

Vitamin D: Senior Health Issues

November, 2014

Distributed by Representative Paul Seaton

Vitamin D has received much attention in recent years. A growing body of scientific research indicates that attaining adequate vitamin D blood serum levels has a wide range of beneficial health impacts.

In 2011 the Alaska State Legislature unanimously passed House Concurrent Resolution 5 which requests the Governor to adopt a prevention of disease model for healthcare in Alaska, with a specific focus on the importance of vitamin D sufficiency.

One of the populations in Alaska that could receive a large benefit from attaining sufficient vitamin D blood levels is our seniors. The attached packet is composed of studies, abstracts, and articles dealing with vitamin D and its impact on senior health from the years 2012, 2013 and 2014. Please take a moment to look through the articles I have attached here, and speak to your health care provider about your vitamin D levels.

In the interest of not burdening you with too much paper I have included a sampling of the materials relating to vitamin D and senior health. To receive a copy of the full studies associated with these abstracts and articles please call my office at 1-800-665-2689.

Sincerely,

A handwritten signature in black ink that reads "Paul K. Seaton". The signature is written in a cursive style with a long horizontal line extending to the right from the end of the name.

Representative Paul Seaton

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Breast Cancer Survival Rates - Meta-analysis of Vitamin D Sufficiency for improving Survival of Patients with Breast Cancer - *Anti-Cancer Research*, March 2014

Non-linear Relationship between Serum 25-hydroxyvitamin D Concentration and Subsequent Hip Fracture

Koning, L. De, D. Henne, B. R. Hemmelgarn, P. Woods, and C. Naugler. "Non-linear Relationship between Serum 25-hydroxyvitamin D Concentration and Subsequent Hip Fracture." *Osteoporosis International* 24.7 (2013): 2061-065.

Summary Serum 25-OH vitamin D levels were compared in 254 hip fracture subjects and 2,402 matched control subjects. There was a significant inverse association between 25-OH vitamin D and hip fracture only between 0 and 70 nmol/L. Vitamin D is integral to bone metabolism, however the utility of serum 25-OH vitamin D as a risk marker for hip fractures is controversial.

Methods We conducted a case-control study of patients admitted to the hospitals with hip fractures in Calgary, Alberta, (catchment population 1.4 million) between January 1, 2007 and August 31, 2011. We searched the laboratory information system of Calgary Laboratory Services for serum 25-OH vitamin D levels within 6 months prior to admission on patients admitted to hospital with hip fractures. Cases were identified through the Calgary Laboratory Services laboratory information system and were matched to controls for age, sex, and month of testing. The hip fracture-25-OH vitamin D association was examined using multiple linear and spline regression.

Results Of 305 subjects initially identified with hip fractures, serum 25-OH vitamin D levels were available for 254 (83 %). These were matched to 2,402 control subjects. We observed a significant ($p < 0.01$) non-linear relationship such that 25-OH vitamin D was inversely associated with hip fracture only below 70 nmol/L (odds ratio 0.81 per 10 nmol/L increase; 95 % CI 0.86–0.93).

Conclusions The utility of 25-OH vitamin D level as a risk marker for hip fracture depends on the cut-off level used and was of potential use only for lower levels of 25-OH vitamin D.

Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial

Divya Sanghi PhD, Abhishek Mishra MSc, Amar Chandra Sharma MSc, Ajai Singh MS, S. M. Natu PhD, Sarita Agarwal PhD, Rajeshwar Nath Srivastava MS “Does Vitamin D Improve Osteoarthritis of the Knee: A Randomized Controlled Pilot Trial” Clinical Orthopaedics and Related Research, July 19th 2013

Background Animal, epidemiologic, and human clinical studies suggest a putative role for vitamin D in osteoarthritis (OA). Inadequate sunlight exposure and lower serum levels of 25(OH)D appear in some reports to be associated with an increased risk for progression of knee OA.

Questions/purposes We asked whether treatment with vitamin D would (1) reduce knee pain (WOMAC and VAS), (2) improve function (WOMAC), and (3) change levels of relevant biochemical markers in patients with knee OA with vitamin D insufficiency.

Methods This randomized controlled pilot trial prospectively enrolled 107 patients with knee OA with vitamin D insufficiency (25(OH)D \leq 50 nmol/L) to receive oral vitamin D or placebo. The primary outcome measures were pain and function, and the secondary were biochemical markers. At baseline, the two groups were comparable. The patients were followed for 1 year.

