PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1.0 CREDIT NUTRITIONAL MEDICINE, AND BY THE CNPBC; ONE CE HOUR.

Vitamin D Part IV

Hyperproliferative disorders.

INTRODUCTION

This article is the fourth part in series on the non-classical, extra-skeletal clinical applications of vitamin D, the "sunshine vitamin". This article focuses on the clinical uses of vitamin D in cancer and psoriasis, hyperproliferative disorders.

Encouraging results in preliminary studies have spurred the development of increasing numbers of noncalcemic vitamin D analogs. This article focuses predominantly on natural forms of vitamin D, notably cholecalciferol or vitamin D3 and its active metabolite, calcitriol.

THE DOSE-RESPONSE CURVE

To be activated, cholecalciferol or vitamin D3 is first converted to calcidiol [25(OH)D] in the liver and then calcitriol [1,25(OH)2D] in the kidneys and peripheral tissues. Calcidiol is the accepted serological marker of vitamin D status (Cannell 2006). Adequate levels are generally considered to be >75nmol/L (>30ng/ml) or higher, with higher levels recommended for cancer prevention, as shall be described below; (Hughes 2009). One nmol/L calcidiol is equivalent to 0.40ng/L (American units) (Hoogendijk 2008).

A commonly used "rule of thumb" is that for every 100 IU of vitamin D intake, serum 25(OH)D increases by 2.5nmol/L (1ng/ml) (Holick 2008). A recent randomized double blind placebo controlled study conducted in New York further investigated the concept of a dosing algorithm and found that the dose of vitamin D3 needed to attain adequate levels ranges between approximately 3,800 to 5,000 IU per day, depending on starting levels as well as idiosyncratic individual factors (Aloia 2008).

Those with a basal concentration between 50 and 80nmol/L were started on 2,000 IU (50mcg) daily, whereas those with a basal concentration <50nmol/L were started on 4,000 IU (100mcg). From there, doses were adjusted at eight-week intervals on the basis of serum 25(OH)D. The following algorithm was used:

- If 25(OH)D <80nmol/L, increase supplement by 50mcg/d (2,000 IU);
- If between 80 and 140nmol/L, do not change;
- If >140nmol/L, decrease by 50mcg/d (2,000 IU) unless current dose is 50mcg/d (2,000 IU) or less; in that case, decrease dose to 20mcg/d (800 IU).

Using this algorithm, all subjects achieved vitamin D adequacy (>75nmol/L) by 18 weeks. A median dose of 3,800 IU (95µg) per day was the estimated requirement to raise serum 25(OH)D3 levels >75nmol/L in those with 25(OH)D >55nmol/L at baseline, while 5,000 IU (125µg) was the requirement for those <55nmol/L.

ANTIPROLIFERATIVE ACTIVITY

Although the precise molecular mechanisms depend on the tissue type in question, calcitriol (the activated form of vitamin D) appears to possess overall antiproliferative, proapoptotic, and differentiation-inducing effects in tumor cells (Deeb 2007). Antiproliferative effects are mediated predominantly by induction of cell-cycle arrest. Please refer to Deeb et al (2007) for an extensive analysis of vitamin D's antitumor mechanisms.

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An RCT with 800 IU vitamin D3 and/or 2g calcium daily conducted in 92 patients with colorectal adenomas found that after six months, expression of p21 (a marker of differentiation) in the colorectal crypts was significantly increased in those receiving calcium or vitamin D3; the proportion of hTERT (marker of long-term proliferation) in the upper part of the crypts was also significantly reduced in those receiving both calcium and vitamin D (Fedirko 2010). The authors concluded that calcium and vitamin D may "promote colorectal epithelial cell differentiation and may 'normalize' the colorectal crypt proliferative zone in sporadic adenoma patients" (Fedirko 2010).

