Viewing Time

The program will take up to one hour to complete.

Target Audience

This program is designed for primary care physicians.

Other health care professionals working with patients and their families may also find this program of interest.

Faculty Disclosure

It is the policy of Children's Hospitals and Clinics of Minnesota to ensure balance, independence, objectivity, and scientific rigor in all its educational programs. Our faculty have been asked to disclose to our program audience any real or apparent conflicts of interest related to the content of their presentation. They have also been requested to let you know when any product mentioned in their presentation is not labeled for the use under discussion or is still under investigation.

Faculty Disclosure

Gregory Plotnikoff, MD, MTS, FACP has disclosed no actual or potential conflict of interest in relation to this educational activity.

During this educational activity **Dr. Plotnikoff** will not be discussing the use of any commercial or investigational product not approved for any purpose by the FDA.

Update on the Vitamin D Controversy

Gregory Plotnikoff , MD, MTS, FACP
Medical Director, Penny George Institute for Health and Healing, Abbott Northwestern Hospital, Minneapolis, Minnesota

Update on the Vitamin D Controversy

A lecture about new discoveries and questions about the health affects of vitamin D.

Program Objectives

Upon completion of this program, participants should be able to:

- Recognize the many roles of vitamin D as a potent secosteroid that regulates gene expression in every human tissue
- Recognize the medical consequences of D deficiency from in utero to early adulthood
- Identify the medical indications for testing for vitamin D deficiency and the best means to replenish D deficiency

Disclaimer

Children's Hospitals and Clinics of Minnesota accepts no responsibility for the materials presented through these Grand Rounds seminars. Each professional host assumes all responsibility for maintaining confidentiality or obtaining authorization, in accordance with all applicable laws.

Accreditation

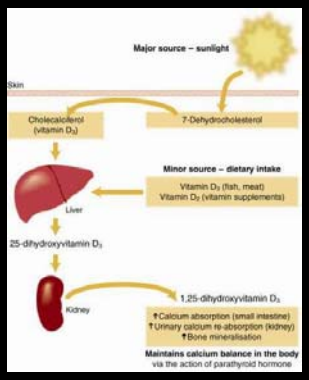
Children's Hospitals and Clinics of Minnesota is accredited by the Minnesota Medical Association to provide continuing medical education for physicians. Children's Hospitals and Clinics of Minnesota designates this educational activity for a maximum of 1 AMA PRA Category 1 Credits™ toward the AMA Physician's Recognition Award. Each physician should only claim those credits that he/she actually spent in the activity.

Receiving CME Credit

To receive CME credit you must view the entire program and complete the evaluation form at the end.

2009 Update on the Vitamin D Controversies

Gregory A. Plotnikoff, MD, MTS, FACP
Medical Director,
Penny George Institute for Health and Healing



Not controversial

- Potent secosteroid that binds to receptors found on every tissue in the body
- Primary regulator of at least 600 crucial genes

Controversy #1

What is normal?
Who is normal?

Taking a "normal" asymptomatic population,
Measuring,
Plotting data using Gaussian distribution,
Yields normative data for assessment.

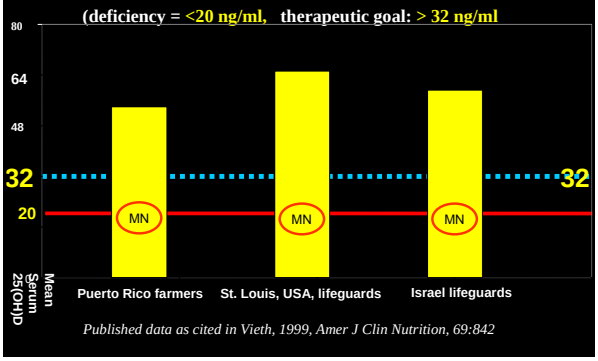
Lack of Rigorous Science

Population	n	age	sun exposure	25(0H)D
Volunteers	**40**	**30**	**8.8 ±6.1**	**68.3 ± 29.5**
Lifeguards	**8**	**18**	**53 ± 10.3**	**161 ± 21.8**

Note: Lifeguards had plasma 25(OH)D levels 2.5 greater than those of "normals"

Haddad JG, Chyu K. JClin Endo Metab. 1971;33: 992-95.

Vitamin D Levels in Outdoor Workers



Published data as cited in Vieth, 1999, Amer J Clin Nutrition, 69:842

Controversy # 2

Short latency "index" diseases
- -beriberi (thiamine)
- -pellagra (niacin)
- -scurvy (ascorbic acid)
- -rickets (25(OH)D2)

RDA: If intake is of the nutrient is sufficient to prevent the index disease, then ipso facto, the intake is adequate for the entire organism.

No Long Latency Diseases?

Long-term consequences of lesser degrees of deficiency?

