.2 to 26.6 +/- 9.3 pg/dl ( $p = 0.02$ ).
- ★ Bone alkaline phosphatase decreased after 8 weeks of **rosuvastatin** treatment, mean 17.7 (range 2.6-214) to mean 9.5 (range 2.3-19.1) u/l ( $p < 0.001$ ) rosuvastatin treatment.
- ★ Yavuz B, et al. Cardiovasc Drugs Ther. 2009 Aug;23(4):295-9.

# Statins, Vitamin D, and Thrombosis

- ★ Both statins and vitamin D appear to lower:
  - ★ C-reactive protein and inflammation
  - ★ Atherogenesis
  - ★ Platelet aggregation
- ★ And raise
  - ★ Endothelial progenitor cells
  - ★ Endothelial cell repair
  - ★ Thrombomodulin
- ★ Wilding PM. Cardiovascular disease, statins and vitamin D. Br J Nursing 2012;21:214-20.

# Vitamin D Recommendations



- ★ Having shown that vitamin D reduces the risk of cardiovascular disease, what are the recommendations for vitamin D and how can optimal serum 25(OH)D concentrations be obtained?

# Vitamin D Researchers' Recommendations



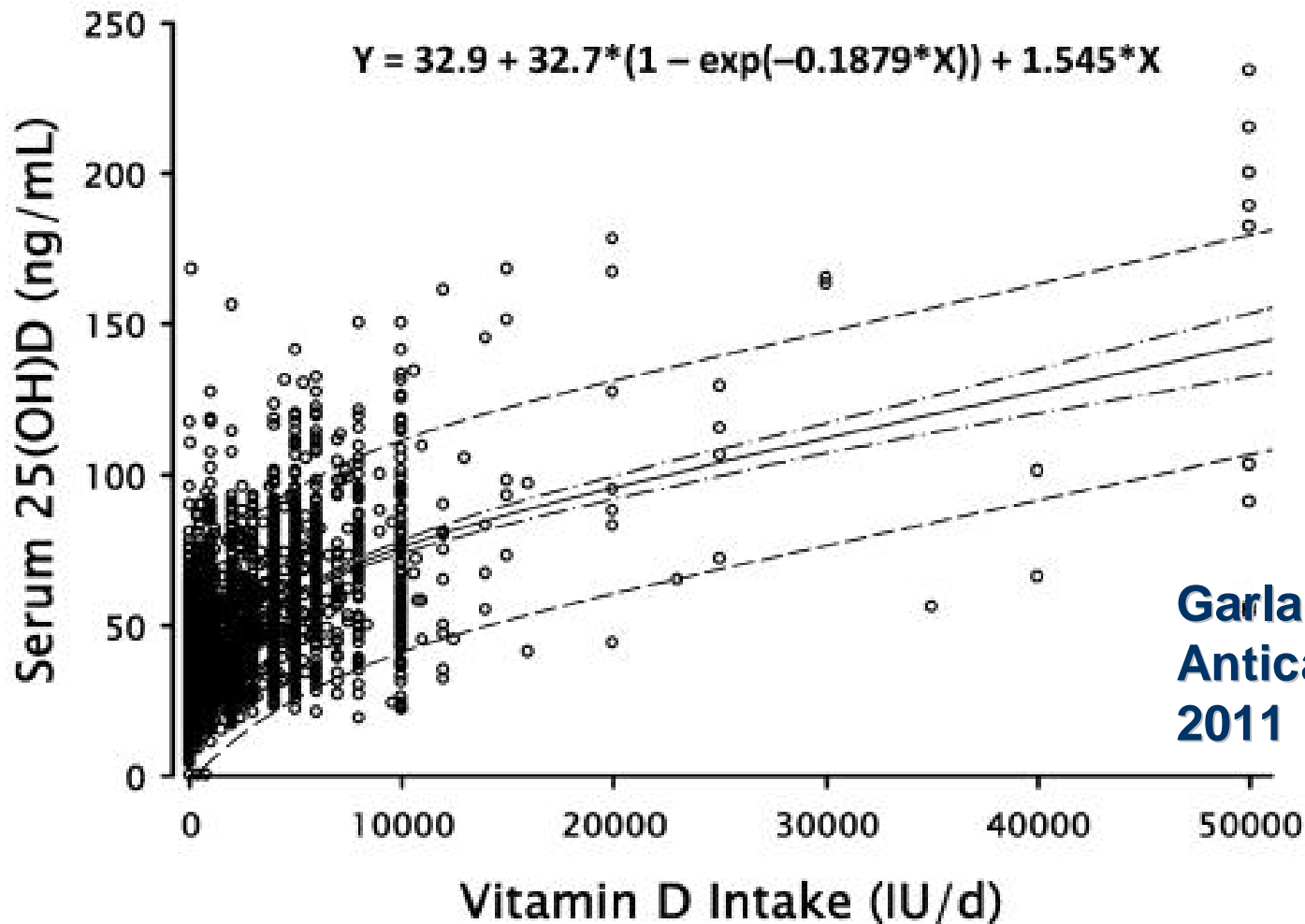
- ★ Recommendations were restricted to clinical practice and concern adult patients with or at risk for fractures, falls, cardiovascular or autoimmune diseases, and cancer. The panel reached substantial agreement about the need for vitamin D supplementation in specific groups of patients in these clinical areas and the need for assessing their 25-hydroxyvitamin D [25(OH)D] serum levels for optimal clinical care.
- ★ A target range of at least 75 to 100 nmol/L was recommended. As response to treatment varies by environmental factors and starting levels of 25(OH)D, testing may be warranted after at least 3 months of supplementation. An assay measuring both 25(OH)D(2) and 25(OH)D(3) is recommended.
- ★ Souberbielle JC, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. *Autoimmun Rev* 2010;9:709-15.