The antiproliferative activity of vitamin D may also explain its observed therapeutic effects on psoriasis

PSORIASIS

In brief, nine of fourteen controlled trials of topical calcitriol for psoriasis show significant positive results. In these studies, topical calcitriol was found to be equal or superior to topical pharmaceutical treatments for psoriasis, or significantly better than placebo/vehicle with respect to lesion size and/or severity. In addition, one study found significant improvement from calcitriol compared to baseline, but versus the comparator, calcipotriol, the comparator was significantly superior to the calcitriol (Bourke 1997). One study found significant improvements in histometric parameters of the psoriatic lesions (Uhoda 2003). Three studies found no significant effect when compared to placebo (Henderson 1989, van de Kerkhof 1989, Liao 2007). Dosage in most studies was 3mcg/g calcitriol cream topically two times daily. Calcitriol cream was comparable or superior to betamethasone, calcipotriol (vitamin D analog), and dithranol (Camarasa 2003, Hutchinson 2000, Lahfa 2003, Ortonne 2003, Perez 1996); and when used in conjunction with UVB radiation, calcitriol allowed for reduction of the radiation dose (Ring 2001). In addition to therapeutic efficacy, many studies reported better tolerability and a higher safety profile in favour of calcitriol.

One of three controlled trials, and one uncontrolled trial show positive results for vitamin D in psoriasis when given orally. Two trials showed no additional effect when given orally in conjunction with UVB therapy (Ezquerra 2007, Perez & Raab 1996, Prystowsky & Knobler 1996, Prystowsky & Muzio 1996).

CANCER

The majority of evidence supporting an anticancer role for vitamin D is epidemiological. A meta-analysis of observational evidence found that having ≥1,000 IU daily intake of vitamin D or ≥82nmol/L serum 25(OH)D was associated with 50% lower risk of colorectal cancer compared with <100 IU/d or <32.5nmol/L (Gorham 2005). A more recent meta analysis of prospective observational evidence by Yin found that risk of colorectal, colon, and rectal cancer was reduced by 43%, 22%, and 59% respectively with an increase of 25(OH)D of 50nmol/L: OR 0.57 (0.43-0.76), 0.78 (0.54–1.13) and 0.41 (0.11–1.49) (2009).

Garland reports that "breast cancer patients with serum 25(OH)D levels greater than 29ng/ml (72nmol/L) at diagnosis had a 42% lower 15-year death rate than those with less than 20ng/ml (50nmol/L) (hazard ratio 0.58, 95% CI 0.35–0.95)" (2009). Likewise, Zhou found a strong association between serum 25(OH)D and overall survival in patients with stage IB-IIB non-small cell lung cancer (NSCLC), adjusted HR 0.45 (95%CI 0.24-0.82) (2007).

Human trials of vitamin D for cancer have been conducted for prevention of breast and colorectal cancer (CRC) and treatment of prostate cancer. These are summarized in Table 1.

Nebraska Study

The most noteworthy trial conducted to date is that by Lappe et al (2007). This large randomized, double blind, placebo controlled trial of calcium and vitamin D supplementation in post-menopausal American women found a significant reduction in all-cancer risk at four years, relative risk 0.402 (95% CI 0.20-0.82; P=0.013) in the vitamin D + calcium group. This fell further to RR 0.232 (96%CI 0.09-0.60; P=0.005) when cancers found within the first year of follow up were excluded. The calcium-only group experienced only a non-significant trend to decreased cancer risk, RR 0.532 (95%CI 0.27-1.03; P=0.063). Doses used were 1,100 IU vitamin D and 1,400-1,500mg calcium per day for four years. There was a "predicted 35% reduced risk of cancer for every 25nmol/L (10ng/ml) increase in serum 25(OH)D"(Lappe 2007).

The dose used in this trial is significant insofar as it was effective in raising serum levels from 71nmol/L at baseline to well over 80nmol/L, with a mean of 96.0 +/- 12.4nmol/L at 12 months in the vitamin D group. This is in contrast to the Women's Health Initiative trial, which found no significant effects on cancer risk but used a dose of 400 IU/d (Chlebowski 2008).

AIPC Study of Calcitriol Enhancing Taxotere (ASCENT)

A second important cancer trial has been conducted by Beer et al in 250 patients with androgen independent prostate cancer (AIPC) (2007). This study administered 45mcg of DN-101, a high dose oral formulation of calcitriol, or placebo to patients one day before their scheduled dose of intravenous docetaxel (36mg/m2). PSA response rates, defined as a 50% reduction, were