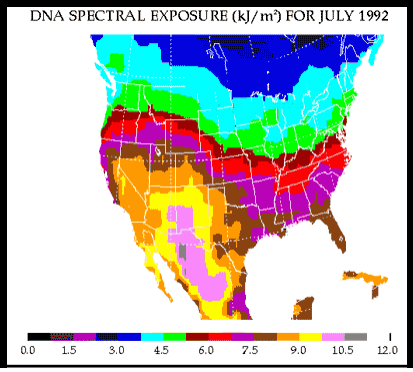
Entirely different metabolic mechanisms involved?

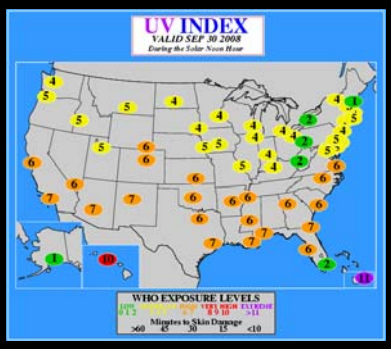
Blinded to these mechanisms?
Attribute to non-nutritional causes?

Controversy #3

- Park EA *JAMA* 1940;115:370-9.
- Blumberg RW, Forbes GB, Fraser D. The prophylactic requirement and the toxicity of vitamin D. *Pediatrics* 1963;31:512-25.

Controversy #4





Deficiency? In 2009? In the US???

D Biomarkers

- intact parathyroid hormone,
- intestinal calcium absorption,
- skeletal integrity,
- insulin sensitivity and β-cell function, and,
- cathelicidin (LL37, hCAP) production by macrophages and monocytes

iPTH

Plot PTH concentration vs. 25(OH)D

inflection point at >20 ng/dl (50 nmol/L)
PTH minimized at 40 ng/dl (100 nmol/L)

Ca++ Absorption

Calcium absorption optimized at >30 ng/dl (80)

By increasing 25-OH-D from 20 to 30 ng/dl:
↑ calcium absorption efficiency by 65%
↓ osteoporotic fracture risk by 35%

Insulin Sensitivity and ß Cell Function

Insulin sensitivity:
By increasing 25(OH)D from 10 ng/ml to 30 ng/ml, insulin sensitivity improves by 60%.

Pereira MA et al. *JAMA* 2002;287(16): 2081-89.

Improvement Comparisons:

Troglitazone	54%
Metformin	13%

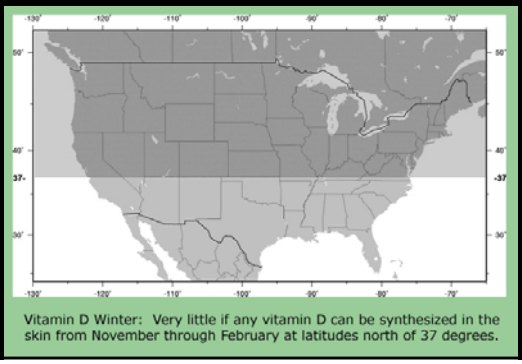
Inzucchi SE et al. *NEJM* 1998;338(13):867-72.

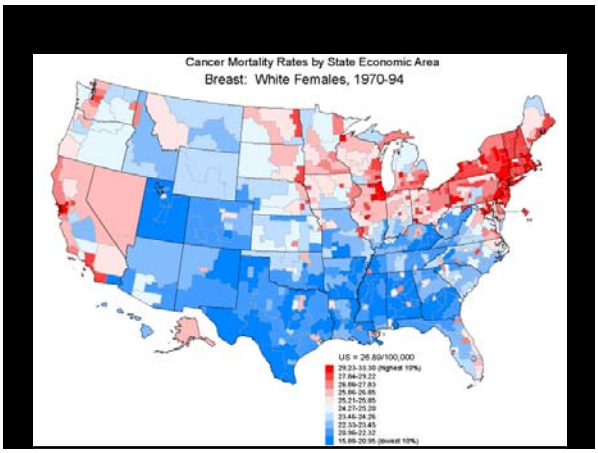
D and the Body's Innate Antimicrobial Peptides

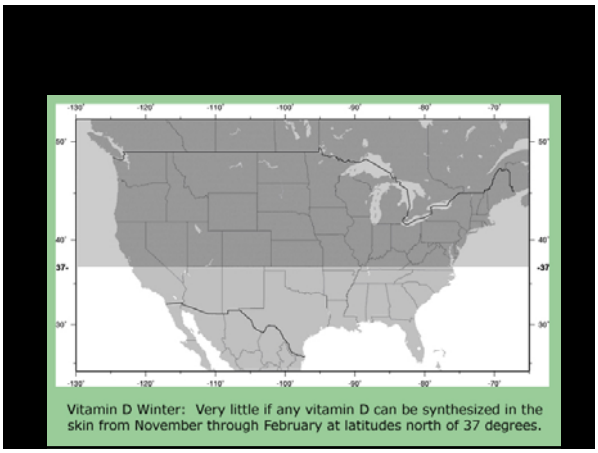
- human cathelicidin antimicrobial peptide (camp) and defensin beta2 (defB2)
- Activated D induces increases in antimicrobial proteins and secretion of antimicrobial activity against pathogens including *Pseudomonas aeruginosa*.