# U.S. Endocrine Society Recommends



- ★ A serum 25(OH)D level of at least 75 nmol/l
  - ★ 0-1 year: 400-1000 IU/day vitamin D3
  - ★ 1-18 years: 600-1000 IU/day
  - ★ 18+ years: 1500-2000 IU/day
  - ★ Those who are obese: 2-3X more
- 
- ★ Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2011 Jul;96(7):1911-30.

# Serum 25(OH)D Response to Oral Vitamin D Intake is Highly Variable

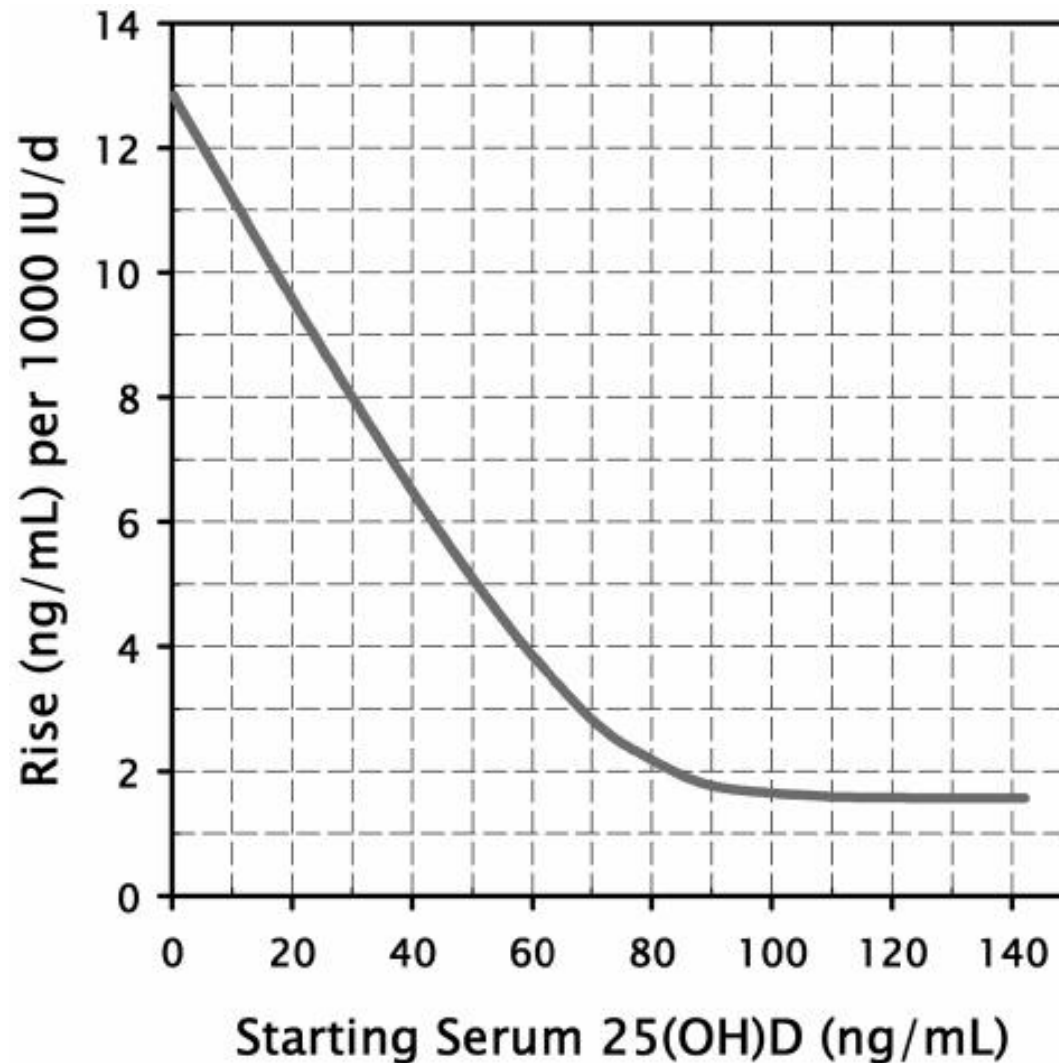




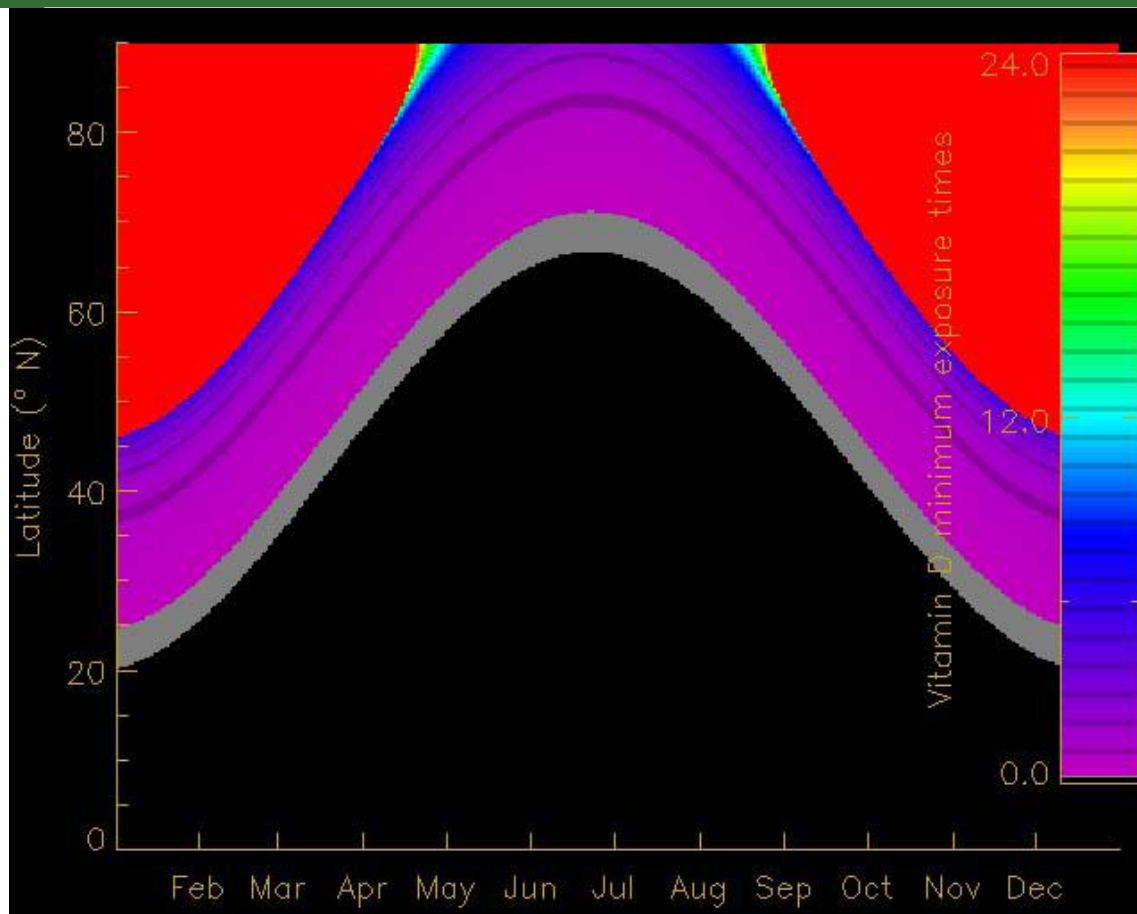
# Increase in 25(OH)D for 1000 IU/d vs Starting Value



R. Heaney  
In Garland  
et al.,  
Anticancer  
Res.,  
2011



# Solar UVB as a Source of Vitamin D



Month of the Year

Webb AR, Engelsen O.  
Photochem Photobiol.  
2006 Nov-Dec;82(6):  
1697-703.

## Additional Resources



- ★ <http://www.grassrootshealth.net/>
- ★ <http://www.healthresearchforum.org.uk/>
- ★ <http://www.pubmed.gov>
- ★ <http://www.sunarc.org/>
- ★ <http://www.vitamindcouncil.org/>
  
- ★ For a copy of this presentation,  
wbgrant@infionline.net