Results At 12 months, knee pain had decreased in the vitamin D group by mean -0.26 (95% CI, -2.82 to -1.43) on VAS and -0.55 (95% CI, -0.07 to 1.02) on the WOMAC, whereas in the placebo group, it increased by mean 0.13 (95% CI, -0.03 to 0.29) on the VAS and 1.16 (95% CI, 0.82 to 1.49) on the WOMAC (effect size = 0.37 and 0.78). Likewise knee function improved in the vitamin D group by mean -1.36 (95% CI, -1.87 to -0.85) over the placebo group which had a mean 0.69 (95% CI, -0.03 to 1.41 ; effect size = 0.06). There were significant biochemical changes in serum total calcium, 25(OH)D and alkaline phosphatase.

Conclusions The results above suggest there is a small but statistically significant clinical benefit to vitamin D treatment in patients with knee OA, although we recommend a long-term study to determine whether these changes are clinically important and whether they will be sustained with time. Further studies with long-term radiologic evaluations are needed.

Low Serum Vitamin D Concentrations in Alzheimer's Disease: A Systematic Review and Meta-Analysis

Cedric Annweiler, David J. Llewellyn, and Olivier Beauchet, "Low Serum Vitamin D Concentrations in Alzheimer's Disease: A Systematic Review and Meta-Analysis" *Journal of Alzheimer's Disease* 33 (2013) 659–674.

Abstract. Vitamin D has been investigated in association with cognitive function in older adults. It is unclear whether hypovitaminosis D could be associated with Alzheimer's disease (AD). Our objective was to systematically review and quantitatively synthesize the association of low serum 25-hydroxyvitamin D (25OHD) concentrations with AD in adults. A Medline and PsycINFO® search was conducted on May 2012, with no limit of date, using the MeSH terms "Vitamin D" OR "Hydroxycholecalciferols" combined with the MeSH terms "Alzheimer disease" OR "Dementia" OR "Cognition" OR "Cognition disorders" OR "Memory" OR "Memory Disorders" OR "Executive Function" OR "Attention" OR "Neuropsychological Tests". Of the 284 selected studies, 10 observational studies (including 9 case-controls and 1 cohort study) met the selection criteria. All were of good quality. The number of AD cases ranged from 20 to 211 (40%–100% female). Finally, 7 case-control studies were eligible for fixed and random-effects meta-analyses of bias-corrected effect size of the difference in serum 25OHD concentrations between AD cases and controls using an inverse-variance method. The pooled effect size in random-effects meta-analysis was 1.40 (95% CI: 0.26;2.54), a 'large' effect size that indicates that serum 25OHD concentrations were 1.4 standard deviation units lower in AD cases compared to cognitively healthy controls ($p = 0.016$). In conclusion, AD cases had lower serum vitamin D concentrations than matched controls. This reinforces the conceptualization of vitamin D as a 'neurosteroid hormone' and as a potential biomarker of AD.

Conclusion: In conclusion, this systematic review and metaanalysis provides compelling evidence that AD cases have lower serum vitamin D concentrations than matched controls. These results reinforce the conceptualization of vitamin D as a 'neurosteroid hormone' [3] that could be a potential biomarker of AD [16]. Of note low vitamin D concentrations and AD are two frequently reported pathological findings in older adults [13–17]. We and others hypothesize that low vitamin D concentrations may contribute to an increased susceptibility to AD; however, further well-designed prospective studies are needed for a better understanding of the involvement of lowvitaminDconcentrations in the natural history of AD. Randomized clinical trials will also be necessary to address the issue of causality and determine whether vitamin D supplementation is effective for the prevention or treatment of AD.

The Association between Vitamin D and Cognition: A Systematic Review

Schaft, J. Van Der, H.I. Koek, E. Dijkstra, H.j.j. Verhaar, Y.t. Van Der Schouw, and M.h. Emmelot-Vonk. "The Association between Vitamin D and Cognition: A Systematic Review." *Ageing Research Reviews* 12.4 (2013): 1013-023. Web.