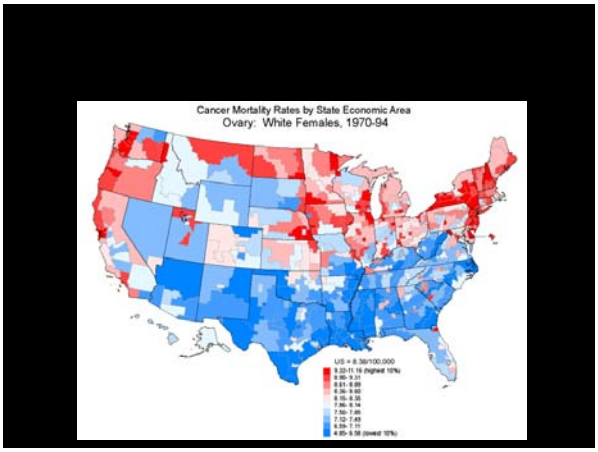
What Pediatric Controversy?

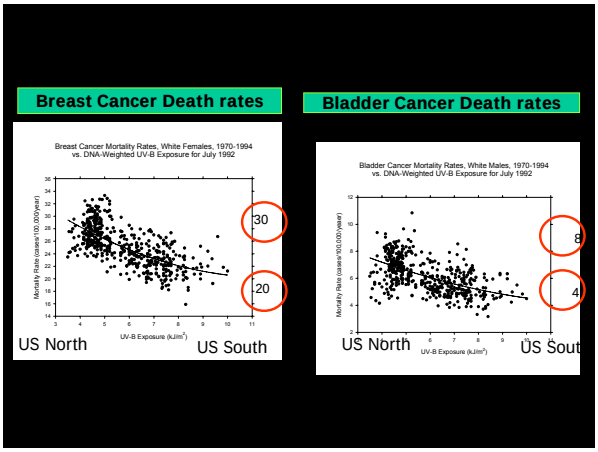
Vitamin D deficiency in 2009 is:
- primarily an adult disease.
- not a problem in Minnesota.
- not a problem in Minnesotan children.
- "none of *our* peds patients are D deficient."

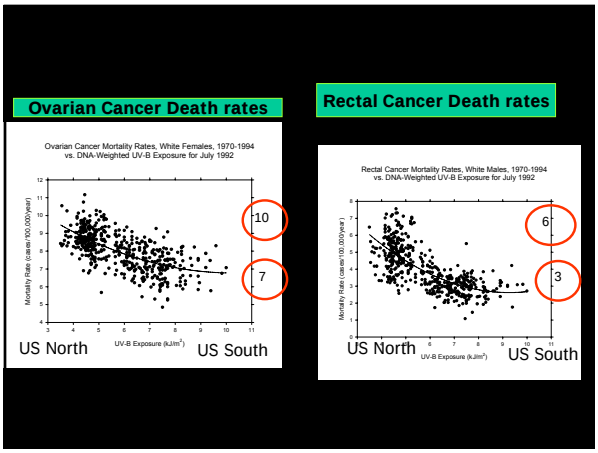


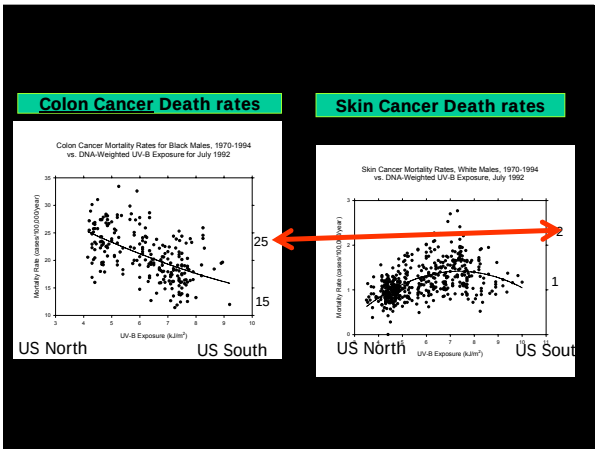

Cancer Mortality Rates by State Economic Area
Breast: White Females, 1970-94


Vitamin D Winter: Very little if any vitamin D can be synthesized in the skin from November through February at latitudes north of 37 degrees.

