West Middlesex University Hospital

DISCLAIMER: Results of database and or Internet searches are subject to the limitations of both the database(s) searched, and by your search request. It is the responsibility of the requestor to determine the accuracy, validity and interpretation of the results.

Date of Search: 08 Nov 2017
Sources Searched: Medline, Embase.

Multiple Sclerosis and High-Dose Vitamin D

See full search strategy

Evidence Summary:

High-Dose Vitamin D Supplementation:

- Low vitamin D status has been associated with multiple sclerosis (MS) prevalence and risk, but the therapeutic potential of vitamin D supplementation had not been fully established.

Based on current evidence high-dose vitamin D supplementation does not appear to:

- Improve clinical outcomes or number of lesions in patients with multiple sclerosis (MS) (Burton, JM et al, 2010)
- Improve imaging findings and may increase relapse rate in patients with relapsing-remitting multiple sclerosis (Steins, MS, 2011)
- Affect disability in patients with MS (Mosayebi G, 2011)
- A randomised pilot study comparing low vs. high dose vitamin D supplementation in 40 patients with MS (Sotirchos E.S , 2016) reported an altering of the immunologic profile for those receiving high-dose. However, it failed to demonstrate a difference in terms of relapse rates.
- The ongoing VIDAMS trial is investigating whether high-dose vitamin D supplementation can reduce the risk of MS activity and will information about the safety and efficacy of vitamin D therapy in MS.

Vitamin D Toxicity:

- The main consequence of vitamin D intoxication is hypercalcemia. Symptoms and signs of excessive vitamin D intake can include:

- **early findings**
  - weakness
  - headache
  - somnolence
  - nausea
  - dry mouth, metallic taste
  - constipation
  - muscle or bone pain

- **late findings**
  - anorexia, weight loss, arrested growth
  - hyperthermia
  - polydipsia, polyuria, nocturia, dehydration
  - calcific conjunctivitis, photophobia
  - rhinorrhea
  - pruritus
  - hypertension, cardiac arrhythmias
  - sensory disturbances
  - elevated blood urea nitrogen (BUN), albuminuria, nephrocalcinosis, urinary tract infections
  - elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol
  - pancreatitis
  - ectopic calcification
  - apathy, decreased libido

- Few studies have been designed to specifically evaluate the safety of vitamin D intake therefore there is no general agreement about the intake levels at which vitamin D may cause harm**.**

- The Institute of Medicine have developed a reference range: The Tolerable Upper Intake Level (UL) for vitamin D **(**2011) It's intention is to specify the level above which the risk for harm begins to increase, and is defined as the highest average daily intake is likely to pose no risk of adverse health effects for nearly all persons in the general population.

- Institute of Medicine 2010 tolerable upper intake levels (UL) for specific life stage groups
  - age 0-6 months - 1,000 units/day (25 mcg)
  - age 6-12 months - 1,500 units/day (37.5 mcg)
  - age 1-3 years - 2,500 units/day (62.5 mcg)
  - age 4-8 years - 3,000 units/day (75 mcg)
  - age > 9 years - 4,000 units/day (100 mcg)
  - pregnancy and lactation age 14-50 years - 4,000 units/day (100 mcg)

- Available data does not indicate a basis for deriving a tolerable upper level for pregnant and lactating women or for adolescents that is different from those for their non-pregnant and non-lactating counterparts.

References:

IOM (Institute of Medicine). 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press.

DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 114491, Vitamin D intake and supplementation; [updated 2017 Feb 19, cited **09/11/2017**]; [about 41 screens]. Available from: http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=11

1. Effects of vitamin D3 in clinically isolated syndrome and healthy control participants: A double-blind randomised controlled trial.

Author(s): O'Connell, Karen; Sulaimani, Jamal; Basdeo, Sharee A; Kinsella, Katie; Jordan, Sinead; Kenny, Orla; Kelly, Siobhan B; Murphy, David; Heffernan, Eric; Killeen, Ronan P; Mulready, Keith; MacMahon, Marguerite; Brady, Jennifer J; McKenna, Carmel; Muldowney, Ciaran; Cassidy, Lorraine; Walsh, Cathal; O'Rourke, Killian; Tubridy, Niall; McGuigan, Chris; Fletcher, Jean M; Hutchinson, Michael

Source: Multiple sclerosis journal - experimental, translational and clinical; 2017; vol. 3 (no. 3); p. 2055217317727296

Publication Date: 2017

Publication Type(s): Journal Article

PubMedID: 28975037

Available at Multiple Sclerosis Journal – Experimental, Translational and Clinical - from Europe PubMed Central - Open Access

Abstract:BACKGROUNDLowserum vitamin D levels are associated with susceptibility to, and severity of, multiple sclerosis. High dose vitamin D has been proposed as a potential immunomodulator in multiple sclerosis.OBJECTIVESWe performed a single centre, investigator-led, exploratory, double-blind, randomised, placebo controlled, trial of vitamin D3 in clinically isolated syndrome and healthy control participants to assess its immunological effects. Secondary end-points included clinical and magnetic resonance imaging outcomes and safety.METHODSClinically isolated syndrome patients and healthy control participants were randomised to: placebo, 5000 IU or 10,000 IU vitamin D3/day (Vigantol oil). Study duration was 24 weeks.RESULTSThe trial did not meet its primary end point, with no difference in the frequency of pro-inflammatory CD4+ T cells (interleukin (IL)-17+/interferon (IFN)-γ+) seen. A higher level of disease freedom (67% versus 50%) was seen in those with serum 1,25 (OH) vitamin D levels>100 nmol/l but this did not reach significance. High dose vitamin D3 was well tolerated with no safety signal.CONCLUSIONSHigh dose vitamin D3 over 24 weeks was well tolerated but without immunological, magnetic resonance imaging or clinical evidence of benefit. The hypothesised therapeutic effects in clinically isolated syndrome or multiple sclerosis patients may require longer periods of administration or may only be seen in patients treated with vitamin D3 as an adjunct to established disease modifying therapies.

Database: Medline

2. Exploring the effect of vitamin D3 supplementation on the anti-EBV antibody response in relapsing-remitting multiple sclerosis.

Author(s): Rolf, Linda; Muris, Anne-Hilde; Mathias, Amandine; Du Pasquier, Renaud; Koneczny, Inga; Disanto, Giulio; Kuhle, Jens; Ramagopalan, Sreeram; Damoiseaux, Jan; Smolders, Joost; Hupperts, Raymond

Source: Multiple sclerosis (Houndmills, Basingstoke, England); Jul 2017 ; p. 1352458517722646

Publication Date: Jul 2017

Publication Type(s): Journal Article

PubMedID: 28731372

Abstract:BACKGROUNDEpstein-Barr virus (EBV) infection and vitamin D insufficiency are potentially interacting risk factors for multiple sclerosis (MS).OBJECTIVESTo investigate the effect of high-dose vitamin D3 supplements on antibody levels against the EBV nuclear antigen-1 (EBNA-1) in patients with relapsing-remitting multiple sclerosis (RRMS) and to explore any underlying mechanism affecting anti-EBNA-1 antibody levels.METHODSThis study utilized blood samples from a randomized controlled trial in RRMS patients receiving either vitamin D3 (14,000 IU/day; n = 30) or placebo (n = 23) over 48 weeks. Circulating levels of 25-hydroxyvitamin-D, and anti-EBNA-1, anti-EBV viral capsid antigen (VCA), and anti-cytomegalovirus (CMV) antibodies were measured. EBV load in leukocytes, EBV-specific cytotoxic T-cell responses, and anti-EBNA-1 antibody production in vitro were also explored.RESULTSThe median antibody levels against EBNA-1, but not VCA and CMV, significantly reduced in the vitamin D3 group (526 (368-1683) to 455 (380-1148) U/mL) compared to the placebo group (432 (351-1280) to 429 (297-1290) U/mL; p = 0.023). EBV load and cytotoxic T-cell responses were unaffected. Anti-EBNA-1 antibody levels remained below detection limits in B-cell cultures.CONCLUSIONHigh-dose vitamin D3 supplementation selectively reduces anti-EBNA-1 antibody levels in RRMS patients. Our exploratory studies do not implicate a promoted immune response against EBV as the underlying mechanism.

Database: Medline

3. Effect of high-dose vitamin D3 supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis.

Author(s): Røsjø, Egil; Lossius, Andreas; Abdelmagid, Nada; Lindstrøm, Jonas C; Kampman, Margitta T; Jørgensen, Lone; Sundström, Peter; Olsson, Tomas; Steffensen, Linn H; Torkildsen, Øivind; Holmøy, Trygve

Source: Multiple sclerosis (Houndmills, Basingstoke, England); Mar 2017; vol. 23 (no. 3); p. 395-402

Publication Date: Mar 2017

Publication Type(s): Journal Article

PubMedID: 27325604

Abstract:BACKGROUNDElevated antibody levels against Epstein-Barr virus (EBV) and a poor vitamin D status are environmental factors that may interact in relapsing-remitting multiple sclerosis (RRMS) aetiology.OBJECTIVESTo examine effects of high-dose oral vitamin D3 supplementation on antibody levels against EBV nuclear antigen 1 (EBNA1) in RRMS.METHODSSerum 25-hydroxyvitamin D3 (25(OH)D) and immunoglobulin G antibody levels against EBNA1 (whole protein and amino acid 385-420 fragment), EBV viral capsid antigen (VCA), cytomegalovirus (CMV) and varicella zoster virus (VZV) were measured in 68 RRMS patients enrolled in a 96-week randomised double-blinded placebo-controlled clinical trial of oral vitamin D3 supplementation (20,000 IU/week) (NCT00785473).RESULTSThe mean 25(OH)D level more than doubled in the vitamin D group and was significantly higher than in the placebo group at study conclusion (123.2 versus 61.8 nmol/L, $p < 0.001$). Compared to the placebo group, both anti-EBNA1 protein and fragment antibody levels decreased in the vitamin D group from baseline to week 48 ($p = 0.038$ and $p = 0.004$, respectively), but not from baseline to week 96. Vitamin D3 supplementation did not affect antibodies against VCA, CMV or VZV.CONCLUSIONThe results indicate that high-dose oral vitamin D3 supplementation can affect humoral immune responses against the latent EBV antigen EBNA1 in RRMS.

Database: Medline

4. Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab.

Author(s): Laursen, Julie Hejgaard; Søndergaard, Helle Bach; Sørensen, Per Soelberg; Sellebjerg, Finn; Oturai, Annette Bang

Source: Multiple sclerosis and related disorders; Nov 2016; vol. 10 ; p. 169-173

Publication Date: Nov 2016

Publication Type(s): Journal Article

PubMedID: 27919484

Abstract:BACKGROUNDVitamin D insufficiency is common among multiple sclerosis patients, and hypovitaminosis D has been associated with multiple sclerosis (MS) risk and disease activity.OBJECTIVETo investigate how recommendations on vitamin D3 supplements affect 25-hydroxyvitamin D (25(OH)D) levels in patients with relapsing-remitting MS (RRMS) and to examine the clinical effects associated with changes in 25(OH)D levels.METHODSIn this prospective cohort study, baseline blood samples were collected from 170 natalizumab-treated RRMS patients during winter 2009-2010 and were repeated the following winter. Vitamin D supplements were recommended according to standard clinical practice in our clinic to patients with serum 25(OH)D<50nmol/l at baseline. Information was obtained on annualized relapse-rate (ARR) the year prior to baseline and the following year.RESULTSWe found that recommending vitamin D supplements in patients with vitamin D insufficiency was associated with a significant increase in serum 25(OH)D concentrations (p=5.1×10-10), which was significantly related with decreases in ARR; for each nmol/l increase in Δ25(OH)D a -0.014 (95% CI -0.026 to -0.003) decrease in ΔARR was observed, p=0.02.CONCLUSIONCorrection of hypovitaminosis D in clinical practice by recommending oral D3 supplements resulted in increases in 25(OH)D levels in serum, which were associated with decreases in ARR in RRMS.