Table 1. Controlled Trials for Prevention and Treatment of Cancer

Type	+/Total Trials	Dose	Outcomes	Reference
Breast	1/2	1,100 IU D3 + 1,400-1,500mg calcium x 4 yrs;	Prevention 1,100 IU D3 + calcium decreased relative risk of incident cancer (all types) to 0.402 (95% CI 0.20-0.82, P=0.013) compared to placebo, while there was no significant reduction in the calcium only group. With respect to breast cancer, there were 8 incident cases among 266 subjects in the placebo group, compared to 5 incident cases among 403 subjects in the D3 + calcium group during years 1-4 of the study.	Lappe 2007
		400 IU D3 + 1,000mg calcium x 7yr	Low dose vitamin D (400 IU/d x 7 yr) in the Women's Health Initiative study found no effect on incidence of invasive breast cancer or benign proliferative breast disease.	Chlebowski 2008, Rohan 2009
Colorectal	1/2	800 IU D3 with or without 2g calcium x 6mo	Prevention Surrogate endpoint RCT found that Vitamin D alone led to a 56% increase in Bax (an apoptosis promoter) in colorectal crypts (P=0.02), as well as modulation of p21 and hTERT, markers of proliferation and differentiation.	Fedirko 2010, Fedirko 2009
			A retrospective analysis of the Women's Health Initiative study found no effect of D3 on incidence of invasive colorectal cancer, but only a low dose of D3 was used (400 IU/d).	Wactawski-Wende 2006
Prostate	1/2	45mcg calcitriol/wk + docetaxel	Treatment D3 + docetaxel decreased risk of death 33% (HR 0.67, P=0.04) and increased median survival to an estimated 24.5 mo vs 16.4 mo in the placebo group.	Beer 2007
			One surrogate study found no significant effect on biomarkers.	Beer 2004a

seen in 63% of DN-101 patients and 52% of placebo (P=0.07). More notably, patients in the treatment group had significantly longer survival. Overall survival showed a "promising" improvement in the DN-101 group over the placebo group with an HR of 0.67(95%CI 0.45-0.97). Median survival was 16.4 months in the placebo group, but it had not yet been reached in the DN-101group at the time of publication, though it was estimated to be 24.5 months.

Addition of calcitriol to the docetaxel regimen resulted in an unexpected decrease in the incidence of serious adverse events in the DN-101 group compared with the placebo group: 27% vs. 41%, P=0.02 (Beer 2006). Serious adverse events due to thrombosis occurred in 1.6% of the treatment arm and 7.2% of the placebo arm, and this remained significant after adjustment for prior history of thrombosis and antithrombotic medication use (P=0.04).

Uncontrolled Trials

In addition, there have been several uncontrolled Phase II trials investigating use of calcitriol in combination with various chemotherapies in patients with prostate cancer. Please see Table 2 for trail outcomes.

RECOMMENDATIONS

Recently, a panel of 16 scientists and physicians issued a call to action urging an increase in the recommended intake of vitamin D to 2,000 IU per day in the absence of medical contraindications; this level is currently considered the upper limit by the National Academy of Sciences, Institute of Medicine, Food, and Nutrition Board (Garland 2009). In a concurrently published review, Garland et al stated:

"Raising the minimum year-around serum 25(OH)D level to 40 to 60ng/ml (100-150nmol/L) would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year, and three fourths of deaths from these diseases in the United States and Canada, based on observational studies combined with a randomized trial. Such intakes also are expected to reduce case-fatality rates of patients who have breast, colorectal, or prostate cancer by half" (Garland 2009).

Administration of vitamin D should be undertaken cautiously in certain cancers, including small cell lung cancer, due to risk of hypercalcemia. Refer to Part 1 of this four-part series of reviews.

CONCLUSION

Epidemiological evidence supports a chemopreventive effect for vitamin D, and this is supported by mechanistic studies demonstrating antiproliferative, proapoptotic, and differentiation-inducing activity. Topically this antiproliferative activity translates into potent antipsoriatic effects. With respect to cancer treatment, observational evidence also suggests superior outcomes in cancer patients with higher vitamin D levels. Although controlled human evidence around use of vitamin D for the treatment and prevention of cancer is still nascent, the results of two large trials support an important role for vitamin D in the field of oncology. According to current projections, optimal use and application of vitamin D could lead to dramatic decreases in disease burden.