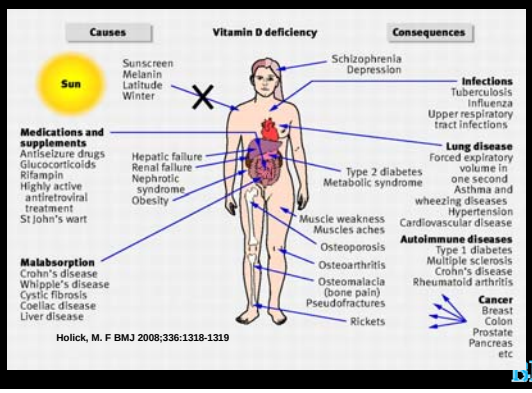

Cancer Mortality Rates by State Economic Area
Ovary: White Females, 1970-94


Breast Cancer Death rates
Bladder Cancer Death rates
US North
US South
US North
US South


Ovarian Cancer Death rates
Rectal Cancer Death rates
US North
US South
US North
US South


Colon Cancer Death rates
Skin Cancer Death rates
US North
US South
US North
US South

Causes and consequences of vitamin D deficiency



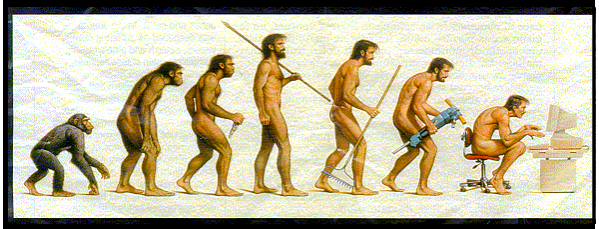
What Pediatric Controversy?

- Prenatal vitamins are sufficient for optimal *in utero* health.
- Breast milk contains sufficient vitamin D.
- Sunlight exposure is dangerous for infants and children.
- The 2008 AAP guideline of 400 IU of D3 is sufficient for Minnesotan children.

Ca++ Dyshomeostasis HF

• *Maiya S et al. *Heart* 2008; 94: 581-4.	16 infants
• *Carlton-Conway D et al. *J R Soc Med* 2004; 97:238-9	2 infants
• *Price DI et al. *Pediatr Cardiol* 2003; 24(5):510-2.	1 infant
• *Abdullah M et al. *Can J Cardiol* 1999; 15(6): 699-701.	1 infant
• *Yaseen H et al. *Pédiatrie* 1993; 48: 547-9.	1 infant
• *Gillor A et al. *Monatsschr Kinderheik* 1989; 137: 108-10.	1 infant
• *Brunvand I et al. *Acta Pediatr* 1995; 84: 106-8.	1 infant
• Shalev H et al. *Harefuah* 1990; 119: 422-3.	2 infants
• Koch a. *Z Kardiol* 1999; 88(1): 10-13.	3.5 yo ♀

The conditions for which our human genome was selected offer a reasonable basis for optimal nutrition.



Anatomically "Modern" humans have existed for 100,000 years

Take Home Points

- 25 hydroxyvitamin D blood test
- Goal: >32 ng/ml with PTH < 50 pcg/ml
- Supplement, supplement, supplement
- Prednisone, carbamezapine, valproic acid
- Greater BMI, darker one's skin, the more tobacco smoke exposure, the more sun screen, the longer hours indoors, the more sun exposure one needs

Comments
and
Questions

Thanks for viewing this presentation!

HOFFMAN
Medical Marketing & Education

To receive CME credit, please click the CME Eval button below and complete the form.

Top 10 Vitamin D Myths

By Gregory A. Plotnikoff, M.D., M.T.S.

ABSTRACT

A growing body of evidence points to the tremendous importance of vitamin D in maintaining health. Yet misconceptions about the need for this vitamin and the clinical care of vitamin D-deficient patients remain. This article deconstructs 10 prevailing myths and addresses such issues as symptoms and clinical indicators of vitamin D deficiency; the various sources of vitamin D, including diet, sun exposure, and supplementation; current laboratory standards for assessing vitamin D levels, and the prevalence of deficiency.

Clinically significant vitamin D deficiency is common worldwide. Numerous international medical authorities have emphasized its seriousness, including the authors of a 1996 *Minnesota Medicine* article.[1] In 1998, editorials in both the *British Medical Journal* and the *New England Journal of Medicine* called for physicians to pay greater attention to treating vitamin D deficiency.[2,3] Commentaries in such esteemed journals as *Science* and the *Journal of the American Medical Association* encouraged physicians to pay much closer attention to vitamin D deficiency and its impact on health.[4,5] And numerous editorials in both subspecialty and primary care journals, including the *Mayo Clinic Proceedings*, have brought the problem to the attention of physicians.[6] Yet, judging by questions e-mailed to me from around the world, physicians everywhere remain uncertain about many clinical issues associated with vitamin D. For that reason, this article addresses the top 10 myths about vitamin D among both physicians and the public.

10. Americans are not deficient in vitamin D.

Worldwide, the prevalence of vitamin D deficiency (defined as 25-hydroxyvitamin D3 or 25-OHD3 less than 20 ng/mL or 50 nmol/L is quite high. This is the case not only in poor countries but also in developed, sunny countries such as Australia, Israel, and Italy. The United States is no exception. The Centers for Disease Control's recent National Health and Nutrition Examination Survey (NHANES III) demonstrated that 42% of African American women were markedly deficient in vitamin D.[7] Results from the same survey demonstrated that 29% of girls age 12 years to 19 years were deficient.[8] In the month of March, 42% of young, healthy volunteers in Boston, which lies at a latitude of 42° North, who did not take vitamins were found to be deficient.[9] In Maine, 48% of adolescent girls were vitamin D deficient in winter.[10] And just north of Minnesota, in Winnipeg, Manitoba, 46% of mothers of newborns were recently found to be deficient.[11] Among internal medicine residents studied in Oregon, 51% were deficient during some part of the year, and 20% were vitamin D deficient year-round.[12]