Database: Medline

5. Vitamin D Status Does Not Affect Disability Progression of Patients with Multiple Sclerosis over Three Year Follow-Up.

Author(s): Muris, Anne-Hilde; Smolders, Joost; Rolf, Linda; Klinkenberg, Lieke J J; van der Linden, Noreen; Meex, Steven; Damoiseaux, Jan; Hupperts, Raymond

Source: PloS one; 2016; vol. 11 (no. 6); p. e0156122

Publication Date: 2016

Publication Type(s): Clinical Trial Multicenter Study Journal Article

PubMedID: 27276080

Available at PLoS ONE - from Public Library of Science (PLoS)

Available at PLoS ONE - from Europe PubMed Central - Open Access

Abstract:BACKGROUND AND OBJECTIVEThe risk of developing multiple sclerosis (MS) as well as MS disease activity is associated with vitamin D (25(OH)D) status. The relationship between the main functional disability hallmark of MS, disability progression, and 25(OH)D status is less well established though, especially not in MS patients with progressive disease.METHODSThis retrospective follow-up study included 554 MS patients with a serum baseline 25(OH)D level and Expanded Disability Status Scale (EDSS) with a minimum follow-up of three years. Logistic regressions were performed to assess the effect of baseline 25(OH)D status on relapse rate. Repeated measures linear regression analyses were performed to assess the effect on disability and disability progression.RESULTSBaseline deseasonalized 25(OH)D status was associated with subsequent relapse risk (yes/no), but only in the younger MS patients (≤ 37.5 years; OR = 0.872, per 10 nmol/L 25(OH)D, p = 0.041). Baseline 25(OH)D status was not significantly associated with either disability or disability progression, irrespective of MS phenotype.CONCLUSIONWithin the physiological range, 25(OH)D status is just significantly associated with the occurrence of relapses in younger MS patients, but is not associated with disability or disability progression over three years follow-up. Whether high dose supplementation to supra physiological 25(OH)D levels prevents disability progression in MS should become clear from long term follow-up of supplementation studies.

Database: Medline

6. Efficacy of high-dose vitamin D3 supplementation in vitamin D deficient pregnant women with multiple sclerosis: Preliminary findings of a randomized-controlled trial.

Author(s): Etemadifar, Masoud; Janghorbani, Mohsen

Source: Iranian journal of neurology; Apr 2015; vol. 14 (no. 2); p. 67-73

Publication Date: Apr 2015

Publication Type(s): Journal Article

PubMedID: 26056550

Abstract:BACKGROUNDThe aim of this preliminary study was to assess the safety and efficacy of high-dose oral vitamin D3 supplementation during pregnancy in women with multiple sclerosis (MS) in Isfahan, Iran.METHODSIn a single center open-label randomized, controlled clinical Phase I/II pilot study, 15 pregnant women with confirmed MS with low serum 25-hydroxyvitamin D (25(OH)D) levels were randomly allocated to receive either 50,000 IU/week vitamin D3 or routine care from 12 to 16 weeks of gestation till delivery. The main outcome measures were mean change in serum 25(OH)D levels, expanded disability status scale (EDSS) score, and number of relapse events during pregnancy and within 6 months after delivery.RESULTSAverage serum 25(OH)D level at the end of trial in vitamin D3 supplemented group was higher than routine care group (33.7 ng/mL vs. 14.6 ng/ml, P 0.050), whereas in routine care group, the mean EDSS increased from 1.3 (0.4) to 1.7 (0.6) (P < 0.070). Women in vitamin D3 group appeared to have fewer relapse events during pregnancy and within 6 months after delivery. No significant adverse events occurred.CONCLUSIONAdding high dose vitamin D3 supplementation during pregnancy to routine care of women with MS had significant effect on the serum 25(OH)D levels, EDSS and number of relapse events during pregnancy and within 6 months after delivery.

Database: Medline

7. Short-term effect of high-dose vitamin D on the level of interleukin 10 in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial.

Author(s): Ashtari, Fereshteh; Toghianifar, Nafiseh; Zarkesh-Esfahani, Sayyed Hamid; Mansourian, Marjan

Source: Neuroimmunomodulation; 2015; vol. 22 (no. 6); p. 400-404

Publication Date: 2015

Publication Type(s): Randomized Controlled Trial Journal Article

PubMedID: 26401986

Abstract:BACKGROUNDMultiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Vitamin D has been related to the prevention of MS and to modulating its course. Recent studies have shown the safety of high-dose vitamin D in MS.OBJECTIVEThis study compared the effects of high-dose vitamin D on interleukin 10 (IL-10) levels in MS patients in a double-blind, randomized clinical trial.METHODSNinety-four patients with relapsing remitting MS (RRMS) were randomized into a treatment and a placebo group. Both groups received conventional MS treatment. The intervention group received 50,000 IU of vitamin D every 5 days for 3 months. IL-10 was measured at baseline and after 3 months.RESULTSSerum levels of IL-10 were (median ± IQR): 12.58 ± 11.97 and 10.97 ± 9.97 pg/ml in the intervention and placebo groups, respectively, at baseline ($p = 0.161$); after 3 months, these levels were 13.76 ± 18.95 and 11.31 ± 19.63 pg/ml, respectively ($p = 0.158$). The IL-10 level increased significantly after receiving high-dose vitamin D for 3 months ($\beta = 0.737$, $p = 0.015$ and $R2 = 0.91$).CONCLUSIONIL-10 levels increased significantly in RRMS patients after taking high-dose vitamin D3 for 3 months. High-dose vitamin D might be useful in promoting an anti-inflammatory state in RRMS patients.

Database: Medline

8. Multiple sclerosis and vitamin D during pregnancy and lactation.

Author(s): Jalkanen, A; Kauko, T; Turpeinen, U; Hämäläinen, E; Airas, L

Source: Acta neurologica Scandinavica; Jan 2015; vol. 131 (no. 1); p. 64-67

Publication Date: Jan 2015

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 25216350

Abstract:BACKGROUNDBoth pregnancy and high vitamin D concentration seem to generate a protective environment against multiple sclerosis (MS) relapses. Longitudinal case-control analysis of vitamin D concentrations during pregnancy and lactation of MS mothers is lacking.AIMS OF THE STUDYTo examine serum 25-hydroxyvitamin-D3 levels of MS patients during and after pregnancy and compare these to the levels measured in healthy controls.METHODSFifteen relapsing-remitting MS mothers underwent repeated testing for 25-hydroxyvitamin-D3 at 10-12, 26-28 and 35-37 gestational weeks and 1, 3 and 6 months post-partum. An identical series of samples was collected from six control mothers.RESULTSThe prevalence of vitamin D deficiency (<50 nmol/l) during pregnancy was high (73%) among MS patients. Vitamin D levels were significantly higher during pregnancy when compared to early post-partum values among MS patients. At the end of the follow-up period, the vitamin D levels returned to levels observed in early pregnancy. In healthy controls, the alterations during and after pregnancy were similar in nature, but the vitamin D concentrations were higher at all time points when compared to MS patients (P = 0.037).CONCLUSIONSVitamin D deficiency during the pregnancy and lactation seems to be common in mothers with MS and needs to be treated adequately.

Database: Medline

9. The case for vitamin D supplementation in multiple sclerosis.

Author(s): Ganesh, Aravind; Apel, Sabrina; Metz, Luanne; Patten, Scott

Source: Multiple sclerosis and related disorders; Oct 2013; vol. 2 (no. 4); p. 281-306

Publication Date: Oct 2013

Publication Type(s): Journal Article Review

PubMedID: 25877840

Abstract:INTRODUCTIONGiven that vitamin D has a role in immunomodulation, and its levels appear to correlate with the development of Multiple Sclerosis (MS), it is conceivable that vitamin D may also influence disease activity in MS patients. In this regard, we conducted a systematic review investigating the evidence for: (1) the role of vitamin D in disease activity in MS, and (2) the therapeutic supplementation of vitamin D in MS.METHODSA comprehensive search of Medline, Embase, Pubmed, clinical trials registries, and conference proceedings, followed by screening and application of inclusion and exclusion criteria, yielded 57 studies for detailed appraisal. Following careful data extraction, studies addressing the role of vitamin D in disease activity were appraised on the basis of common epidemiological principles, while those involving vitamin D supplementation were assessed for potential bias using Cochrane guidelines. The overall evidence was interpreted in the context of the Bradford-Hill criteria of causation, and the number needed to treat (NNT) to prevent one patient from relapsing over a year was calculated for each supplementation study examining relapse rate.RESULTS/DISCUSSIONBoth cross-sectional and longitudinal studies have fairly consistently demonstrated a strong positive correlation between vitamin D deficiency and subsequent relapse and/or disability in patients with MS. As well, there appears to be a negative correlation between vitamin D levels and inflammatory markers in MS patients, suggesting that vitamin D modifies serum cytokines to a more anti-inflammatory profile. Therefore, vitamin D fulfills the Bradford-Hill criteria for strong and consistent association, biological plausibility, and coherence. However, the criteria of temporality, dose-response, and experimental evidence are yet to be adequately met, although there is preliminary evidence from longitudinal studies and randomized clinical trials (RCTs) of supplementation that vitamin D can attenuate the autoimmune response in patients, and potentially reduce relapse rates and burden of disease. Currently published data on relapse prevention with vitamin D indicates the possibility of small NNTs in the range of 1.36-25.00, but they arise from very heterogeneously designed studies.CONCLUSIONSUltimately, the current evidence does not permit inference of a causal relationship between vitamin D deficiency and disease activity in MS. Vitamin D supplementation appears to be a promising treatment worthy of further exploration, but owing to the paucity of RCTs with placebo or comparator arms, the evidence is not definitive and appropriate dosing remains uncertain.

Database: Medline

10. Vitamin D supplementation for patients with multiple sclerosis treated with interferon-beta: a randomized controlled trial assessing the effect on flu-like symptoms and immunomodulatory properties.

Author(s): Golan, Daniel; Halhal, Basheer; Glass-Marmor, Lea; Staun-Ram, Elsebeth; Rozenberg, Orit; Lavi, Idit; Dishon, Sara; Barak, Mira; Ish-Shalom, Sophia; Miller, Ariel

Source: BMC neurology; Jun 2013; vol. 13 ; p. 60

Publication Date: Jun 2013

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article

PubMedID: 23767916

Abstract:BACKGROUNDFlu-like symptoms (FLS) are common side effects of interferon beta (IFN-β) treatment in patients with Multiple Sclerosis (PwMS) and are associated with post-injection cytokine surge. We hypothesized that vitamin D3 supplementation would ameliorate FLS by decreasing related serum cytokines' levels.METHODSIn a randomized, double blind study of 45 IFNβ-treated PwMS, 21 patients were assigned to 800 IU of vitamin D3 per day (low dose), while 24 patients received 4,370 IU per day (high dose) for one year. FLS were assessed monthly by telephonic interviews. Serum levels of 25-hydroxy-D (25-OH-D), calcium, PTH, IL-17, IL-10 and IFN-γ were measured periodically. EDSS, relapses, adverse events and quality of life (QoL) were documented.RESULTS25-OH-D levels increased to a significantly higher levels and PTH levels decreased in the high dose group. There was no significant change in FLS. IL-17 levels were significantly increased in the low dose group, while patients receiving high dose vitamin D had a heterogeneous IL-17 response. No significant differences in relapse rate, EDSS, QoL, serum IL-10 and IFNγ were found. Hypercalcemia or other potential major adverse events were not observed.CONCLUSIONVitamin D supplementation to IFN-β treated PwMS, at the doses used, seems safe and associated with dose-dependent changes in IL-17 serum levels, while not affecting IFN-β related FLS.TRIAL REGISTRATIONClinicalTrials.gov ID: NCT01005095.