Table 2. Uncontrolled Trials of Calcitriol in Prostate Cancer

Design	Outcome	Reference
25mcg DN-101 (calcitriol) weekly plus naproxen daily x 1 year AIPC patients with recurrent disease, N=21	Prolongation of PSA doubling time (PSADT) was achieved in 75% of patients. Treatment was well tolerated.	Srivinas 2009
180mcg DN-101 (calcitriol) + mitoxantrone x 1 dose q21 days; plus continuous prednisone. AIPC, N=19	5 of 19 patients (26%, 95%CI 9-51%) had a PSA response (decrease by 50%). Median time to PSA progression was 16 wk. Median survival was 16 months (6-26 mo). 47% of patients (21-73%) had an analgesic response. Although authors deemed the PSA results insignificant, the analgesic response was deemed "encouraging."	Chan 2008
0.5mcg calcitriol + dexamethasone daily; plus carboplatin weekly Hormone refractory prostate cancer, N=34	PSA response was seen in 13 of 34 patients (38.2%, 95%CI 22.2-56.4%). Median survival was 97.7 weeks (61-114). Although there were significant adverse events, likely due to the chemotherapy and corticosteroid treatment; the side effect profile was deemed "acceptable."	Flaig 2006
8, 10, and 12mcg calcitriol 3x/wk + dexamethasone AIPC with bone metastasis and rising PSA, N=43	8 patients had partial PSA responses (PSA decline of at least 50% lasting for at least 28 days). There was subjective clinical improvement in some patients. Toxicity was minimal.	Trump 2006
60mcg calcitriol x 1 dose, estramustine x 5 days, and docetaxel x 1 day; in cycles of 21 days N=24	6 of 11 evaluable chemonaive patients (55%) and one patient (9%) who had had prior docetaxel therapy met PSA response. The treatment protocol was "generally well tolerated." Asymptomatic grade 1-2 hypercalcemia was seen in 4 patients.	Tiffany 2005
0.5mcg/kg calcitriol + carboplatin, 1 x each q4wk. Metastatic AIPC, N=17	1 of 17 patients (6%, 95%CI 0-28%) had a PSA response. 4 patients (24%) had PSA reductions between 24-38%. However, 15 met criteria for an analgesic response.	Beer 2004b
0.5mcg/kg calcitriol + docetaxel; 1 dose each weekly for 6 of 8 weeks per cycle. AIPC, N=37	Treatment resulted in an "analgesic response" in 14 of 29 evaluable patients (48%, 95%CI 30-67%). This was despite a worsening in physical function, fatigue, appetite, and global health status. Median time to progression was 41 weeks (26-56).	Beer 2004c
0.5mcg/kg calcitriol + docetaxel each qwk for 6 of 8 wk in a cycle. Metastatic AIPC, N=37	30 of 37 patients (81%, 95%CI 68-94%) achieved a PSA response. 22 patients (59%, 43-75%) had a >75% reduction in PSA. Median survival was 19.5 months (95%CI 15.3 to uncalcuable). 1-yr survival was 89% (95%CI 74-95%). Toxicity was similar to that expected from docetaxel alone.	Beer 2003
2,000 IU/d vitD2 + 500mg calcium x 12 wk No chemotherapy Advanced hormone refractory PC, N=16	7 of the 16 patients (44%) had "decreased" baseline vitD (defined as <38nmol/L or 15.5ng/ml). With vitD treatment, 4 patients (25%) had improved pain scores, and 6 (37%) had improved muscle strength. There was no change in use of pain medication.	Van Veldhuizen 2000
Up to 2.5mcg calcitriol daily Early recurrent prostate cancer, N=7	There was a significant decrease in rate of PSA rise in 6 of 7 patients, compared to baseline; overall this was significant, P=0.02. Dose dependent hypercalciuria limited maximal doses to between 1.5-2.5mcg daily.	Gross 1998

References:
Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, Pollack S, Yeh JK. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration..Am J Clin Nutr. 2008 Jun;87(6):1952-8.

Beer TM, Myrthue A, Garzotto M, O'hara MF, Chin R, Lowe BA, Montalto MA, Corless CL, Henner WD. Randomized study of high-dose pulse calcitriol or placebo prior to radical prostatectomy. Cancer Epidemiol Biomarkers Prev. 2004(a) Dec;13(12):2225-32.

Beer TM, Garzotto M, Katovic NM. High-dose calcitriol and carboplatin in metastatic androgen-independent prostate cancer. Am J Clin Oncol. 2004(b) Oct;27(5):535-41.

Beer TM, Eilers KM, Garzotto M, Hsieh YC, Mori M. Quality of life and pain relief during treatment with calcitriol and docetaxel in symptomatic metastatic androgen-independent prostate carcinoma. Cancer. 2004(c) Feb 15;100(4):758-63.