Abstract Vitamin D insufficiency and deficiency are a major health care problem. The association between vitamin D levels and cognitive function is still under debate. We conducted a systematic review to assess the association between levels of vitamin D and cognition. Therefore, the databases of Embase and Pubmed were searched through June 2012 for observational studies relating vitamin D levels to cognition. Our initial search yielded 2182 articles. After applying exclusion criteria, there were 28 studies eligible for inclusion: 25 cross-sectional and 6 prospective studies (3 studies show cross-sectional as well as prospective data). The main finding of the 25 cross-sectional studies was a statistically significant worse outcome on one or more cognitive function tests or a higher frequency of dementia with lower vitamin D levels or intake in 18 out of 25 (72%) studies, whereas 7 (28%) studies failed to show an association. Four out of 6 (66.7%) prospective studies showed a higher risk of cognitive decline after a follow-up period of 4–7 years in participants with lower vitamin D levels at baseline.

Conclusion this review supports the hypothesis that hypovitaminosis D is associated with worse outcome on one or more cognitive function tests or a higher frequency of dementia in cross-sectional as well as prospective studies. Further studies should focus on the role of vitamin D supplementation in the prevention of cognitive decline in participants with low vitamin D levels.

Vitamin D level Predicts Mortality Following Surgery

Posted on January 23, 2013 by Vitamin D Council

Research presented at the Society of Critical Care Medicine meeting reports that vitamin D deficiency before coronary artery bypass graft surgery predicts risk of mortality after 3 months.

Coronary artery bypass grafting (CABG) is a surgery which helps improve blood flow to the heart. CABG is used to treat people who have severe coronary heart disease.

Takuhiro Moromizato, MD, of Brigham and Women's Hospital in Boston, and colleagues found that patients with vitamin D deficiency or insufficiency had a significantly higher risk of mortality within 90 days of CABG compared to those with sufficient vitamin D levels.

In this retrospective cohort study, the authors collected data from 324 patients included in the Research Patient Data Registry in Boston between 2001 and 2011. All participants had vitamin D levels assessed up to a year prior to hospitalization.

The authors found that 90-day mortality was higher in patients who were deficient (< 15 ng/ml) and insufficient (15-30 ng/ml) compared to those who had sufficient levels (> 30 ng/ml). Nine percent of patients with vitamin D deficiency died within 3 months after the surgery, 7.5% of those with insufficient levels, compared to 1.9% of patients with sufficient levels.

Deficiency remained a significant predictor of mortality after adjusting for age, gender, race, and acute kidney injury. Both deficiency and insufficiency findings were significant when additionally controlling for end-stage renal disease.

Of course, the study does not prove causality. The authors recognize the potential for selection bias and unmeasured confounders as limitations to the study.

Source

Fiore K. Vitamin D level predicts death in CABG. Medpage Today. January 22, 2013.

Serum 25-hydroxyvitamin D Levels and Overall Mortality. A Systematic Review and Meta-analysis of Prospective Cohort Studies

Schöttker, Ben, Dorothee Ball, Carolin Gellert, and Hermann Brenner. "Serum 25-hydroxyvitamin D Levels and Overall Mortality. A Systematic Review and Meta-analysis of Prospective Cohort Studies." *Ageing Research Reviews* 12.2 (2013): 708-18. Web.

Objective: To provide a systematic review and meta-analysis of prospective, population-based cohort studies on the association of serum 25-hydroxyvitamin D (25(OH)D) and all-cause mortality.

Methods: Relevant studies were identified by systematically searching Medline, EMBASE and ISI Web of Knowledge. Reported hazard ratios (HRs) for 25(OH)D categories were recalculated employing comprehensive trend estimation from summarized dose-response data and pooled in a random effects model meta-analysis.

Results: Overall, 12 original studies were included in the review and meta-analysis comprising 32,142 mainly elderly study participants with measured 25(OH)D of whom 6921 died during follow-up. An inverse association between 25(OH)D levels and all-cause mortality was found in all but two studies that was statistically significant in several of the individual studies. In meta-analysis, 25(OH)D levels were significantly inversely associated with all-cause mortality with a pooled HR of 0.92 (95% confidence interval: 0.89-0.95) for a 20 nmol/l increase in 25(OH)D levels.

Conclusion: In this meta-analysis of prospective, population-based cohort studies, a 20 nmol/l increase in 25(OH)D levels was associated with an 8% lower mortality in the general elderly population. This agrees with results from meta-analyses on randomized controlled trials that found a decrease in mortality with vitamin D3 supplementation of a comparable magnitude.