Database: Medline

11. Vitamin D and multiple sclerosis: a critical review and recommendations on treatment.

Author(s): Faridar, Alireza; Eskandari, Ghazaleh; Sahraian, Mohammad Ali; Minagar, Alireza; Azimi, Amirreza

Source: Acta neurologica Belgica; Dec 2012; vol. 112 (no. 4); p. 327-333

Publication Date: Dec 2012

Publication Type(s): Journal Article Review

PubMedID: 22767049

Available at Acta Neurologica Belgica - from SpringerLink

Available at Acta Neurologica Belgica - from Free Medical Journals . com

Abstract: Multiple sclerosis (MS) is an immune-mediated and degenerative disease of nervous system, which affects mostly young adults. Vitamin D deficiency is a well-known environmental risk factor for MS and is considerable in terms of immediate clinical implications. In addition to its classical action on regulation of bone homeostasis, vitamin D may have a potent impact on cytokine profiles and neuro-inflammation. Given the immunomodulatory effects of vitamin D and its high rate of deficiency in MS patients, prescribing vitamin D is a remarkable issue in MS. The results from several experimental and clinical studies indicate that vitamin D supplementation may ameliorate the inflammation during the relapse phase and attenuate disease progression. We present the experimental and clinical studies, which assessed the effects of vitamin D on the pathophysiology, prevalence and management of MS. The authors also discuss current recommendations on prescription of this vitamin to MS patients.

Database: Medline

12. Can vitamin D reduce inflammation in relapsing-remitting multiple sclerosis?

Author(s): Holmøy, Trygve; Torkildsen, Øivind

Source: Expert review of neurotherapeutics; 2016; vol. 16 (no. 3); p. 233-235

Publication Date: 2016

Publication Type(s): Editorial

PubMedID: 26796244

Database: Medline

13. Vitamin D supplementation and systemic inflammation in relapsing-remitting multiple sclerosis.

Author(s): Røsjø, Egil; Steffensen, Linn H; Jørgensen, Lone; Lindstrøm, Jonas C; Šaltytė Benth, Jūratė; Michelsen, Annika E; Aukrust, Pål; Ueland, Thor; Kampman, Margitta T; Torkildsen, Øivind; Holmøy, Trygve

Source: Journal of neurology; Dec 2015; vol. 262 (no. 12); p. 2713-2721

Publication Date: Dec 2015

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article

PubMedID: 26429571

Abstract: Observational studies have suggested that vitamin D may reduce inflammation in relapsing-remitting multiple sclerosis (RRMS), but this has not been clearly confirmed in randomized controlled trials. To further explore the possible anti-inflammatory effects of vitamin D in RRMS, we examined the effect of high-dose oral vitamin D3 on eleven markers of systemic inflammation in 68 RRMS patients enrolled in a double-blinded randomized placebo-controlled trial of vitamin D3 supplementation (20,000 IU/week) (NCT00785473). Serum inflammation markers and 25-hydroxyvitamin D (25(OH)D) were measured at baseline and week 96, and no restrictions were set on additional standard immunomodulatory treatment for RRMS. The mean 25(OH)D level rose from 56 ± 29 to 123 ± 34 nmol/L among patients receiving vitamin D3 supplementation, whereas only a minor increase from 57 ± 22 to 63 ± 24 nmol/L was seen in the placebo group. However, no significant differences appeared between the vitamin D group and the placebo group for any of the inflammation markers. Patients on immunomodulatory therapy had significantly higher levels of interleukin-1 receptor antagonist and chemokine (C-X-C motif) ligand 16 than patients without immunomodulatory treatment, but there were no clear synergistic effects between immunomodulatory therapy and vitamin D3 supplementation on any of the inflammation markers. The rise in 25(OH)D levels after vitamin D3 supplementation was unaffected by immunomodulatory treatment. We conclude that in this study of RRMS patients, high-dose oral vitamin D3 supplementation prominently increased serum 25(OH)D levels without affecting markers of systemic inflammation, while a more anti-inflammatory phenotype was found among patients on immunomodulatory treatment.

Database: Medline

14. The influence of vitamin D on postpartum relapse and quality of life in pregnant multiple sclerosis patients.

Author(s): Runia, T F; Neuteboom, R F; de Groot, C J M; de Rijke, Y B; Hintzen, R Q

Source: European journal of neurology; Mar 2015; vol. 22 (no. 3); p. 479-484

Publication Date: Mar 2015

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 25430875

Abstract:BACKGROUND AND PURPOSEIn relapsing-remitting MS patients, lower serum vitamin D concentrations are associated with higher relapse risk. In a number of conditions, low vitamin D has been associated with fatigue. Pregnant women are at particular risk for vitamin D insufficiency. Our objective was to investigate whether vitamin D status is associated with postpartum relapse and quality of life during pregnancy.METHODSForty-three pregnant relapsing-remitting MS patients and 21 pregnant controls were seen at regular times before, during and after pregnancy. At every clinical assessment visit, samples for 25-hydroxyvitamin D (25(OH)D) measurements and quality of life questionnaires were taken.RESULTSLower 25(OH)D concentrations were not associated with postpartum relapse risk. Pregnancy 25(OH)D levels of patients and controls were not significantly different. In controls, but not patients, higher 25(OH)D concentrations were correlated with better general health, social functioning and mental health, but not with vitality.CONCLUSIONLow vitamin D levels are not associated with postpartum relapse. In pregnant MS patients, vitamin D levels are similar to levels in healthy women and are not associated with quality of life. Therefore, with regard to quality of life and postpartum relapse, no arguments were found for advising pregnant MS patients to take more vitamin D supplements than healthy women.

Database: Medline

15. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis.

Author(s): Runia, Tessel F; Hop, Wim C J; de Rijke, Yolanda B; Buljevac, Dragan; Hintzen, Rogier Q

Source: Neurology; Jul 2012; vol. 79 (no. 3); p. 261-266

Publication Date: Jul 2012

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 22700811

Abstract:OBJECTIVEThere is increasing evidence that vitamin D can be protective against the development of multiple sclerosis (MS), but it may also be beneficial for the clinical course of the disease. Our objective was to prospectively investigate if 25-hydroxy-vitamin D (25-OH-D) levels are associated with exacerbation risk in MS in a study with frequent serum measurements.METHODSThis was a prospective longitudinal study in 73 patients with relapsing-remitting MS. Blood samples for 25-OH-D measurements were taken every 8 weeks. Associations between 25-OH-D levels and exacerbation rates were assessed using Poisson regression (generalized estimating equations) with the individual serum levels as time-dependent variable.RESULTSDuring follow-up (mean 1.7 years), 58 patients experienced a total of 139 exacerbations. Monthly moving averages of 25-OH-D levels were categorized into low (100 nmol/L) levels. Exacerbation risk decreased significantly with higher serum vitamin D levels: respective relative exacerbation rates for the medium and high-level category as compared to the low-level category were 0.7 and 0.5 (p value for trend: p = 0.007). The association between 25-OH-D concentrations and exacerbation rate was log linear without a threshold. With each doubling of the serum 25-OH-D concentration the exacerbation rate decreased by 27% (95% confidence interval 8%-42%, p = 0.008).CONCLUSIONSOur finding that higher vitamin D levels are associated with decreased exacerbation risk in relapsing-remitting MS suggests a beneficial effect of vitamin D on disease course in MS. However, the possibility of reverse causality cannot be ruled out completely. Randomized intervention studies are therefore needed to investigate the effect of vitamin D supplementation in MS.

Database: Medline

16. Preventive effect of vitamin D3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial.

Author(s): Derakhshandi, Hajar; Etemadifar, Masoud; Feizi, Awat; Abtahi, Seyed-Hossein; Minagar, Alireza; Abtahi, Mohammad-Ali; Abtahi, Zahra-Alsadat; Dehghani, Alireza; Sajjadi, Sepideh; Tabrizi, Nasim

Source: Acta neurologica Belgica; Sep 2013; vol. 113 (no. 3); p. 257-263

Publication Date: Sep 2013

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article

PubMedID: 23250818

Available at Acta Neurologica Belgica - from SpringerLink

Available at Acta Neurologica Belgica - from Free Medical Journals . com

Abstract: Multiple sclerosis (MS) presents with optic neuritis (ON) in 20 % of cases and 50 % of ON patients develop MS within 15 years. In this study, we evaluated the preventive effects of vitamin D3 administration on the conversion of ON to MS (primary outcome) and on the MRI lesions (secondary outcome) of ON patients with low serum 25 (OH) D levels. Thirty ON patients (15 in each of 2 groups, aged 20-40 years) with serum 25 (OH) D levels of less than 30 ng/ml were enrolled in a double blind, randomized, parallel-group trial. The treatment group (cases) received 50,000 IU of vitamin D3 weekly for 12 months and the control group (controls) received a placebo weekly for 12 months. Finally, the subsequent relapse rate and changes in MRI plaques were compared between the two

groups. Risk reduction was 68.4 % for the primary outcome in the treatment group (relative risk = 0.316, p = 0.007). After 12 months, patients in the treatment group had a significantly lower incidence rate of cortical, juxtacortical, corpus callosal, new T2, new gadolinium-enhancing lesions and black holes. The mean number of total plaques showed a marginally significant decrease in the group receiving vitamin D3 supplementation as compared with the placebo group (p = 0.092). Administration of vitamin D3 supplements to ON patients with low serum vitamin 25 (OH) D levels may delay the onset of a second clinical attack and the subsequent conversion to MS.

Database: Medline

17. Vitamin D and pregnancy in multiple sclerosis patients

Author(s): Runia T.F.; Neuteboom R.F.; De Rijke Y.B.; Hintzen R.Q.

Source: Multiple Sclerosis; Oct 2013; vol. 19 (no. 11); p. 398-399

Publication Date: Oct 2013

Publication Type(s): Conference Abstract

Available at Multiple Sclerosis (Houndmills, Basingstoke, England) - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Background: Vitamin D is an environmental factor thought to be involved in the development and disease course of multiple sclerosis (MS). In relapsing-remitting MS patients, lower serum vitamin D concentrations are associated with a higher relapse risk. Also, in a number of conditions, low vitamin D has been associated with fatigue. Pregnant women are known to be at particular risk for vitamin D insufficiency. Therefore, our objectives were to investigate whether vitamin D status is associated with postpartum relapse, and with quality of life during pregnancy. Furthermore, we investigated if vitamin D levels differ between pregnant MS patients and healthy controls. Methods: In the Rotterdam Study on Pregnancy in MS (Neuteboom et al.,2010), we prospectively followed 43 pregnant relapsing-remitting MS patients and 21 pregnant healthy controls. All patients were seen before pregnancy, in the late first trimester, in the early third trimester, 4-8 weeks postpartum and 9 months postpartum. The controls had the same visits except for the pre-pregnancy visit. At every visit, blood samples for serum 25-OH-vitamin D measurements were taken. Differences between patients and controls and associations of vitamin D with postpartum relapse, breastfeeding and several quality-of-life items (SF36, MSIS and Guy's neurological disability scale) were calculated with alpha set at 0.01. Results: We found significantly higher vitamin D levels in the third trimester and lower levels after delivery (p 0.6). Conclusions: Although low vitamin D has been associated with MS relapse risk, and vitamin D levels are lower after delivery, we did not find an association with postpartum relapse. In pregnant MS patients, vitamin D levels are similar to levels in healthy women and are not associated with quality of life. Therefore, there is no need for MS patients to take more vitamin D supplements during pregnancy than healthy pregnant women.