Beer TM, Venner PM, Ryan CW, Petrylak DP, Chatta G, Dean Ruether J, Chi KN, Curd JG, DeLoughery TG. High dose calcitriol may reduce thrombosis in cancer patients. Br J Haematol. 2006 Nov;135(3):392-4.

Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta GS, Ruether JD, Redfern CH, Fehrenbacher L, Saleh MN, Waterhouse DM, Carducci MA, Vicario D, Dreicer R, Higano CS, Ahmann FR, Chi KN, Henner WD, Arroyo A, Clow FW; Ascent Investigators. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. J Clin Oncol. 2007 Feb 20;25(6):669-74.

Bourke JF, Iqbal SJ, Hutchinson PE. A randomized double-blind comparison of the effects on systemic calcium homeostasis of topical calcitriol (3mcg/g) and calcipotriol (50 mcg/g) in the treatment of chronic plaque psoriasis vulgaris. Acta Derm Venereol. 1997 May;77(3):228-30.

Camarasa JM, Ortonne JP, Dubertret L. Calcitriol shows greater persistence of treatment effect than betamethasone dipropionate in topical psoriasis therapy. J Dermatolog Treat. 2003 Jan;14(1):8-13.

Cannell, JJ. "Vitamin D3 Cholecalciferol Physiology" and Vitamin D3 Cholecalciferol Pharmacology." The Vitamin D Council. 2006. www.vitamindcouncil.org. Accessed 14 December 2009.

Chan JS, Beer TM, Quinn DI, Pinski JK, Garzotto M, Sokoloff M, Dehaze DR, Ryan CW.A phase II study of high-dose calcitriol combined with mitoxantrone and prednisone for androgen-independent prostate cancer. BJU Int. 2008 Dec;102(11):1601-6.

Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawsk-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA, Shikany JM, Vitolins M, Khandekar J, Hubbell FA; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst. 2008 Nov 19;100(22):1581-91.

Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007 Sep;7(9):684-700.

Ezquerra GM, Regaña MS, Millet PU. Combination of acitretin and oral calcitriol for treatment of plaque-type psoriasis. Acta Derm Venereol. 2007;87(5):449-50.

Fedirko V, Bostick RM, Long Q, Flanders WD, McCullough ML, Sidelnikov E, Daniel CR, Rutherford RE, Shaukat A. Effects of supplemental vitamin D and calcium on oxidative DNA damage marker in normal colorectal mucosa: a randomized clinical trial. Cancer Epidemiol Biomarkers Prev. 2010 Jan;19(1):280-91.

Fedirko V, Bostick RM, Flanders WD, Long Q, Shaukat A, Rutherford RE, Daniel CR, Cohen V, Dash C. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. Cancer Prev Res (Phila Pa). 2009 Mar;2(3):213-23.

Flaig TW, Barqawi A, Miller G, Kane M, Zeng C, Crawford ED, Glode LM. A phase II trial of dexamethasone, vitamin D, and carboplatin in patients with hormone-refractory prostate cancer. Cancer. 2006 Jul 15;107(2):266-74.

Garland CF, Gorham ED, Mohr SB, Garland FC..Vitamin D for cancer prevention: global perspective..Ann Epidemiol. 2009 Jul;19(7):468-83.

Gross C, Stamey T, Hancock S, Feldman D. Treatment of early recurrent prostate cancer with 1,25-dihydroxyvitamin D3 (calcitriol). J Urol. 1998 Jun;159(6):2035-9; discussion 2039-40. Erratum in: J Urol 1998 Sep;160(3 Pt 1):840.

Henderson CA, Papworth-Smith J, Cunliffe WJ, Highet AS, Shamy HK, Czarnetzki BM. A double-blind, placebo-controlled trial of topical I,25-dihydroxycholecalciferol in psoriasis. Br J Dermatol. 1989 Oct;121(4):493-6.

Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry. 2008 May;65(5):508-12.

Hughes DA, Norton R. Vitamin D and respiratory health. Clin Exp Immunol. 2009 Oct;158(1):20-5.

Hutchinson PE, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 microg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. Dermatology. 2000;201(2):139-45.

Lahfa M, Mrowietz U, Koenig M, Simon JC. Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. Eur J Dermatol. 2003 May-Jun;13(3):261-5.