Association of 25-hydroxyvitamin D with type 2 diabetes among Patients undergoing Coronary Angiography

O'hartaigh, Bríain, G. Neil Thomas, Günther Silbernagel, Jos A. Bosch, Stefan Pilz, Adrian Loerbroks, Marcus E. Kleber, Tanja B. Grammer, Bernhard O. Böhm, and Winfried März. "Association of 25-hydroxyvitamin D with Type 2 Diabetes among Patients Undergoing Coronary Angiography: Cross-sectional Findings from the LUDwigshafen Risk and Cardiovascular Health (LURIC) Study." *Clinical Endocrinology* 79.2 (2013): 192-98. Web.

Objective: Evidence suggests that vitamin D may protect against the onset of diabetes. However, the mechanisms underlying the role of vitamin D on glycaemic status are unclear and warrant further investigation. We sought to determine the relationship between serum 25-hydroxyvitamin D (25[OH]D) and glycaemic status among intermediate-to-high-risk patients scheduled for coronary angiography.

Methods: Participants were 3316 male and female patients (mean \pm SD age, 62.7 \pm 10.6 years). Four categories were formed according to serum 25[OH]D levels. The association between serum 25[OH]D and diabetes was assessed using multivariable logistic regression.

Results: Fasting and 2 h post-load glucose, HbA1c and the HOMA-IR indices diminished with increasing serum 25[OH]D levels ($P < 0.001$). However, no associations were observed between insulin, pro-insulin or C-peptide and serum 25[OH]D concentrations. The pro-inflammatory markers IL-6 and hs-CRP also decreased considerably with higher vitamin D levels ($P < 0.001$). After full adjustment, those with optimal serum 25[OH]D levels had a reduced odds for fasting diabetes (OR = 0.63; 95% CI, 0.46-0.86; Ptrend = 0.01), 2 h post-load diabetes (OR = 0.46; 95% CI, 0.29-0.74; Ptrend = 0.004), both fasting/2 h post-load diabetes (OR = 0.61; 95% CI, 0.42-0.87; Ptrend = 0.001) and all of the combined hyperglycaemic states (OR = 0.68; 95% CI, 0.52-0.80; Ptrend = 0.01).

Conclusions: Higher serum 25[OH]D levels were associated with better glycaemic status and lower inflammation. Should these observations be confirmed in future studies, vitamin D supplementation may prove a useful adjunct in attenuating the onset of diabetes.

Vitamin D and Periodontal Health in Older Men

Alshouibi, E. N., E. K. Kaye, H. J. Cabral, C. W. Leone, and R. I. Garcia. "Vitamin D and Periodontal Health in Older Men." *Journal of Dental Research* 92.8 (2013): 689-93.

Abstract Vitamin D, an anti-inflammatory mediator, has potential benefits for physical and oral health. Although it is produced endogenously, some individuals have a greater need for dietary and supplemental sources. This repeated-measures cross-sectional study assessed associations between total vitamin D intake and periodontal health in older men. Participants were 562 members of the Department of Veterans Affairs Dental Longitudinal Study, mean age 62.9 years, who were examined 1 to 4 times between 1986 and 1998. A calibrated examiner measured probing pocket depth (PPD) and attachment loss (AL) on each tooth. Alveolar bone loss (ABL) was determined from radiographs. Severe periodontal disease was defined as PPD \geq 5 mm on \geq 1 tooth and AL \geq 6 mm at \geq 2 sites (not on same tooth), and moderate-to-severe alveolar bone loss as ABL \geq 40% at \geq 3 sites. Generalized estimating equations were used to compute the odds ratios (OR) and 95% confidence intervals (95% CI) of having periodontal disease by level of vitamin D intake. Total vitamin D intake \geq 800 IU was associated with lower odds of severe periodontal disease (OR = 0.67, 95% CI = 0.55-0.81) and moderate-to-severe ABL (OR = 0.54, 95% CI = 0.30-0.96) relative to intake $<$ 400 IU/day. Vitamin D intake may protect against periodontal disease progression.

Conclusion We examined the associations of total vitamin D intake with severe periodontal disease and moderate-to-severe alveolar bone loss and found evidence of a significant protective relationship of vitamin D intake on these measures of periodontal disease. Our findings support earlier work showing an inverse relationship of periodontal disease indicators with vitamin D intake or status (Miley *et al.*, 2009; Bashutski *et al.*, 2011). Use of combined calcium (1,000 mg/day) and vitamin D (400 IU/ day) oral supplements by individuals attending a periodontal disease maintenance program was associated with lower probing depths compared with depths in those not taking supplements (Miley *et al.*, 2009). Over follow-up, the supplement users tended to have less periodontal disease (attachment level, bleeding on probing, and alveolar crest height) than nonusers, although the differences were not statistically significant ($p > .05$) at the one-year time point (Garcia *et al.*, 2011).