Database: EMBASE

18. High dose Vitamin D intake and quality of life in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial

Author(s): Ashtari F.; Toghianifar N.; Zarkesh-Esfahani S.H.; Mansourian M.

Source: Neurological Research; Oct 2016; vol. 38 (no. 10); p. 888-892

Publication Date: Oct 2016

Publication Type(s): Article

PubMedID: 27597724

Abstract: Background: Low level of vitamin D is associated with a more severe course and low quality of life in relapsing-remitting multiple sclerosis (RRMS). Low dose vitamin D intake has improved quality of life in RRMS patients. Objective: This study explored the effect of high dose vitamin D intake on quality of life in RRMS patients in a double blind randomized clinical trial. Methods: 94 RRMS patients were randomized to two groups. One group received 50,000 IU vitamin D3 every five days for 3 months. The other group received placebo. Interferon-beta (IFN-beta) continued as the main treatment in both groups. Quality of life was assessed using MSQOL-54 Persian version at the beginning and at the end of the study. Results: After 3 months, the vitamin D group had a significant difference in mental health composite with placebo group, 62.41 +/- 13.99 vs. 60.99 +/- 17.99 (p-value = 0.041). Change in health was 75.74 +/- 25.73 and 70.59 +/- 26.45 in vitamin D and placebo group, respectively (p-value = 0.036). Conclusions: Mental QOL improved significantly after taking high dose vitamin D for 3 months in vitamin D group relative to placebo.

Database: EMBASE

19. Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: A randomized, double-blind, placebo-controlled clinical trial

Author(s): Toghianifar N.; Ashtari F.; Zarkesh-Esfahani S.H.; Mansourian M.

Source: Journal of Neuroimmunology; 2015; vol. 285 ; p. 125-128

Publication Date: 2015

Publication Type(s): Article

PubMedID: 26198928

Abstract: Background: Vitamin D has immunomodulatory effects in multiple sclerosis (MS). Vitamin D acts through various mechanisms such as secretion of cytokines. Interleukin-17 (IL-17) is a critical interleukin in inflammatory response in MS. Objective: This study assessed the effect of oral high dose vitamin D intake on IL-17 levels in MS patients in a double blind randomized clinical trial. Methods: 94 patients with a diagnosis of relapsing remitting multiple sclerosis (RRMS) were randomized to two groups. One group received 50,000 IU vitamin D3 every five days for 12. weeks. The other group was given placebo. Both groups received interferon-beta (IFN-beta) treatment. Serum levels of IL-17 were measured at the beginning of the study and after 12. weeks. Results: IL-17 serum levels were 56.75. +/-. 28.72. pg/ml and 30.31. +/-. 75.85. pg/ml in the intervention and placebo group at the beginning of the study, respectively (Median. +/-. IQR, p = 0.338). After 12. weeks, IL-17 levels were 58.93. +/-. 67.93. pg/ml and 46.13. +/-. 94.70. pg/ml in the intervention and placebo group, respectively (Median. +/-. IQR, p = 0.960). The multiple linear regression analysis indicated that the consumption of vitamin D3 was positively and significantly associated with the logarithm of IL-17 measures (beta = 1.719; p = 0.002 and R2 = 0.91), adjusted by EDSS scores. Conclusion: IL-17 levels showed significant change in RRMS patients after receiving high dose vitamin D3 for 12. weeks.

Database: EMBASE

20. High dose vitamin d on interleukin-10 in multiple sclerosis: A randomised double-blind, placebo-controlled clinical trial

Author(s): Ashtari F.; Nafisehtoghianifar; Zarkesh-Esfahani S.; Mansourian M.

Source: Multiple Sclerosis; Mar 2016; vol. 22 (no. 3); p. 423-424

Publication Date: Mar 2016

Publication Type(s): Conference Abstract

Abstract: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Vitamin D has been related to prevention of MS development and modulating its course. This study compared the effects of high dose vitamin D on interleukin- 10 levels on MS patients in a double blind randomized clinical trial. Methods: 94 patients with relapsing remitting multiple sclerosis (RRMS) were randomized to treatment vs placebo groups. Both groups received conventional MS treatments. The intervention group received 50,000 IU vitamin D every five days for 3 months. Demographic characteristics, EDSS score, disease duration, number of attacks and medications were recorded. Serum levels of Vitamin D and interleukin 10 (IL-10) were measured and compared at baseline and after 3 months. Results: serum levels of IL-10 were 41.66+/-85.16pg/ml and 21.08+/-35.62 in the intervention and placebo group at baseline, respectively (p=0.161). After 3 months, IL-10 levels were 71.07+/-16.65 and 32.23+/-38.49 in the intervention and placebo group, respectively (p=0.158). In linear regression model, interleukin levels showed significant difference in intervention and placebo groups (p=0.022, beta=0.032). Conclusions: IL-10 levels are reduced significantly in RRMS patients after taking high dose vitamin D for 3 months. High dose vitamin D might be useful in reducing inflammatory state in RRMS patients.

Database: EMBASE

21. Vitamin D status does not influence disability progression of multiple sclerosis patients over three years follow-up

Author(s): Muris A.-H.; Rolf L.; Hupperts R.; Smolders J.; Klinkenberg L.; Van Der Linden N.; Meex S.; Damoiseaux J.

Source: Multiple Sclerosis; Sep 2015; vol. 23 (no. 11); p. 164

Publication Date: Sep 2015

Publication Type(s): Conference Abstract

Abstract: Introduction: The risk of developing multiple sclerosis (MS) as well as MS disease activity is associated with vitamin D (25(OH) D) status. The relationship between the main functional disability hallmark of MS, disability progression, and 25(OH)D status is less well established though, especially not in progressive MS patients. Methods: This retrospective 3-year follow-up study included 554 MS patients with a baseline 25(OH)D serum level and Expanded Disability Status Scale (EDSS) with a minimum follow-up of three years. Logistic regressions were performed to assess the effect of baseline 25(OH)D on relapse rate. Repeated measures linear regression analyses were performed to assess the effect on disability and disability progression. Results: Baseline deseasonalized 25(OH)D status was associated with subsequent relapse risk (yes/no), but only in the younger MS patients (<= 37.5 years; OR=0.872, per 10nmol/L 25(OH)D, p=0.041). Baseline 25(OH)D was not significantly associated with either disability or disability progression, irrespective of MS phenotype. Discussion and conclusion: Within the physiological range, 25(OH)D status appears to affect the occurrence of relapses in younger MS patients, but does not significantly diminish disability or disability

progression. Whether high dose supplementation to supra physiological 25(OH)D levels prevents disability progression in MS should become clear from long term follow-up of supplementation studies.

Database: EMBASE

22. Dose-response and safety of high dose vitamin D supplementation: Subgroup analysis of an exploratory randomized double blind placebo controlled trial

Author(s): O'Connell K.; Kenny O.; Kinsella K.; Jordan S.; Tubridy N.; McGuigan C.; Hutchinson M.; Mulready K.; Brady J.; McKenna C.; Muldowney C.; Basdeo S.; Fletcher J.; Murphy D.; Heffernan E.; O'Laoide R.; Cassidy L.; O'Rourke K.

Source: Multiple Sclerosis; Sep 2014; vol. 20 (no. 1); p. 105

Publication Date: Sep 2014

Publication Type(s): Conference Abstract

Available at Multiple Sclerosis (Houndmills, Basingstoke, England) - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Background: Increasing evidence links vitamin D deficiency to both susceptibility to, and severity of, multiple sclerosis. We report the dose- response results in a sub-group analysis of a double blind randomized placebo-controlled clinical trial examining the immunological effects of two doses of vitamin D (5000 IU or 10,000 IU daily) compared to placebo over 24 weeks in both healthy control participants and patients presenting with CIS. Objectives: To assess the dose response, safety and tolerability of high dose vitamin D in healthy control participants over 24 weeks. Methods: Healthy control participants, aged 25 -40 years, with a 2:1 female to male ratio and no contraindications to high dose vitamin D supplementation were randomized to receive either, placebo, 5000 IU or 10000 IU of vitamin D for a 24 week period in a 1:1:1 fashion. All participants had renal function and serum calcium measured at 4 weekly intervals and vitamin D and PTH at baseline and weeks 4, 8,16, 24. Adverse events were recorded at each visit. Results: 38 healthy control participants {mean age 30 years (SD:4.5), 26 (68%) women} were recruited from November 2012 to June 2013. Mean baseline serum 25(OH)D was 52 (SD: 24.6) nmol/L and PTH 4.7 (1.7) pmol/L. Using a cut-off of serum 25(OH)D 72.5nmol/L. After seasonal adjustment of vitamin D levels, 76% participants remained deficient or insufficient at baseline. The greatest mean changes in serum 25(OH)D levels were seen between baseline and 16 weeks of dosing: placebo group: -4.2 (SD: 22.5) nmol/L, 5000 IU group: +83.2 (27.2) nmol/L, 10,000 IU group +154.8 (66.2). Serum levels plateaued after 16 weeks. No increases in serum calcium, urea and creatinine levels were observed despite a maximum vitamin D level of 402 nmol/L achieved. No serious adverse events were reported in the course of this study. Conclusions: This study adds to the growing evidence that: a) vitamin D deficiency remains highly prevalent in higher latitudes and b) high dose vitamin D supplementation is safe.

Database: EMBASE

23. Vitamin D supplementation in multiple sclerosis patients: Considering the safety issues

Author(s): Nabavi S.M.; Sabet Z.; Morsali D.; Aminzadeh M.

Source: Journal of Neurology; Jun 2012; vol. 259 (no. 1)

Publication Date: Jun 2012

Publication Type(s): Conference Abstract

Available at Deutsche Zeitschrift für Nervenheilkunde - from SpringerLink

Available at Deutsche Zeitschrift für Nervenheilkunde - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Introduction: Many reports postulate, hypovitaminosis D is a potential risk factors of multiple sclerosis (MS).Also, there are some reports in beneficial effects of vitamin D3 supplementation in patients with MS and, potentially a variety of autoimmune disease. Objective: The objective of this short report was to determine the safety of high dose (pharmacologic dose) of vit D3 in patients with MS. Design: In our clinic, we prescribed vit D3 50.000/week in a 6 months protocol for 44 definite Relapsing remitting MS with disease duration from 0-1 year, mean EDSS 1. we assessed the baseline and 6 month serum 25(OH) D levels and other markers of safety and intoxication(ca.p, alkaline phosphatase, PTH, urine 24 ca, Urine 24 Cr)in these group. Results: Mean (+/-SD) serum concentration 25(OH)D Increased from 7.3+/-15 ng/dl in baseline up to 45.6+/-34.9ng/dl in month 6. Serum calcium, creatinine concentration and the 24 h urinary calcium concentration remained in normal range of the reference values for any participants (9.2+/- 4.2 and 119+/- 64, respectively) without any laboratory clues of toxicity. Also any patient revealed the clinical signs of VitD toxicity. Conclusions: The data supports the tolerability of pharmacologic doses of vit D3(At least 50000 unit per week) and it emphasis that vitamin D intake beyond the physiological recommended dosage is safe in Multiple sclerosis patients.