9. Diet provides adequate vitamin D.

Vitamin D is rarely found in foods. For example, one needs to drink at least a quart of milk a day to get an adequate intake (AI) level of 400 IU/d. The highest concentrations of vitamin D are found in ocean salmon and sun-exposed mushrooms.[13]

According to the NHANES III data for adults older than 51 years, only 4% of men and 1% of women met or exceeded the AI level of vitamin D through food consumption. The lowest intakes were reported by teenaged girls and women. And among children ages 1 year to 8 years, only 59% of non-Hispanic white children met AI levels.

8. Just a few minutes a day of sun exposure is sufficient to generate enough vitamin D.

This common recommendation does not take into account the fact that the capacity to make vitamin D depends on multiple factors including latitude, season, skin type/melanin concentration, age, use of sun screen, body mass index, smoking status, and medication use. The further north one is, the darker one's skin is, the older one is, the higher one's BMI, the more one smokes, and the more one spends time inside, the more difficult it is to make vitamin D. Considering these factors, elderly, obese, African American women in Minnesota with limited mobility would be at the highest risk for vitamin D deficiency. However, this is misleading. Numerous studies demonstrate that many young women without these risk factors are still significantly deficient.

7. Supplementation guarantees vitamin D sufficiency.

Among the 42% of African American women found to be vitamin D deficient in the NHANES III study, 28% were taking the recommended amount of vitamin D as a daily supplement.[1] Among hospital inpatients, 43% of those with vitamin D intakes above the recommended daily allowance were found to be vitamin D deficient.[14] At the University of Wisconsin, of 51 infants with documented rickets, 73% were enrolled in the Wisconsin WIC program, which pro-

vides access to health care and nutritional counseling.[15] Expert opinion is that the average adult needs at least 800 IU/d to 1,000 IU/d of vitamin D3 (cholecalciferol) to attain a serum level of 75 nmol/L (30 ng/mL).[16]

6. Absence of rickets or osteomalacia is proof of vitamin D sufficiency.

Vitamin D insufficiency is frequently subclinical. Frank symptoms are only found in those with advanced disease. Long latency diseases related to long-term vitamin D deficiency, such as osteoporosis, cancer, and autoimmune diseases, are often asymptomatic.

Vitamin D sufficiency can only be assessed by measurement of serum 25-OHD3. Routine testing of calcium, alkaline phosphatase, and phosphate has no predictive value for deficiency.[17]

5. Vitamin D is only necessary for calcium homeostasis and bone metabolism.

The vitamin D receptor (VDR) is a 1,25-dihydroxyvitamin D3 (1,25(OH)2D3)-ligand activated transcription factor that interacts with co-regulators and the transcriptional preinitiation complex to alter the rate of target gene transcription. The VDR is a member of the superfamily of nuclear receptors for steroid hormones. The VDR is found not only in the intestine, kidney, bone, and parathyroid gland but also in most tissues of the body, including activated T and B lymphocytes, mononuclear cells, ß-islet cells, and the brain, heart, gonads, breast, and prostate.

Documented noncalcium homeostasis actions include 1) suppression of cell growth/anti-proliferative actions in myeloproliferative disorders and in colorectal and prostate cancer; 2) proapoptotic effects in breast and colon cancer; 3) immune modulation relevant to infectious agents such as mycobacteria, autoimmune disease including multiple sclerosis, and tolerance in transplantation; 4) skin cell proliferation and function relevant to psoriasis.[18] 1,25(OH)2D3 stimulates insulin production, affects myocardial contractility, regulates the renin-angiotensin system, and increases the relative size and number of type II muscle fibers.[19-22]

4. Vitamin D deficiency is not an important public health concern.

Because vitamin D has an impact on so many physiological processes, vitamin D deficiency has implications for public health. Prevention of the spread of tuberculosis is a crucial issue in crowded cities in advanced societies. A recent study of 210 immigrant tuberculosis patients in London showed that 76% were vitamin D deficient and 56% had undetectable levels.[23] Vitamin D is an important agent for enhancement of monocyte-macrophage immune function.[15]