The Association between Serum Levels of Vitamin D and Recurrent Urinary Tract Infections in Premenopausal Women

Nseir, William, Muhamad Taha, Hytam Nemarny, and Julnar Mograbi. "The Association between Serum Levels of Vitamin D and Recurrent Urinary Tract Infections in Premenopausal Women." *International Journal of Infectious Diseases* 17.12 (2013): E1121-1124. Web.

Objectives: To examine whether there is any association between serum levels of 25-hydroxy vitamin D (25(OH) vitamin D) and the recurrence of urinary tract infections (UTIs) among premenopausal women.

Methods: During a period of 3 years, 93 premenopausal women with a medical history of recurrent UTIs were enrolled from the Infectious Diseases Unit. Cases with recurrent UTIs were compared to 93 age-matched (± 5 years) women with no history of recurrent UTI (control group), in terms of serum 25(OH) vitamin D and different risk factors for recurrent UTI. Recurrent UTI was defined as three or more episodes of UTI over a 12-month period.

Results: The mean age of women with recurrent UTIs was 43.8 ± 9 years and of controls was 39 ± 10 years ($p=0.839$). The mean serum levels of 25(OH) vitamin D among women with recurrent UTIs were significantly lower than those of controls ($9.8 \text{ ng/ml} \pm 4$ vs. $23 \text{ ng/ml} \pm 6$; $p < 0.001$). Multivariate analysis showed that a serum 25(OH) vitamin D level of $< 15 \text{ ng/ml}$ (odds ratio 4.00, 95% confidence interval 3.40-4.62; $p=0.001$) was associated with recurrent UTIs in premenopausal women.

Conclusions: In this retrospective study, we found that recurrent UTIs in premenopausal women are associated with vitamin D deficiency.

Vitamin D supplementation program cuts down on health care costs in New Zealand

Posted on August 8, 2013 by Vitamin D Council

Widespread vitamin D supplementation in aged care facilities has saved the New Zealand government over a half-million dollars the past two years, according to a new press release.

In 2010 the MidCentral District Health Board (DHB) began encouraging health professionals to prescribe vitamin D to residents in aged care facilities. Between March 2010 and June 2012, the percentage of aged care residents supplementing with vitamin D jumped from 15 to 74 percent.

The main goal was to reduce falls-related fractures, and so far, they've had great success. "Comparisons from before and after the start of the project show a 32 per cent reduction in aged residential care residents going to the emergency department with falls-related fractures," says Associate Minister of Health Jo Goodhew. "And a 41 per cent reduction in their hospital admissions due to these fractures."

Their results corroborate with past research, which shows that vitamin D supplementation can reduce falls and falls-related fractures

Due to the reduced admissions to the hospital, the vitamin D project has saved MidCentral DHB more than \$540,000 (about \$430,000 USD). There are also likely further savings due to reduced need for clinical support, hospital pharmacy services and rehabilitation.

Says Mrs. Goodhew, "The benefits of preventing falls in older people cannot be overstated. Preventing falls enables older people to maintain their independence and confidence."

Source Live News. Vitamin D project helps prevent falls and saves health costs. <http://livenews.co.nz/2013/08/08/vitamin-d-project-helps-prevent-falls-and-saves-health-costs/>

Alzheimer's Amyloid Plaque Removal May Be Aided By Vitamin D And Omega 3

<http://www.medicalnewstoday.com/articles/255957.php>

In a small pilot study, a team of US researchers has discovered how vitamin D3, a form of vitamin D, and omega 3 fatty acids may help the immune system clear the brain of amyloid plaques, one of the physical hallmarks of Alzheimer's disease. Due to appear this week in the print issue of the *Journal of Alzheimer's Disease*, the new study builds on previous work by the same team, from the University of California - Los Angeles (UCLA). Co-author Milan Fiala, a researcher at UCLA's David Geffen School of Medicine, says in a statement released on Monday: "Our new study sheds further light on a possible role for nutritional substances such as vitamin D3 and omega-3 in boosting immunity to help fight Alzheimer's."