Database: EMBASE

24. Effect of high-dose Vitamin D supplementation on antibody responses against Epstein-Barr virus in relapsing-remitting multiple sclerosis

Author(s): Rosjo E.; Lossius A.; Holmoy T.; Abdelmagid N.; Olsson T.; Lindstrom J.C.; Kampman M.T.; Jorgensen L.; Sundstrom P.; Steffensen L.H.; Torkildsen O.

Source: Multiple Sclerosis; Mar 2017; vol. 23 (no. 3); p. 395-402

Publication Date: Mar 2017

Publication Type(s): Article

Abstract: Background: Elevated antibody levels against Epstein-Barr virus (EBV) and a poor vitamin D status are environmental factors that may interact in relapsing-remitting multiple sclerosis (RRMS) aetiology. Objectives: To examine effects of high-dose oral vitamin D3 supplementation on antibody levels against EBV nuclear antigen 1 (EBNA1) in RRMS. Methods: Serum 25-hydroxyvitamin D3 (25(OH)D) and immunoglobulin G antibody levels against EBNA1 (whole protein and amino acid 385-420 fragment), EBV viral capsid antigen (VCA), cytomegalovirus (CMV) and varicella zoster virus (VZV) were measured in 68 RRMS patients enrolled in a 96-week randomised double-blinded placebo-controlled clinical trial of oral vitamin D3 supplementation (20,000 IU/week) (NCT00785473). Results: The mean 25(OH)D level more than doubled in the vitamin D group and was significantly higher than in the placebo group at study conclusion (123.2 versus 61.8 nmol/L, p 3 supplementation did not affect antibodies against VCA, CMV or VZV. Conclusion: The results indicate that high-dose oral vitamin D3 supplementation can affect humoral immune responses against the latent EBV antigen EBNA1 in RRMS.Copyright © SAGE Publications.

Database: EMBASE

25. Circulating vitamin D binding protein levels are not associated with relapses or with vitamin D status in multiple sclerosis

Author(s): Smolders J.; Peelen E.; Hupperts R.; Thewissen M.; Menheere P.; Damoiseaux J.

Source: Multiple Sclerosis Journal; Apr 2014; vol. 20 (no. 4); p. 433-437

Publication Date: Apr 2014

Publication Type(s): Article

PubMedID: 23959712

Available at Multiple Sclerosis (Houndmills, Basingstoke, England) - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Background: A low vitamin D status has been associated with multiple sclerosis (MS). Most circulating vitamin D metabolites are bound to vitamin D binding protein (DBP). Objectives: The purpose of this study was to explore whether there is an association between MS and DBP. Methods: We compared DBP concentrations in blood samples of controls (n = 30) and subjects with relapsing-remitting MS (RRMS) during remission (n = 29) and relapse (n = 15). Furthermore, we explored correlations of DBP with 25- hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D levels (1,25(OH)2D), and the effect of high-dose vitamin D3 supplementation on DBP levels in RRMS patients (n = 15). Results: DBP-concentration did not differ between the sub-groups measured, and there was no correlation between DBP and vitamin D metabolite concentration within the physiological range. Upon supplementation of high doses vitamin D3, DBP concentration remained unaltered. After supplementation, serum 1,25(OH)2D(R = 0.517, p = 0.049), but not 25(OH)D, correlated positively with DBP. Conclusions: We found no association between DBP, MS, and vitamin D status within the physiological range. After high - dose vitamin D supplementation, DBP concentrations may be relevant for vitamin D metabolism. © The Author(s) 2013.

Database: EMBASE

26. Immune regulatory effects of high dose vitamin D₃ supplementation in a randomized controlled trial in relapsing remitting multiple sclerosis patients receiving IFNbeta; the SOLARIUM study

Author(s): Muris A.-H.; Rolf L.; Hupperts R.; Smolders J.; Thewissen M.; Damoiseaux J.

Source: Journal of Neuroimmunology; Nov 2016; vol. 300 ; p. 47-56

Publication Date: Nov 2016

Publication Type(s): Article

PubMedID: 27806875

Abstract: Multiple sclerosis (MS) is characterized by a disturbed immune homeostasis and low serum vitamin D levels are associated with an increased disease activity. While vitamin D has been hypothesized to promote the maintenance of immune homeostasis, vitamin D supplementation could be of benefit to patients with MS. The SOLAR study investigated the effects of high dose vitamin D3 supplementation on clinical outcomes in a randomized controlled trial. Here we present the immune regulatory effects, investigated in the SOLARIUM sub-study. Thirty Dutch relapsing remitting (RR) MS patients treated with IFNbeta-1a received high dose vitamin D3 supplementation and 23 patients received placebo during a period of 48 weeks. Lymphocytes were phenotypically characterized by flow cytometry and in vitro cytokine secretion was assessed in the presence or absence of 1,25(OH)2D3 using Luminex technology. Changes in immune regulatory parameters were determined within subjects as well as between treatment groups. The proportion of cells in the

immune regulatory cell compartment (nTreg, iTreg and Breg) was not altered upon high dose vitamin D3 supplementation. Proportions of T helper subsets were not affected by vitamin D3, except for the proportion of IL4+ Th cells, which decreased in the placebo but not in the vitamin D3 group. T cell cytokine secretion increased, most pronounced for IL5 and latency activated protein of TGFbeta, in the placebo group but not in the vitamin D3 group. Lymphocytes remained equally reactive to in vitro 1,25(OH)2D3. In conclusion, high dose vitamin D3 supplementation did not result in a relative increase in lymphocytes with a regulatory phenotype. However, this study supports the hypothesis that vitamin D contributes to the maintenance of immune homeostasis by preventing further disturbance of the T cell compartment early in the disease course of MS.

Database: EMBASE

27. Safety and immunologic effects of high-vs low-dose cholecalciferol in multiple sclerosis

Author(s): Sotirchos E.S.; Bhargava P.; Baynes M.; Ntranos A.; Gocke A.; Mowry E.M.; Calabresi P.A.; Eckstein C.; Van Haren K.; Steinman L.

Source: Neurology; Jan 2016; vol. 86 (no. 4); p. 382-390

Publication Date: Jan 2016

Publication Type(s): Article

PubMedID: 26718578

Abstract: Objective: To study the safety profile and characterize the immunologic effects of high- vs low-dose cholecalciferol supplementation in patients with multiple sclerosis (MS). Methods: In this double-blind, single-center randomized pilot study, 40 patients with relapsing-remitting MS were randomized to receive 10,400 IU or 800 IU cholecalciferol daily for 6 months. Assessments were performed at baseline and 3 and 6 months. Results: Mean increase of 25-hydroxyvitamin D levels from baseline to final visit was larger in the high-dose group (34.9 ng/mL; 95% confidence interval [CI] 25.0-44.7 ng/mL) than in the low-dose group (6.9 ng/mL; 95% CI 1.0-13.7 ng/mL). Adverse events were minor and did not differ between the 2 groups. Two relapses occurred, one in each treatment arm. In the high-dose group, we found a reduction in the proportion of interleukin-17+ CD4+ T cells (p 0.016), CD161+ CD4+ T cells (p 0.03), and effector memory CD4+ T cells (p 0.021) with a concomitant increase in the proportion of central memory CD4+ T cells (p 0.018) and naive CD4+ T cells (p 0.04). These effects were not observed in the low-dose group. Conclusions: Cholecalciferol supplementation with 10,400 IU daily is safe and tolerable in patients with MS and exhibits in vivo pleiotropic immunomodulatory effects in MS, which include reduction of interleukin-17 production by CD4+ T cells and decreased proportion of effector memory CD4+ T cells with concomitant increase in central memory CD4+ T cells and naive CD4+ T cells. Classification of evidence: This study provides Class I evidence that cholecalciferol supplementation with 10,400 IU daily is safe and well-tolerated in patients with MS and exhibits in vivo pleiotropic immunomodulatory effects.

Database: EMBASE

28. The Vitamin D to Ameliorate Multiple Sclerosis (VIDAMS) trial: Study design for a multicenter, randomized, double-blind controlled trial of vitamin D in multiple sclerosis

Author(s): Bhargava P.; Cassard S.; Steele S.U.; Mowry E.M.; Azevedo C.; Pelletier D.; Sugar E.A.; Waubant E.

Source: Contemporary Clinical Trials; Nov 2014; vol. 39 (no. 2); p. 288-293

Publication Date: Nov 2014

Publication Type(s): Article

PubMedID: 25311447

Abstract: Background: Lower levels of vitamin D are associated with increased MS risk and with greater clinical and brain MRI activity in established relapsing MS. Objective: The VIDAMS trial (NCT01490502) is evaluating whether high-dose vitamin D supplementation reduces the risk of MS activity. Design/methods: Eligibility criteria include diagnosis of RRMS, age 18 to 50years, and Expanded Disability Status Scale 3 5000IU versus 600IU daily. Clinical visits occur every 12weeks for 96weeks. Results: Sixteen sites throughout the United States are participating in the trial. Complete enrollment is expected by late 2014, with follow-up through 2016. No interim analyses are planned. The primary outcome for the trial is the proportion of patients experiencing a relapse in each group. Other clinical, patient-reported, and MRI outcomes will be evaluated. Conclusions: The VIDAMS trial will provide critical information about the safety and efficacy of vitamin D therapy in RRMS, with implications for MS patients worldwide.

Database: EMBASE

29. The effect of vitamin D-related interventions on multiple sclerosis relapses: A meta-analysis

Author(s): James E.; Dobson R.; Kuhle J.; Baker D.; Giovannoni G.; Ramagopalan S.V.

Source: Multiple Sclerosis; Oct 2013; vol. 19 (no. 12); p. 1571-1579

Publication Date: Oct 2013

Publication Type(s): Review

PubMedID: 23698130

Available at Multiple Sclerosis (Houndmills, Basingstoke, England) - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Observational studies have shown an association between lower vitamin D levels and higher risk of relapse among people with multiple sclerosis (MS). This has raised interest in potential clinical benefits of vitamin D supplementation in the management of MS. The objectives were to examine the effect of vitamin D based interventions on the relative risk of relapse in MS. Any randomised controlled trial assessing the effect on the relative risk of relapse of any formulation or dose of vitamin D, in participants with MS, was eligible. The inverse variance with random effects model in Review Manager 5.1 was used to calculate the odds ratio of relapses in high dose vitamin D treated patients vs. controls. Five studies were published as of September 2012, yielding a total of 129 high-dose vitamin D-treated patients and 125 controls. We found no significant association between high-dose vitamin D treatment and risk of MS relapse (OR 0.98, 95% CI 0.45-2.16). In conclusion, although no significant association between high-dose vitamin D treatment and risk of MS relapses was found, the studies were limited by several methodological limitations. Further larger, more prolonged studies are merited.

Database: EMBASE

30. What is needed to keep persons with multiple sclerosis vitamin D-sufficient throughout the year?

Author(s): Steffensen L.H.; Kampman M.T.; Brustad M.