Approximately one-third of all persons 65 years of age or older fall at least once a year, resulting in more than 1.5 million emergency room visits and more than 300,000 hospitalizations. The direct cost to society for fractures in the elderly exceeds $10 billion per year.[24] Only 50% of postmenopausal hip fractures are associated with osteoporosis. Thus, prevention of falls is crucial. And for this to happen, adequate vitamin D intake is crucial. Vitamin D deficiency in the elderly results not only in osteopenia but also in sarcopenia (reduced muscle numbers and strength). Increased fracture risk follows from reduced strength of bones as well as reduced strength of muscles and the consequence of increased body sway (imbalance) and tendency to fall.[25] Sarcopenia and decreased grip strength are associated with serum levels less than 75 nmol/L (30 ng/mL).[26] Oral supplementation to this level on average for 5 years in 2,686 healthy persons aged 65 years to 85 years reduced by 33% the incidence of typical osteoporotic fractures.[27] For elderly patients attending a fall clinic, those with serum levels less than 28 nmol/L had impaired balance and reflexes and significantly more falls than those with serum levels greater than 44 nmol/L.[28] Both active and inactive ambulatory persons older than 60 years with 25-OHD concentrations between 40 and 94 nmol/L (16 to 38 ng/mL) have demonstrated better lower-extremity muscle function than peers with concentrations less than 40 nmol/L (16 ng/mL).[29]

Pain is a leading reason for primary care and referral visits. In many cases, the pain is unexplainable, disproportionate to the history or physical exam, and very expensive to treat. A recent study of 150 young immigrant and nonimmigrant patients with nonspecific, musculoskeletal pain found 93% were vitamin D deficient and 5 out of 150 had undetectable levels.[30]

For large populations, vitamin D deficiency increases the risk of developing malignancies, chronic inflammatory and autoimmune diseases, as well as metabolic syndrome.[31] The prevalence of these diseases correlates with latitude and UV-B exposure. Animal studies have demonstrated that vitamin D can block or minimize the development of type I diabetes, rheumatoid arthritis, inflammatory bowel disease, as well as multiple sclerosis.

3. Current laboratory norms are accurate definitions of vitamin D sufficiency.

Several facts suggest that the current norms are too low. First, parathyroid hormone (PTH) is secreted by the body in response to insufficient calcium absorption. Elevated levels indicate long-standing inadequacy and a high bone-remodeling rate. PTH levels minimize with 25-OHD serum levels of at least 50 nmol/L (20 ng/mL).[32]

Second, fractional oral calcium absorption is optimized at approximately 80 nmol/L (30 ng/mL). Third, osteoporotic fractures are minimized when the serum 25-OHD is raised to 80 nmol/L.[33]

Several experts who attended the November 2004 NIH

Where Is the Evidence?

Both epidemiologic and in vitro data have generated provocative hypotheses regarding vitamin D deficiency and increased risk of 13 types of cancer including breast, colon, and prostate; type I diabetes; multiple sclerosis; hypertension; rheumatoid arthritis; and chronic, unexplained musculoskeletal pain.[1,2] Prospective, randomized trials are urgently needed to assess the role of vitamin D supplementation in the prevention and treatment of these diseases.

In the meantime, what is the strength of the evidence base from randomized controlled trials for vitamin D supplementation?

Two meta-analyses published this year deserve close attention. In the first, Porthouse et al reported in the April 30 issue of the *British Medical Journal* that daily oral supplementation of 800 IU/d of cholecalciferol and 1,000 mg/d of calcium in 3,314 women age 70 and older who had at least 1 reported risk for hip fracture did not prevent fractures.[3] This study was heavily criticized because serum levels of vitamin D were not measured, the dose was considered insufficient for a population with an extremely high prevalence of significant deficiency, and the sample size was insufficient to detect a difference of less than 30%.

Two weeks later, in the *Journal of the American Medical Association*, Bischoff-Ferrari et al reported the results of a meta-analysis of 5 randomized controlled trials for hip fracture prevention (n=9,294) and 7 for nonvertebral fracture prevention (n=9,820).[4] They found that oral vitamin D supplementation of 700 IU/d to 800 IU/d reduced the relative risk of hip fracture by 26% and any nonvertebral fracture by 23% compared with calcium or placebo. They noted that 400 IU/d was insufficient to prevent fractures and that optimal fracture prevention appeared to occur in trials in which subjects achieved a mean 25-hydroxyvitamin D (25-OHD) level of appromately 100 nmol/L (40 ng/mL).

The importance of vitamin D supplementation of at least 800 IU/d was also demonstrated by the same team in a 2004 meta-analysis of vitamin D for the prevention of falls.[5] At this dose, falls were reduced by 35%. Lower doses were not effective in reducing falls.

Overall, they noted that in 5 randomized controlled trials (n=1,237) vitamin D supplementation reduced the corrected odds ratio of falling by 22% (OR, 0.78; 95% CI 0.64-0.92) compared with placebo or calcium. They documented that the number of patients needed to be treated to prevent 1 fracture was just 15.

Current recommendations for vitamin D intake of 200 IU/d to 600 IU/d thus may not be sufficient for prevention of either falls or fractures. Additionally, current laboratory reference values based on a reference population may not match physiologic needs for prevention of serious, long-latent disease in specific populations. For those reasons, physicians should be aware that patients may require annual measurement of serum 25-OHD levels and need greater vitamin D supplementation than that which can be obtained from milk or multivitamins.

REFERENCES

1. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003;89(5):552-72.
2. Holick MF. Vitamin D: a millennium perspective. J Cell Biochem. 2003;88(2):296-307.
3. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ. 2005;330(7498):1003-6.
4. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005;293(180):2257-64.
5. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. JAMA. 2004;291(16):1999-2006.