Vitamin D3 is essential for bone and immune system health. The main source of the vitamin, which is made in the skin, is sunshine. Deficiencies may occur during winter months or in those who are indoors most of the time, such as people with Alzheimer's disease. Omega 3 fatty acids are fats commonly found in marine and plant oils. They are considered essential fatty acids, meaning that they cannot be synthesized in the body but are vital for healthy metabolism. They are thought to play an important role in reducing inflammation throughout the body.

In their earlier work, the researchers showed how certain mechanisms regulated by vitamin D3 help clear amyloid-beta, the abnormal protein found in sticky plaques that clog up the important communication space between brain cells in people with Alzheimer's. In the new study, they extend what they discovered about vitamin D3, and highlight the role of a fatty acid called omega-3 DHA (docosahexaenoic acid). They identify key genes and signaling pathways controlled by vitamin D3 and omega-3 DHA, that may help the immune system regulate inflammation and get rid of plaque.

For their study, Fiala and colleagues isolated immune cells from blood samples taken from Alzheimer's patients and healthy volunteers for comparison. The immune cells they were interested in are known as macrophages: these go around gobbling up waste products like amyloid beta that can otherwise clog up the spaces between cells and interfere with cell-to-cell signaling. The researchers incubated the macrophages for a

few hours with amyloid beta. To some of the cells they then added either an active form of vitamin D3, or an active form of omega 3 DHA, and watched what effect this had on inflammation and the ability of the macrophages to absorb amyloid beta.

They found that both the active forms of vitamin D3 and omega 3 DHA improved the ability of the macrophages from the Alzheimer's patients' blood samples to absorb amyloid beta. They also noticed there was less of the cell-death that is normally triggered by amyloid beta. The researchers also observed that vitamin D3 and omega 3DHA used different receptors and the same signaling pathways. One of the main contributions of the new study is that it shows key differences between the macrophages of the Alzheimer's patients and of the healthy controls, and that within the Alzheimer's patients, there were differences in macrophages. The key differences were in gene expression and trascription patterns. The Alzheimer's patients' macrophages expressed inflammatory genes differently to those of the healthy controls, and there were two distinct groups of Alzheimer's patients.

In one group, the macrophages had increased transcription of inflammatory genes, while in the other, the transcription was decreased. Transcription is the first step of reading the instructions in DNA to make proteins. The researchers say more work is needed to find out if these two different transcription patterns of inflammatory genes are signs of either two stages of Alzheimer's, or even two types of the disease. Fiala suggests perhaps their findings are highlighting differences linked to either insufficient intake of the essential nutrients, or the body's ability to use them.

"We may find that we need to carefully balance the supplementation with vitamin D3 and omega-3 fatty acids, depending on each patient in order to help promote efficient clearing of amyloid-beta," says Fiala. "This is a first step in understanding what form and in which patients these nutrition substances might work best," he adds. Funds from the Alzheimer's Association supported the initial phase of the study. Fiala is a consultant with Smartfish, a Norwegian biotech company that is producing a drink with an active form of omega-3 DHA. In 2009, Fiala co-authored a paper that showed how curcuminoids, substances found in the spice turmeric, enhanced the surface binding of amyloid beta to macrophages and that vitamin D strongly stimulated the uptake and absorption of amyloid beta in macrophages.

Written by Catharine Paddock PhD

Pre-hospital Vitamin D Concentration, Mortality, and Bloodstream Infection in a Hospitalized Patient Population

Lange, Nancy, Augusto A. Litonjua, Fiona K. Gibbons, Edward Giovannucci, and Kenneth B. Christopher. "Pre-hospital Vitamin D Concentration, Mortality, and Bloodstream Infection in a Hospitalized Patient Population." *The American Journal of Medicine* 126.7 (2013): 640.e19-40.e27. Web.

Objective: The study objective was to examine the association between pre-hospital serum vitamin D concentration and mortality after hospitalization.

Methods: We performed a retrospective cohort study in 2 tertiary hospitals in Boston, Mass, on 23,603 patients aged ≥ 18 years in whom 25(OH)D was measured before hospitalization between 1993 and 2010. The main outcome measures were all-cause mortality by day 30 post-hospital admission, in-hospital mortality, and community-acquired bloodstream infection.