Source: Journal of Neurology; Jan 2013; vol. 260 (no. 1); p. 182-188

Publication Date: Jan 2013

Publication Type(s): Article

PubMedID: 22850935

Available at Deutsche Zeitschrift für Nervenheilkunde - from SpringerLink

Available at Deutsche Zeitschrift für Nervenheilkunde - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: Vitamin D sufficiency has been associated with lower risk of multiple sclerosis and may also have a favorable effect on the course of the disease. The aim of this work was to identify predictors of serum 25-hydroxy vitamin D (25[OH]D) levels in persons with multiple sclerosis (MS) and to assess the effect of high-dose vitamin D3 supplementation on vitamin D status. A 96-week randomized controlled trial was performed to assess the effect of supplementation with 20,000 IU of vitamin D3 weekly on bone mineral density in 68 patients. We collected data on vitamin D intake and UV-exposure and repeatedly measured serum 25(OH)D levels. Half of the participants had sufficient winter vitamin D levels at baseline (>=50 nmol/l). Vitamin D status was predicted by sun exposure during the last 3 months and by ingested vitamin D from diet and supplements. In the placebo group, the proportion of the participants with sufficient levels increased from 55 % in winter to 92 % during the summer. In the intervention group, all participants had winter 25(OH)D levels above 50 nmol/l at the end of the study. MS patients who have no sun exposure and low dietary vitamin D intake during the winter months should be recommended to take vitamin D supplements to achieve serum 25(OH)D levels of at least 50 nmol/l. © 2012 Springer-Verlag.

Database: EMBASE

31. A randomized trial of high-dose vitamin D2 in relapsing-remitting multiple sclerosis

Author(s): Stein M.S.; Baker J.E.; Mitchell P.J.; Harrison L.C.; Butzkueven H.; Kilpatrick T.J.; Liu Y.; Gray O.M.; Kolbe S.C.; Egan G.F.; Ditchfield M.R.

Source: Neurology; Oct 2011; vol. 77 (no. 17); p. 1611-1618

Publication Date: Oct 2011

Publication Type(s): Article

PubMedID: 22025459

Abstract: Objective: Higher latitude, lower ultraviolet exposure, and lower serum 25-hydroxyvitamin D (25OHD) correlate with higher multiple sclerosis (MS) prevalence, relapse rate, and mortality. We therefore evaluated the effects of high-dose vitamin D2 (D2) in MS. Methods: Adults with clinically active relapsing-remitting MS (RRMS) were randomized to 6 months' double-blind placebo-controlled high-dose vitamin D2, 6,000 IU capsules, dose adjusted empirically aiming for a serum 25OHD 130-175 nM. All received daily low-dose (1,000 IU) D2 to prevent deficiency. Brain MRIs were performed at baseline, 4, 5, and 6 months. Primary endpoints were the cumulative number of new gadolinium-enhancing lesions and change in the total volume of T2 lesions. Secondary endpoints were Expanded Disability Status Scale (EDSS) score and relapses. Results: Twenty-three people were randomized, of whom 19 were on established interferon or glatiramer acetate (Copaxone) treatment. Median25OHDrose from54to69nM(low-dose D2) vs59to120 nM (high-dose D2) (p = 0.002). No significant treatment differences were detected in the primary MRI endpoints. ExitEDSS,after adjustment for entryEDSS,washigher following high-doseD2than following low-

doseD2(p=0.05). There were4relapses with high-doseD2vs none with low-doseD2(p=0.04). Conclusion: We did not find a therapeutic advantage in RRMS for high-dose D2 over low-dose D2 supplementation. Classification of evidence: This study provides Class I evidence that high-dose vitamin D2 (targeting 25OHD 130-175 nM), compared to low-dose supplementation (1,000 IU/d), was not effective in reducing MRI lesions in patients with RRMS. Copyright © 2011 by AAN Enterprises, Inc.

Database: EMBASE

32. Safety and T cell modulating effects of high dose vitamin D₃ supplementation in multiple sclerosis

Author(s): Smolders J.; Peelen E.; Tervaert J.W.C.; Hupperts R.; Thewissen M.; Damoiseaux J.; Menheere P.

Source: PLoS ONE; 2010; vol. 5 (no. 12)

Publication Date: 2010

Publication Type(s): Article

PubMedID: 21179201

Available at PLoS ONE - from Public Library of Science (PLoS)

Available at PLoS ONE - from Europe PubMed Central - Open Access

Abstract: Background: A poor vitamin D status has been associated with a high disease activity of multiple sclerosis (MS). Recently, we described associations between vitamin D status and peripheral T cell characteristics in relapsing remitting MS (RRMS) patients. In the present study, we studied the effects of high dose vitamin D3 supplementation on safety and T cell related outcome measures. Methodology/Principal Findings: Fifteen RRMS patients were supplemented with 20 000 IU/d vitamin D3 for 12 weeks. Vitamin D and calcium metabolism were carefully monitored, and T cell characteristics were studied by flowcytometry. All patients finished the protocol without side-effects, hypercalcaemia, or hypercalciuria. The median vitamin D status increased from 50 nmol/L (31-175) at week 0 to 380 nmol/L (151-535) at week 12 (P+ Tregs remained unaffected. Although Treg suppressive function improved in several subjects, this effect was not significant in the total cohort (P = 0.143). An increased proportion of IL-10+ CD4+ T cells was found after supplementation (P = 0.021). Additionally, a decrease of the ratio between IFN-gamma+ and IL-4+ CD4+ T cells was observed (P = 0.035). Conclusion/Significance: Twelve week supplementation of high dose vitamin D3 in RRMS patients was well tolerated and did not induce decompensation of calcium metabolism. The skewing towards an anti-inflammatory cytokine profile supports the evidence on vitamin D as an immune-modulator, and may be used as outcome measure for upcoming randomized placebo-controlled trials. © 2010 Smolders et al.

Database: EMBASE

33. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis

Author(s): Burton J.M.; O'Connor P.; Kimball S.; Vieth R.; Dosch H.-M.; Cheung R.; D'Souza C.; Bar-Or A.; Gagne D.; Ursell M.

Source: Neurology; Jun 2010; vol. 74 (no. 23); p. 1852-1859

Publication Date: Jun 2010

Publication Type(s): Article

PubMedID: 20427749

Abstract: Objective: Low vitamin D status has been associated with multiple sclerosis (MS) prevalence and risk, but the therapeutic potential of vitamin D in established MS has not been explored. Our aim was to assess the tolerability of high-dose oral vitamin D and its impact on biochemical, immunologic, and clinical outcomes in patients with MS prospectively. Methods: An open-label randomized prospective controlled 52-week trial matched patients with MS for demographic and disease characteristics, with randomization to treatment or control groups. Treatment patients received escalating vitamin D doses up to 40,000 IU/day over 28 weeks to raise serum 25-hydroxyvitamin D [25(OH)D] rapidly and assess tolerability, followed by 10,000 IU/day (12 weeks), and further downtitrated to 0 IU/day. Calcium (1,200 mg/day) was given throughout the trial. Primary endpoints were mean change in serum calcium at each vitamin D dose and a comparison of serum calcium between groups. Secondary endpoints included 25(OH)D and other biochemical measures, immunologic biomarkers, relapse events, and Expanded Disability Status Scale (EDSS) score. RESULTS: Forty-nine patients (25 treatment, 24 control) were enrolled [mean age 40.5 years, EDSS 1.34, and 25(OH)D 78 nmol/L]. All calcium-related measures within and between groups were normal. Despite a mean peak 25(OH)D of 413nmol/L, no significant adverse events occurred. Although there may have been confounding variables in clinical outcomes, treatment group patients appeared to have fewer relapse events and a persistent reduction in T-cell proliferation compared to controls. Conclusions: High-dose vitamin D (~10,000 IU/day) in multiple sclerosis is safe, with evidence of immunomodulatory effects. Classification of evidence: This trial provides Class II evidence that high-dose vitamin D use for 52 weeks in patients with multiple sclerosis does not significantly increase serum calcium levels when compared to patients not on high-dose supplementation. The trial, however, lacked statistical precision and the design requirements to adequately assess changes in clinical disease measures (relapses and Expanded Disability Status Scale scores), providing only Class level IV evidence for these outcomes.

Database: EMBASE

34. Effect of vitamin D3 supplementation on relapses, disease progression, and measures of function in persons with multiple sclerosis: exploratory outcomes from a double-blind randomised controlled trial.

Author(s): Kampman, Margitta T; Steffensen, Linn H; Mellgren, Svein I; Jørgensen, Lone

Source: Multiple sclerosis (Houndmills, Basingstoke, England); Aug 2012; vol. 18 (no. 8); p. 1144-1151

Publication Date: Aug 2012

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article

PubMedID: 22354743

Abstract:BACKGROUNDHigh vitamin D levels may reduce the risk of relapses and disease progression in multiple sclerosis.METHODSThis 96-week randomised controlled trial was designed to assess the effect of vitamin D(3) supplementation on bone mineral density in persons with multiple sclerosis. Supplementation with 20,000 IU vitamin D(3) weekly raised median serum 25-hydroxy vitamin D (25[OH]D) to 121 nmol/L. The modified intention to treat analysis included 35 persons in the vitamin D(3) group and 33 in the placebo group. Participants were age 21 to 50 years and fully ambulatory (median Expanded Disability Status Scale (EDSS) 2.5). We studied the effect of supplementing vitamin D(3) on the exploratory outcomes annualised relapse rate (ARR), EDSS, multiple sclerosis functional composite (MSFC) components, grip strength, and fatigue.RESULTSAfter 96 weeks, there was no significant difference between groups in ARR (absolute difference 0.10, 95% CI -0.07 to 0.27; p = 0.25), EDSS (absolute difference -0.01, 95% CI -0.35 to 0.35; p = 0.97), MSFC components, grip strength, or fatigue.CONCLUSIONSupplementation with 20,000 IU vitamin D(3) weekly did not result in beneficial effects on the measured multiple sclerosis-related outcomes. This study was not powered to address clinical outcomes, but none of the results were suggestive of an effect in this unselected population of fully ambulatory persons with multiple sclerosis.

Database: Medline

35. Therapeutic effect of vitamin D3 in multiple sclerosis patients

Author(s): Mosayebi G.; Ghazavi A.; Jand Y.; Ghasami K.; Kokhaei P.

Source: Immunological Investigations; 2011; vol. 40 (no. 6); p. 627-639

Publication Date: 2011

Publication Type(s): Article

PubMedID: 21542721

Abstract: Multiple sclerosis (MS) is an inflammatory disease in which the myelin sheaths around the axons of the central nervous system are damaged. The damage leads to demyelination and scarring as well as a broad spectrum of signs and symptoms. The epidemiological data suggest a possible influence of vitamin D as an immunomodulatory agent on multiple sclerosis susceptibility as well as on clinical course of the disease. We investigated the effects of short-term vitamin D3 therapy on Iranian patients with MS. In a prospective randomized controlled trial study, 62 MS patients received 300,000 IU/month vitamin D3 or placebo as intramuscular injection for 6 months. Our results showed no significant difference between the treatment and the control groups in the expanded disability status scale scores and number of gadolinium-enhancing lesions during the 6-month treatment period. After 6 months, the levels of cell proliferation in the vitamin D treatment group were significantly lower than the control group. Also, the levels of transforming growth factor-beta and interleukin-10 in the vitamin D treatment group were significantly higher than the control group.

This result suggests that vitamin D therapy may help prevent the development of MS and could be a useful addition to the therapy. © 2011 Informa Healthcare USA, Inc.

Database: EMBASE

36. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline

Author(s): Holick M.F.; Binkley N.C.; Bischoff-Ferrari H.A.; Gordon C.M.; Hanley D.A.; Heaney R.P.; Murad M.H.; Weaver C.M.