Vitamin D and Cancer Conference asserted that the physiologic lower end of normal should be set at 80 nmol/L (32 ng/mL) based on invitro and randomized controlled trial data.

2. Vitamin D supplementation is toxic.

The vitamin D supplementation curve is flat up to 250 micrograms (10,000 IU) of vitamin D/d, after which long-term supplementation will produce toxicity.[34] Published and publicized cases of vitamin D toxicity and hypercalcemia have involved intakes far greater than this amount. Robert Heaney from Creighton University has documented that humans require approximately 4,000 IU/d.[35] This can be easily obtained with safe sun exposure (no burns). One cannot experience vitamin D toxicity from sun exposure because the body has the capacity to shift vitamin D production when adequate levels have been achieved and stored.

Vitamin D3 (cholecalciferol) is preferred to D2 (ergocalciferol) as a supplement because the half-life is longer, it is more potent, its bind to the vitamin D-binding protein is stronger, and ingestion does not result in unique biologically active metabolites.[36]

1. None of my patients is vitamin D deficient.

Surprisingly, more than 50% of women already receiving treatment from physicians for osteoporosis are vitamin D

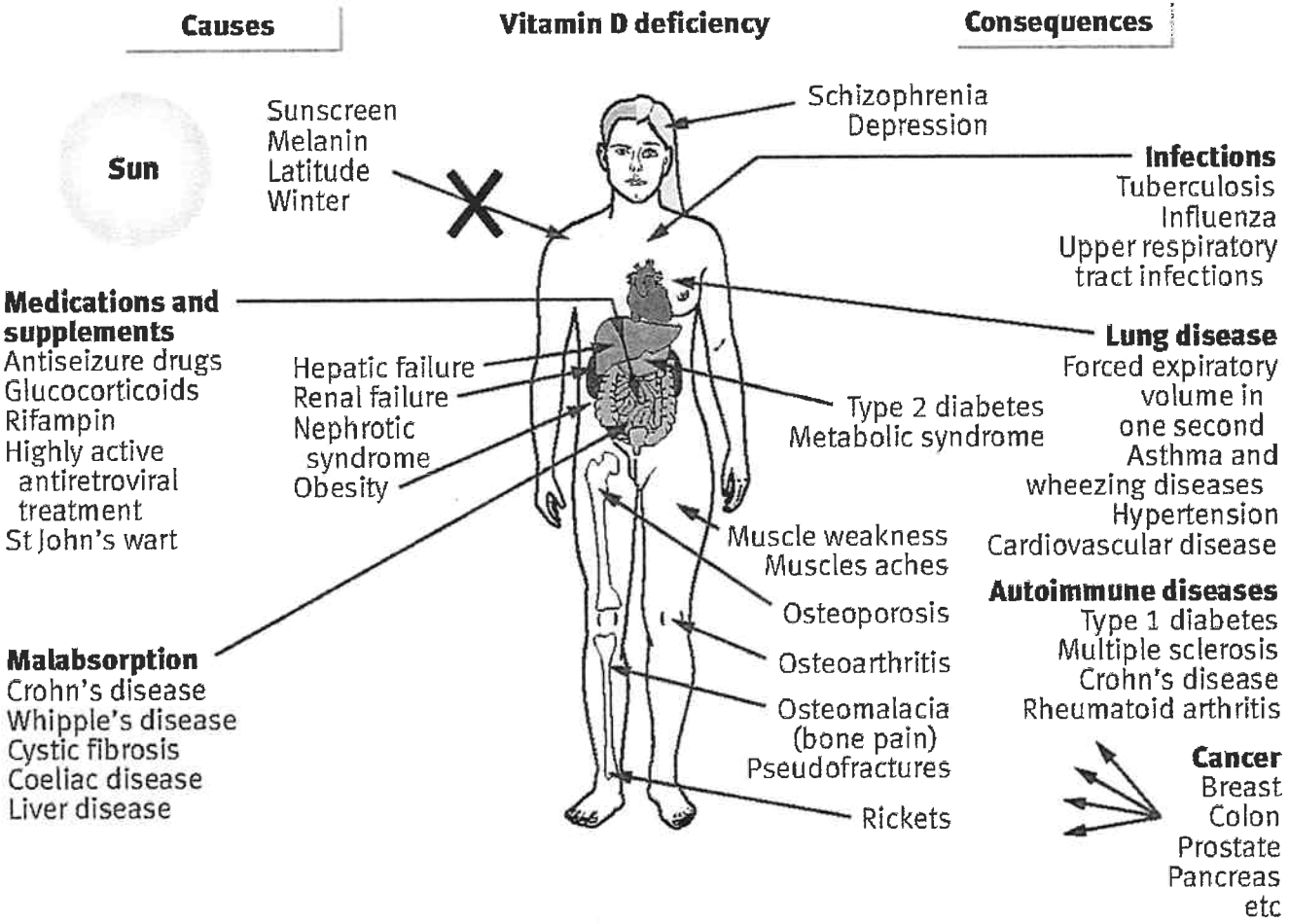
deficient.[37] Other patients at extremely high risk for deficiency include those on long-term prednisone, certain anticonvulsant medications, and all medications that have photosensitivity precautions. Additionally, persons with medical conditions that require sun avoidance, such as systemic lupus erythematosus or sickle-cell disease, are at extremely high risk. Persons with significant kidney or liver disease, congestive heart failure, or peripheral arterial disease are at great risk for unrecognized clinically significant deficiency. And finally, any person whose medical condition significantly limits his or her sun exposure (ie, patients who require long-term hospitalization) or fat absorption is at very high risk for significant deficiency. MM