Results: Compared with patients with pre-hospital 25(OH)D ≥ 30 ng/mL, patients with pre-hospital 25(OH)D ≤ 15 ng/mL or 15 to 30 ng/mL have higher odds of mortality 30 days after hospital admission. After adjustment for age, gender, race, Deyo-Charlson index, season, type (surgical vs medical), creatinine, blood urea nitrogen, hematocrit, and time between 25(OH)D draw and hospital admission, the adjusted odds ratio (OR) of 30-day mortality in patients with 25(OH)D ≤ 15 ng/mL is 1.45 (95% confidence interval [CI], 1.21-1.74; $P < .0001$) and the adjusted OR of 30-day mortality in patients with 25(OH)D 15 to 30 ng/mL is 1.30 (95% CI, 1.10-1.54; $P = .003$) both compared with patients with pre-hospital 25(OH)D ≥ 30 ng/mL. In a subgroup analysis of patients who had blood cultures drawn ($n = 5628$), pre-hospital serum 25(OH)D ≤ 15 ng/mL was associated with increased odds of community-acquired bloodstream infection (adjusted OR, 1.29; 95% CI, 1.06-1.57; $P = .01$) relative to patients with 25(OH)D ≥ 30 ng/mL.

Conclusions: Analysis of 23,603 hospitalized patients identified both 25(OH)D ≤ 15 ng/mL and 25(OH)D 15 to 30 ng/mL before hospital admission as associated with the odds of all-cause patient mortality at 30 days after hospitalization. In addition, pre-hospital serum 25(OH)D ≤ 15 ng/mL is significantly associated with the odds of community-acquired bloodstream infection.

Clear Link Found Between Vitamin D Deficiency and Alzheimer's Disease

Published on Yahoo Health, August 6th 2014

Older adults who are severely deficient in vitamin D may be more than twice as likely to develop dementia or Alzheimer's disease than those who don't have a deficiency, according to the largest study of its kind, published Wednesday in the journal *Neurology*.

"We expected to find an association between low Vitamin D levels and the risk of dementia and Alzheimer's disease, but the results were surprising — we actually found that the association was twice as strong as we anticipated," noted lead researcher David Llewellyn of the University of Exeter Medical School in a news release.

Llewellyn, who could not be reached for comment by Yahoo Health, looked at several years-worth of data on 1,658 Americans ages 65 and older who had taken part in the National Heart, Blood and Lung Institute's Cardiovascular Health Study. He and his team found that adults who were just moderately deficient in vitamin D had a 53 percent increased risk of developing dementia — the general term for any severe decline in mental ability — while the risk jumped to 125 percent for those who had a severe deficiency. Similarly, for Alzheimer's disease — the most common type of dementia — the moderately deficient adults were 69 percent more likely to develop it, while the severely deficient had a 122 percent increased risk.

"Clinical trials are now needed to establish whether eating foods such as oily fish or taking vitamin D supplements can delay or even prevent the onset of Alzheimer's disease and dementia," Llewellyn said. "We need to be cautious at this early stage, and our latest results do not demonstrate that low vitamin D levels cause dementia. That said, our findings are very encouraging, and even if a small number of people could benefit, this would have enormous public health implications given the devastating and costly nature of dementia."

Currently, more than five million Americans are living with Alzheimer's disease, which is the sixth leading cause of death in this country, according to the Chicago-

based Alzheimer's Association. One in three seniors dies with Alzheimer's or another form of dementia. "We think this study is important," Keith Fargo, director of scientific programs and outreach with the Alzheimer's Association (a major funder of Llewellyn's research), told Yahoo Health in response to the findings. "It's a relatively large study, and it looks like it does show a pretty substantial link.... It just doesn't show us why there is a link." One hypothesis, Fargo noted, is that the brain — including the hippocampus, which is one of the first areas to break down with Alzheimer's — is full of vitamin D receptors.

There has been a growing body of research on the disease's connection with vitamin D — the main sources of which are sunshine and supplements, with minor sources including egg yolks and oily fish like salmon and sardines. Earlier this year, a study out of Denmark, for example, also showed a link between Alzheimer's disease prevalence and low levels of vitamin D, while earlier studies conducted in Australia and France found tenuous connections between taking doses of vitamin D and having an improved memory. The vitamin has also been linked, in various studies, to preventing asthma, diabetes, and cancer.

"People tend to not believe vitamin D news, because it seems too good to be true," John Cannell, MD, executive director of the California-based nonprofit Vitamin D Council, told Yahoo Health. "But vitamin D has a profound mechanism of action, as it's really a steroid hormone that turns genes on and off, and no other vitamin works that way. There are at least 1,000 different genes directly influenced by vitamin D." The council recommends a combination of cautious sun exposure combined with supplements in winter months.