Source: Journal of Clinical Endocrinology and Metabolism; Jul 2011; vol. 96 (no. 7); p. 1911-1930

Publication Date: Jul 2011

Publication Type(s): Review

PubMedID: 21646368

Abstract: Objective: The objective was to provide guidelines to clinicians for the evaluation, treatment, and prevention of vitamin D deficiency with an emphasis on the care of patients who are at risk for deficiency. Participants: The Task Force was composed of a Chair, six additional experts, and a methodologist. The Task Force received no corporate funding or remuneration. Consensus Process: Consensus was guided by systematic reviews of evidence and discussions during several conference calls and e-mail communications. The draft prepared by the Task Force was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and cosponsoring associations, and it was posted on The Endocrine Society website for member review. At each stage of review, the Task Force received written comments and incorporated needed changes. Conclusions: Considering that vitamin D deficiency is very commonin all age groups and that few foods contain vitamin D, the Task Force recommended supplementation at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. The Task Force also suggested the measurement of serum 25-hydroxyvitamin D level by a reliable assay as the initial diagnostic test in patients at risk for deficiency. Treatment with either vitamin D2 or vitamin D3 was recommended for deficient patients. At the present time, there is not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the noncalcemic benefit for cardiovascular protection. Copyright © 2011 by The Endocrine Society.

Database: EMBASE

37. Vitamin D: Deficiency, sufficiency and toxicity

Author(s): Alshahrani F.; Aljohani N.

Source: Nutrients; Sep 2013; vol. 5 (no. 9); p. 3605-3616

Publication Date: Sep 2013

Publication Type(s): Review

PubMedID: 24067388

Available at Nutrients - from Europe PubMed Central - Open Access

Available at Nutrients - from Free Medical Journals . com

Abstract: The plethora of vitamin D studies over the recent years highlight the pleomorphic effects of vitamin D outside its conventional role in calcium and bone homeostasis. Vitamin D deficiency, though common and known, still faces several challenges among the medical community in terms of proper diagnosis and correction. In this review, the different levels of vitamin D and its clinical implications are highlighted. Recommendations and consensuses for the appropriate dose and duration for each vitamin D status are also emphasized. © 2013 by the authors; licensee MDPI, Basel, Switzerland.

Database: EMBASE

38. Vitamin d is not as toxic as was once thought: A historical and an up-to-date perspective

Author(s): Holick M.F.

Source: Mayo Clinic Proceedings; May 2015; vol. 90 (no. 5); p. 561-564

Publication Date: May 2015

Publication Type(s): Review

PubMedID: 25939933

Available at Mayo Clinic Proceedings - from ProQuest (Hospital Premium Collection) - NHS Version

Database: EMBASE

39. Prevalence of hypercalcemia related to hypervitaminosis D in clinical practice.

Author(s): Pérez-Barrios, C; Hernández-Álvarez, E; Blanco-Navarro, I; Pérez-Sacristán, B; Granado-Lorencio, F

Source: Clinical nutrition (Edinburgh, Scotland); Dec 2016; vol. 35 (no. 6); p. 1354-1358

Publication Date: Dec 2016

Publication Type(s): Journal Article

PubMedID: 26995293

Abstract:BACKGROUND & AIMSRecent interest in vitamin D has led to a substantial increase in the use of vitamin D supplements. Vitamin D intoxication may be a concern as hypervitaminosis D can result in irreversible calcification of soft tissues so that it is important to detect early markers of vitamin D intoxication. Our aim was to assess the simultaneous presence of biochemical markers of vitamin D toxicity (i.e. hypervitaminosis D, hypercalcemia) and determine the concentrations of 25-OH-vitamin D at which the risk of hypercalcemia, and thus toxicity, might begin.METHODSWe evaluated retrospectively a 6-year period during which 25.567 samples were assessed for 25-OH-vitamin D status by UHPLC. Hypervitaminosis D was defined at serum 25-OH-vitamin D >160 nmol/L. Serum and urine calcium, phosphorus and iPTH were also recorded, if available. Medical history revision was performed in subjects displaying simultaneously hypervitaminosis D and

hypercalcemia.RESULTSOverall, hypervitaminosis D was found in 475 samples (1.86%) of which 51 displayed hypercalcemia (11.1%). A total of 382 samples were identified as the first record of hypervitaminosis D and 39 presented hypercalcemia (10.2%), most of them at 25-OH-vitamin D levels between 161 and 375 nmol/L. Only in 15 subjects, hypercalcemia could be directly attributed to vitamin D and serum 25-OH-vitamin D ranged between 164 and 1139 nmol/l. In no case, serum calcium achieved concentrations considered as critical values (>13 mg/dl).CONCLUSIONHypercalcemia due to vitamin D represented <4% of the total hypervitaminosis D detected and <0.1% of the tests performed. However, a highly variable response was observed and most subjects presented hypercalcemia at serum concentrations of 25-OH-vitamin D < 375 nmol/L.

Database: Medline

40. Maternal hypervitaminosis D reduces fetal bone mass and mineral acquisition and leads to neonatal lethality.

Author(s): Lieben, L; Stockmans, I; Moermans, K; Carmeliet, G

Source: Bone; Nov 2013; vol. 57 (no. 1); p. 123-131

Publication Date: Nov 2013

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 23895994

Abstract: Pregnancy challenges maternal calcium handling because sufficient calcium has to be transferred to the fetus to ensure fetal bone mass acquisition. 1,25(OH)2 vitamin D [1,25(OH)2D] is an important regulator of calcium homeostasis during adulthood, yet its role seems redundant for the maternal adaptations to pregnancy as well as during fetal development. However, not only deficiency but also excess of 1,25(OH)2D can be harmful and we therefore questioned whether high maternal 1,25(OH)2D levels may injure fetal development or neonatal outcome, as maternal-fetal transport of 1,25(OH)2D has been largely disputed. To this end, vitamin D receptor (VDR) null (Vdr(-/-)) females, displaying high 1,25(OH)2D levels, were mated with Vdr(+/-) males to obtain pregnancies with fetuses that are responsive (Vdr(+/-)) or resistant (Vdr(-/-)) to 1,25(OH)2D. Surprisingly, most of the Vdr(+/-) neonates died shortly after birth, whereas none of the Vdr(-/-). Mechanistically, we noticed that in Vdr(+/-) embryos, serum calcium levels were normal, but that skeletal calcium storage was reduced as evidenced by decreased mineralized bone mass as well as bone mineral content. More precisely, bone formation was decreased and the level of bone mineralization inhibitors was increased. This decreased fetal skeletal calcium storage may severely compromise calcium balance and survival at birth. In conclusion, these data indicate that high maternal 1,25(OH)2D levels are transferred across the placental barrier and adversely affect the total amount of calcium stored in fetal bones which is accompanied by neonatal death.

Database: Medline

41. Prolonged vitamin D intoxication: presentation, pathogenesis and progress.

Author(s): Bell, D A; Crooke, M J; Hay, N; Glendenning, P

Source: Internal medicine journal; Oct 2013; vol. 43 (no. 10); p. 1148-1150

Publication Date: Oct 2013

Publication Type(s): Case Reports Journal Article

PubMedID: 24134173

Abstract: Vitamin D toxicity from unactivated vitamin D (calciferol) therapy is currently a rare cause of hypercalcaemia. However, the frequency of this event may increase as high-dose unactivated vitamin D preparations become available. Prolonged vitamin D toxicity can cause reversible hypercalcaemia and partially reversible renal impairment. Parathyroid hormone may not be suppressed with unactivated vitamin D toxicity, especially if renal disease coexists.

Database: Medline

42. Safety issues of vitamin D supplementation.

Author(s): Zittermann, Armin; Prokop, Sylvana; Gummert, Jan F; Börgermann, Jochen

Source: Anti-cancer agents in medicinal chemistry; Jan 2013; vol. 13 (no. 1); p. 4-10

Publication Date: Jan 2013

Publication Type(s): Journal Article Review

PubMedID: 23094916

Abstract: Vitamin D deficiency is a re-emerging global health problem, which is primarily due to inadequate vitamin D synthesis in the skin. Supplement use is an effective measure to improve vitamin D status. However, some safety issues have to be considered, which are highlighted in this review article: The concept of vitamin D safety consists of two models, the safe tolerable upper intake level (UL) method, and the idea of adequate circulating 25-hydroxyvitamin D (25[OH]D) levels. Oral vitamin D intakes up to 250 μg/d have not been associated with harm. Hypercalcemia, the hallmark of vitamin D intoxication, may only occur if circulating 25(OH)D levels are consistently above 375-500 nmol/l. However, some observational studies indicate that already circulating 25(OH)D levels > 125 nmol/l are related to an increased morbidity and mortality risk. Therefore, the Institute of Medicine has set the UL for adults at 100 μg/d, and the adequate circulating 25(OH)D level at 50 to 125 nmol/l. In clinical practice, oral vitamin D dosing has to consider that the increment in circulating 25(OH)D depends on baseline 25(OH)D levels and the person's body weight. It is reasonable to assess 25(OH)D before and 3-6 months after initiation of oral vitamin D administration and to adjust the dose, if necessary. In future, two issues have to be clarified: First, would it be more appropriate to define instead of a fixed UL a variable UL, based on the individual's body weight? Second, what are the underlying mechanisms, if any, for potentially harmful vitamin D effects at circulating 25(OH)D levels between 125 and 375 nmol/l.

Database: Medline

43. Pharmacokinetics of vitamin D toxicity.

Author(s): Jones, Glenville

Source: The American journal of clinical nutrition; Aug 2008; vol. 88 (no. 2); p. 582S

Publication Date: Aug 2008

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article Review

PubMedID: 18689406

Abstract: Although researchers first identified the fat-soluble vitamin cholecalciferol almost a century ago and studies have now largely elucidated the transcriptional mechanism of action of its hormonal form, 1alpha,25-dihydroxyvitamin D(3) [1alpha,25(OH)(2)D(3)], we know surprisingly little about mechanisms of vitamin D toxicity. The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life approximately 2 mo). Its main transported metabolite, 25-hydroxyvitamin D(3) [25(OH)D(3)], shows a half-life of approximately 15 d and circulates at a concentration of 25-200 nmol/L, whereas the hormone 1alpha,25(OH)(2)D(3) has a half-life of approximately 15 h. Animal experiments involving vitamin D(3) intoxication have established that 25(OH)D(3) can reach concentrations up to 2.5 mumol/L, at which it is accompanied by hypercalcemia and other pathological sequelae resulting from a high Ca/PO(4) product. The rise in 25(OH)D(3) is accompanied by elevations of its precursor, vitamin D(3), as well as by rises in many of its dihydroxy- metabolites [24,25(OH)(2)D(3); 25,26(OH)(2)D(3); and 25(OH)D(3)-26,23-lactone] but not 1alpha,25(OH)(2)D(3). Early assumptions that 1alpha,25(OH)(2)D(3) might cause hypercalcemia in vitamin D toxicity have been replaced by the theories that 25(OH)D(3) at pharmacologic concentrations can overcome vitamin D receptor affinity disadvantages to directly stimulate transcription or that total vitamin D metabolite concentrations displace 1alpha,25(OH)(2)D from vitamin D binding, increasing its free concentration and thus increasing gene transcription. Occasional anecdotal reports from humans intoxicated with vitamin D appear to support the latter mechanism. Although current data support the viewpoint that the biomarker plasma 25(OH)D concentration must rise above 750 nmol/L to produce vitamin D toxicity, the more prudent upper limit of 250 nmol/L might be retained to ensure a wide safety margin.