Gregory Plotnikoff is an associate professor of internal medicine and pediatrics at the University of Minnesota. He splits his time between Minneapolis and Tokyo, where he is a visiting associate professor at Keio University Medical School.

REFERENCES

1. Eugster EA, Sane KS, Brown DM. Minnesota Rickets. Need for a policy change to support vitamin D supplementation. Minn Med. 1996;79(8):29-32.
2. Compston JE. Vitamin D deficiency: time for action. BMJ. 1998;317(7171):1466-7.
3. Utiger RD. The need for more vitamin D. N Engl J Med. 1998;338(12):828-9.
4. Stokstad E. The vitamin D deficit. Science. 2003;302:1886-8.
5. Meier C. Scientists probe role of vitamin D: deficiency a significant problem, experts say. JAMA. 2004;292(12):1416-8.
6. Holick MF. Vitamin D deficiency: what a pain it is. Mayo Clin Proc. 2003;78(12):1457-9.
7. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr. 2002;76(1):187-92.
8. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone. 2002;30(5):771-7.
9. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med. 2002;112(8):659-62.
10. Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick. Adolescent girls in Maine are at risk for vitamin D insufficiency. J Am Diet Assoc. 2005;105(6):971-4.
11. Weiler H, Fitzpatrick-Wong S, Veitch R, et al. Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. CMAJ. 2005;172(6):757-61.
12. Haney EM, Stadler D, Bliziotes MM. Vitamin D insufficiency in internal medicine residents. Calcif Tissue Int. 2005;76(1):11-6.
13. Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr. 2005;135(10):2478-85.
14. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998;338(12):777-83.
15. Mylott BM, Kump T, Bolton ML, Greenbaum LA. Rickets in the dairy state. WMJ. 2004;103(5):84-7.
16. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16(7):713-6.
17. Singh SK, Manjure S, Stott P, Shetty A, Iversen SA, Williams CR. Does routine blood bone biochemistry predict vitamin D insufficiency in elderly patients with low-velocity fractures? J Orthop Surg (Hong Kong). 2004;12(1):31-4.
18. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. Am J Physiol Renal Physiol. 2005;289(1):F8-28.
19. Lee S, Clark SA, Gill RK, Christakos S. 1,25 dihydroxyvitamin D3 and pancreatic ß-cell function: vitamin D receptors, gene expression, and insulin secretion. Endocrinology. 1994;134(4):1602-10.
20. Weishaar RE, Simpson RU. The involvement of the endocrine system in regulating cardiovascular function: emphasis on vitamin D3. Endocr Rev. 1989;10(3):1-15.
21. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. J Steroid Biocehm Mol Biol. 2004;89-90(1-5):387-92.
22. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovascular Dis. 2005;20(3):187-92.
23. Ustianowski A, Shaffer R, Collins S, Wilkinson RJ, Davidson RN. Prevalence and association of vitamin D deficiency in foreign-born persons with tuberculosis in London. J Infect. 2005;50(5): 432-7.
24. Bringhurst FR, Demay MB, Kronenberg HM: Mineral metabolism. In Williams Textbook of Endocrinology. Edited by Larson PR, Kronenberg HM., Melmed S, Polonsky KS. Amsterdam: Elsevier; 2003: 1317-20.
25. Venning G. Recent developments in vitamin D deficiency and muscle weakness among elderly people. BMJ. 2005;330(7490): 524-6.
26. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88(12):5766-72.
27. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double-blind controlled trial. BMJ. 2003;326(7387): 469-74.
28. Dhesi JK, Bearne LM, Moniz C, et al. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. J Bone Miner Res. 2002;17(5):891-7.
29. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or = 60 y. Am J Clin Nutr. 2004;80(3):752-8.
30. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc. 2003;78(12):1463-70.
31. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest. 2005;35(5): 290-304.
32. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet. 1998;351(9105):805-6.
33. Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol Biol. 2005;July 15.
34. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. Am J Clin Nutr. 1999;69(5):842-56.
35. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003;77(1):204-10.
36. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab. 2004;89(11):5387-91.
37. Holick MF, Siris ES, Binkley N et al. Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab. 2005;90(6):3215-24.

Causes and consequences of vitamin D deficiency



Holick, M. F BMJ 2008;336:1318-1319

BMJ