Cannell called the new study's findings "pretty exciting," mainly because of its size and structure. "It's important because it's the first cohort study of a large population — meaning that it's forward-looking, having followed people over several years," he said. "The next step is a randomized controlled trial, but this is as close as you can get without that."

Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for Breast Cancer

Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa SE, O'Dea AP, Klemp JR, Fabian CJ "Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for Breast Cancer" *Breast Cancer Research Treatment* January, 2010.

Abstract Vitamin D deficiency and insufficiency may contribute to musculoskeletal symptoms and bone loss observed in women taking aromatase inhibitors (AIs). This study was conducted to determine the prevalence of suboptimal vitamin D levels in women initiating adjuvant letrozole for breast cancer and to determine whether supplementation with 50,000 IU of vitamin D3 weekly could reduce musculoskeletal symptoms and fatigue in women who have suboptimal vitamin D levels. Sixty women about to begin an adjuvant AI were enrolled. Baseline 25OHD levels were obtained, and women completed symptom questionnaires. They were then started on letrozole, along with standard dose calcium and vitamin D. Four weeks later, women with baseline 25OHD levels ≤ 40 ng/ml started additional vitamin D3 supplementation at 50,000 IU per week for 12 weeks. 25OHD levels were re-assessed at 4, 10, and 16 weeks; the questionnaires were repeated at weeks 4 and 16. At baseline, 63% of women exhibited vitamin D deficiency (< 20 ng/ml) or insufficiency (20-31 ng/ml). 25OHD levels > 40 ng/ml were achieved in all 42 subjects who received 12 weeks of supplementation with 50,000 IU vitamin D3 weekly, with no adverse effects. After 16 weeks of letrozole, more women with 25OHD levels > 66 ng/ml (median level) reported no disability from joint pain than did women with levels < 66 ng/ml (52 vs. 19%; $P = 0.026$). Vitamin D deficiency and insufficiency are prevalent in post-menopausal women initiating adjuvant AI. Vitamin D3 supplementation with 50,000 IU per week is safe, significantly increases 25OHD levels, and may reduce disability from AI-induced arthralgias.

Conclusion As approaches to breast cancer treatment become more complex, the importance of chemoprevention is increasingly evident. While *in vitro* studies have shown that estrogen receptor (ER)-positive breast cancer cell lines are directly growth-inhibited by 1,25(OH)2D3, ER-negative tumor invasion and angiogenesis are indirectly inhibited by 1,25(OH)2D3 [52,53]. However, 1,25(OH)2D3 may be more beneficial in the chemopreventative setting; it is thought to regulate differentiation and maintain mammary gland homeostasis in the presence of mitogenic signals from the microenvironment [53]. If 1,25(OH)2D3 signaling is lacking or impaired, estrogen-stimulated epithelial proliferation may escape regulatory control. Our study adds to those supporting the relevance of vitamin D3 as a chemopreventative agent, and we report a novel mechanistic role for IL1 α in the 1,25(OH)2D3-mediated growth regulation of normal mammary epithelial cells.

Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study

Roy S, Sherman A, Monari-Sparks MJ, Schweiker O, Hunter K “Correction of Low Vitamin D Improves Fatigue: Effect of Correction of Low Vitamin D in Fatigue Study” *North American Journal of Medical Sciences* August 2014; 6(8): 396-402

Background Fatigue is a common presenting complaint of patients in the primary care offices. Low levels of vitamin D have been associated with fatigue in cancer patients. Normalization of vitamin D level improves their fatigue. Whether low vitamin D plays a role in fatigue in medically stable patients is not known.

Aims This prospective non-randomized therapeutic study observed the prevalence of low vitamin D in fatigue and the effect of normalization of vitamin D on fatigue.

Materials and Methods One hundred and seventy four adult patients, who presented in our primary care office with fatigue and stable chronic medical conditions, completed fatigue assessment questionnaires. Patients with low vitamin D levels received ergocalciferol therapy for 5 weeks. Scores of pre- and post-treatment fatigue assessment questionnaires were compared.

Results Prevalence of low vitamin D was 77.2% in patients who presented with fatigue. After normalization of vitamin D levels fatigue symptom scores improved significantly ($P < 0.001$) in all five subscale categories of fatigue assessment questionnaires.

Conclusion The prevalence of low vitamin D is high in patients who present with fatigue and stable chronic medical conditions, if any. Normalization of vitamin D levels with ergocalciferol therapy significantly improves the severity of their fatigue symptoms.