Database: Medline

44. Assessing vitamin D status.

Author(s): Heaney, Robert P

Source: Current opinion in clinical nutrition and metabolic care; Sep 2011; vol. 14 (no. 5); p. 440-444

Publication Date: Sep 2011

Publication Type(s): Journal Article Review

PubMedID: 21832900

Abstract:PURPOSE OF REVIEWTo characterize methods evaluating and to summarize studies linking various serum 25-hydroxyvitamin D [25(OH)D] concentrations with health status.RECENT FINDINGSElucidation of the cell-biologic mechanism of vitamin D action, and numerous clinical trials and observational studies relating vitamin D status to health and disease.CONCLUSIONThe distinction between deficiency and insufficiency is not useful or necessary. Serum 25(OH)D values below 120 nmol/l (48 ng/ml) are associated with preventable disease and are therefore indicative of deficiency. The upper limit of the normal range can be set at 225 nmol/l (90 ng/ml), although toxicity is rare below 500 nmol/l (200 ng/ml).

Database: Medline

45. A brief history of vitamin D toxicity

Author(s): Moon J.C.

Source: Journal of Applied Nutrition; 1997; vol. 49 (no. 1); p. 18-31

Publication Date: 1997

Publication Type(s): Review

Abstract: The margin between the prophylactic dose of vitamin D and the toxic dose is very narrow. The problem of preventing rickets by adding vitamin D to food without producing toxic effects has not been solved. Significant evidence from animal experiments and humans poisoned by excess vitamin D suggest that current usage of vitamin D in North America contributes to atherosclerosis, renal calculi, and toxic metal accumulations. Addition of vitamin D to foods and supplements is not adequately controlled, resulting in large differences between label-stated and measured content of vitamin D in fortified foods. Vitamin D is very unstable both to light and to heat. Attempts to stabilize it have resulted in some stabilized forms that are hundreds of times more toxic than unstabilized forms, and call attention to the need for caution in use of these newer forms of vitamin D. The total amount of vitamin D currently being delivered to North Americans, estimated at more than 8 tons per year, is many times more than is necessary for rickets prophylaxis. Reclassification of vitamin D as a potent hormone is strongly recommended.

Database: EMBASE

46. Dietary reference intervals for Vitamin D

Author(s): Cashman K.D.

Source: Scandinavian Journal of Clinical and Laboratory Investigation; Apr 2012; vol. 72 ; p. 136-143

Publication Date: Apr 2012

Publication Type(s): Review

Abstract: Dietary reference intervals relate to the distribution of dietary requirement for a particular nutrient as defined by the distribution of physiological requirement for that nutrient. These have more commonly been called Dietary Reference Values (DRV) or Dietary Reference Intakes (DRI), amongst other names. The North American DRI for vitamin D are the most current dietary reference intervals and arguably arising from the most comprehensive evaluation and report on vitamin D nutrition to date. These are a family of nutrient reference values, including the Estimated Average Requirement (EAR), the Recommended Dietary Allowance (RDA), the Adequate Intake, and Tolerable Upper Intake Level. In particular, the EAR is used for planning and assessing diets of populations; it also serves as the basis for calculating the RDA, a value intended to meet the needs of nearly all people. The DRVs for vitamin D in the UK and the European Community have been in existence for almost two decades, and both are currently under review. The present paper briefly overviews these three sets of dietary reference intervals as case studies to highlight both the similarities as well as possible differences that may exist between reference intervals for vitamin D in different countries/regions. In addition, it highlights the scientific basis upon which these are based, which may explain some of the differences. Finally, it also overviews how the dietary reference intervals for vitamin D may be applied, and especially in terms of assessing the adequacy of vitamin D intake in populations. © 2012 Informa Healthcare.

Database: EMBASE

47. The science supporting the 2011 dietary reference intake for vitamin D: A risk assessment framework

Author(s): Brannon P.M.

Source: Birth Defects Research Part A - Clinical and Molecular Teratology; May 2012; vol. 94 (no. 5); p. 300

Publication Date: May 2012

Publication Type(s): Conference Abstract

Abstract: The Institute of Medicine Committee evaluated critically the totality of the evidence for over 25 health outcomes to select the outcome(s) to specify the Dietary Reference Intakes (DRI) for vitamin D. For pregnancy, maternal and fetal bone health, pre-eclampsia and pregnancy-induced hypertension (PIH), obstructed labor and Cesarean section (C-section), vaginosis, birth weight and small for gestational age (SGA) were evaluated. For pre-eclampsia, PIH, obstructed labor, and C-section, observational studies report conflicting relationships with the maternal biomarker of exposure, blood 25-hydroxyvitamin D (250HD) levels. For vaginosis, two observational studies report an inverse relationship with maternal 250HD levels. For birth weight and SGA, five RCT's report conflicting effects of maternal supplemental vitamin D. Ten observational studies report conflicting evidence on the relationship of birth weight or SGA to maternal 250HD levels. The evidence for maternal or fetal nonbone health is inconclusive, lacks causality and could not be used to specify the DRI. Bone health was selected as the outcome. The RCT evidence did not support a change in the requirement for vitamin D for this outcome. Observational studies consistently report no relationship of maternal 250HD levels with fetal/neonatal calcium homeostasis, but mixed results relative other aspects of bone health. An integrated bone health assessment across the life cycle linked blood 250HD levels of 40nmol/L (16ng/ml) with the Estimated Average Requirement (EAR) and 50nmol/L (20ng/ml) with the Recommended Dietary Allowance (RDA) to meet the needs, respectively, of 50% and 91.5% of generally healthy pregnant women. A simulated dose-response analysis of total dietary intake and achieved blood 250HD levels based on studies conducted during the winter at latitudes above 50degreeN or in Antarctica (conditions of minimal sun exposure) estimated 400IU/d for the EAR and 600IU/d for the RDA. The Tolerable Upper Intake Level (UL) was set at 4000IU/d based on frank toxicity adjusted for emerging evidence of a U-shaped risk curve for other adverse outcomes. Although no evidence for a U-shaped risk curve was available for pregnancy, such evidence has been reported subsequently for SGA. Research needs were also identified and will be discussed.

Database: EMBASE

48. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know.

Author(s): Ross, A Catharine; Manson, JoAnn E; Abrams, Steven A; Aloia, John F; Brannon, Patsy M; Clinton, Steven K; Durazo-Arvizu, Ramon A; Gallagher, J Christopher; Gallo, Richard L; Jones, Glenville; Kovacs, Christopher S; Mayne, Susan T; Rosen, Clifford J; Shapses, Sue A

Source: The Journal of clinical endocrinology and metabolism; Jan 2011; vol. 96 (no. 1); p. 53-58

Publication Date: Jan 2011

Publication Type(s): Journal Article

PubMedID: 21118827

Abstract: This article summarizes the new 2011 report on dietary requirements for calcium and vitamin D from the Institute of Medicine (IOM). An IOM Committee charged with determining the population needs for these nutrients in North America conducted a comprehensive review of the evidence for both skeletal and extraskeletal outcomes. The Committee concluded that available scientific evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship and providing a sound basis for determination of intake requirements. For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements. Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative. Based on bone health, Recommended Dietary Allowances (RDAs; covering requirements of ≥97.5% of the population) for calcium range from 700 to 1300 mg/d for life-stage groups at least 1 yr of age. For vitamin D, RDAs of 600 IU/d for ages 1-70 yr and 800 IU/d for ages 71 yr and older, corresponding to a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/liter), meet the requirements of at least 97.5% of the population. RDAs for vitamin D were derived based on conditions of minimal sun exposure due to wide variability in vitamin D synthesis from ultraviolet light and the risks of skin cancer. Higher values were not consistently associated with greater benefit, and for some outcomes U-shaped associations were observed, with risks at both low and high levels. The Committee concluded that the prevalence of vitamin D inadequacy in North America has been overestimated. Urgent research and clinical priorities were identified, including reassessment of laboratory ranges for 25-hydroxyvitamin D, to avoid problems of both undertreatment and overtreatment.

Database: Medline

Strategy 309763

#	Database	Search term	Results
1	Medline	("vitamin D").ti,ab	51048
2	Medline	exp "VITAMIN D"/	51477
3	Medline	(1 OR 2)	72295
4	Medline	("multiple sclerosis").ti,ab	62594
5	Medline	exp "MULTIPLE SCLEROSIS"/	50935
6	Medline	(4 OR 5)	70251
7	Medline	(3 AND 6)	1070
8	Medline	(relaps* OR flare*).ti,ab	166971
9	Medline	exp "SYMPTOM FLARE UP"/ OR exp RECURRENCE/	166145
10	Medline	(8 OR 9)	303560
11	Medline	(7 AND 10)	216
12	Medline	exp "MULTIPLE SCLEROSIS, RELAPSING-REMITTING"/	4826
13	Medline	(3 AND 12)	108
14	EMBASE	*"MULTIPLE SCLEROSIS"/	73712
15	EMBASE	*"VITAMIN D"/	23727
16	EMBASE	exp RELAPSE/	109903
17	EMBASE	(14 AND 15 AND 16)	58
18	EMBASE	*"RELAPSING REMITTING MULTIPLE SCLEROSIS"/	39537
19	EMBASE	(15 AND 18)	200

20	EMBASE	exp "DISEASE EXACERBATION"/	64710
21	EMBASE	(14 AND 15 AND 20)	3
22	EMBASE	(15 AND 18 AND 20)	1
23	EMBASE	("high dos*" ADJ2 "vitamin D").ti,ab	696
24	EMBASE	(14 AND 23)	27
25	EMBASE	exp "DRUG MEGADOSE"/	137257
26	EMBASE	(14 AND 15 AND 25)	40
27	Medline	("high* dos*" ADJ2 "vitamin D").ti,ab	547
28	Medline	(10 AND 27)	14
29	EMBASE	exp "VITAMIN SUPPLEMENTATION"/	27907
30	EMBASE	exp "VITAMIN D"/	123692
31	EMBASE	(18 AND 25 AND 29 AND 30)	14
32	EMBASE	(14 AND 16 AND 25 AND 29 AND 30)	12
33	EMBASE	("high* dos*").ti,ab	236770
34	EMBASE	(14 AND 29 AND 30 AND 33)	29
35	EMBASE	exp "DRUG TOXICITY"/	101979
36	EMBASE	(14 AND 29 AND 30 AND 35)	0
37	EMBASE	(14 AND 30 AND 35)	1
38	EMBASE	(18 AND 30 AND 35)	1
39	EMBASE	("vitamin d*" ADJ2 toxicit*).ti,ab	197

40	EMBASE	exp "DRUG DOSE ESCALATION"/	19936
41	EMBASE	(14 AND 30 AND 40)	25
42	EMBASE	exp "DRUG INTOXICATION"/ OR exp "DRUG OVERDOSE"/	38133
43	EMBASE	(14 AND 30 AND 42)	3
44	EMBASE	("vitamin d toxicity").ti	61
45	EMBASE	*"VITAMIN D INTOXICATION"/	197
46	EMBASE	45 [Publication types Review]	12
47	EMBASE	*"MAXIMUM PERMISSIBLE DOSE"/	298
48	EMBASE	(15 AND 47)	0
49	EMBASE	exp "MAXIMUM PERMISSIBLE DOSE"/	7093
50	EMBASE	(30 AND 49)	34
51	Medline	("hypervitaminosis d").ti,ab	307
52	Medline	("vitamin D" ADJ2 intoxication).ti,ab	276
53	Medline	("upper limit").ti,ab	12498
54	Medline	(2 AND 53)	100
55	EMBASE	exp "DRUG INTOXICATION"/	20038
56	EMBASE	(30 AND 55)	113
57	EMBASE	exp "VITAMIN D"/to	952
58	EMBASE	(49 AND 57)	0
59	EMBASE	*COLECALCIFEROL/	8534

60	EMBASE	(55 AND 59)	28
61	EMBASE	("upper intake level*").ti,ab	363
62	EMBASE	(30 AND 61)	89