Langner A, Verjans H, Stapór V, Mol M, Fraczykowska M. Topical calcitriol in the treatment of chronic plaque psoriasis: a double-blind study. Br J Dermatol. 1993 May;128(5):566-71.

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007 Jun;85(6):1586-91.

Lebwohl M, Menter A, Weiss J, Clark SD, Flores J, Powers J, Balin AK, Kempers S, Glinert RJ, Fleming T, Liu Y, Graeber M, Pariser DM. Calcitriol 3mcg/g ointment in the management of mild to moderate plaque type psoriasis: results from two placebo-controlled, multicenter, randomized double-blind, clinical studies. J Drugs Dermatol. 2007 Apr;6(4):428-35.

Liao YH, Chiu HC, Tseng YS, Tsai TF. Comparison of cutaneous tolerance and efficacy of calcitriol 3mcg g(-1) ointment and tacrolimus 0.3mg g(-1) ointment in chronic plaque psoriasis involving facial or genitofemoral areas: a double-blind, randomized controlled trial. Br J Dermatol. 2007 Nov;157(5):1005-12.

Ortonne JP, Humbert P, Nicolas JF, Tsankov N, Tonev SD, Janin A, Czernielewski J, Lahfa M, Dubertret L. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3mcg g(-1) ointment and calcipotriol 50mcg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. Br J Dermatol. 2003 Feb;148(2):326-33.

Pèrez A, Chen TC, Turner A, Raab R, Bhawan J, Poche P, Holick MF. Efficacy and safety of topical calcitriol (1,25-dihydroxyvitamin d3) for the treatment of psoriasis. Br J Dermatol. 1996 Feb;134(2):238-46.

Perez A, Raab R, Chen TC, Turner A, Holick MF. Safety and efficacy of oral calcitriol (1,25-dihydroxyvitamin D3) for the treatment of psoriasis. Br J Dermatol. 1996 Jun;134(6):1070-8.

Prystowsky JH, Muzio PJ, Sevran S, Clemens TL. Effect of UVB phototherapy and oral calcitriol (1,25-dihydroxyvitamin D3) on vitamin D photosynthesis in patients with psoriasis. J Am Acad Dermatol. 1996 Nov;35(5 Pt 1):690-5.

Prystowsky JH, Knobler EH, Muzio PJ. Oral calcitriol (1,25-dihydroxyvitamin D3) does not augment UVB phototherapy for plaque psoriasis. J Am Acad Dermatol. 1996 Aug;35(2 Pt 1):272-4.

Ring J, Kowalzick L, Christophers E, Schill WB, Schöpf E, Ständer M, Wolff HH, Altmeyer P. Calcitriol 3 microg g-1 ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. Br J Dermatol. 2001 Mar;144(3):495-9.

Rohan TE, Negassa A, Chlebowski RT, Ceria-Ulep CD, Cochrane BB, Lane DS, Ginsberg M, Wassertheil-Smoller S, Page DL. A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease. Breast Cancer Res Treat. 2009 Jul;116(2):339-50.

Srinivas S, Feldman D. A phase II trial of calcitriol and naproxen in recurrent prostate cancer. Anticancer Res. 2009 Sep;29(9):3605-10.

Tiffany NM, Ryan CW, Garzotto M, Wersinger EM, Beer TM. High dose pulse calcitriol, docetaxel and estramustine for androgen independent prostate cancer: a phase I/II study. J Urol. 2005 Sep;174(3):888-92.

Trump DL, Potter DM, Muindi J, Brufsky A, Johnson CS. Phase II trial of high-dose, intermittent calcitriol (1,25 dihydroxyvitamin D3) and dexamethasone in androgen-independent prostate cancer. Cancer. 2006 May 15;106(10):2136-42.

Uhoda I, Quatresooz P, Hermanns-Lê T, Piérard-Franchimont C, Arrese JE, Piérard GE. Histometric assessment of psoriatic plaques treated by vitamin D3 derivatives. Dermatology. 2003;206(4):366-9.

van de Kerkhof PC, van Bokhoven M, Zultak M, Czarnetzki BM. A double-blind study of topical 1 alpha,25-dihydroxyvitamin D3 in psoriasis. Br J Dermatol. 1989 May;120(5):661-4.

Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Aliment Pharmacol Ther. 2009 Jul 1;30(2):113-25.

Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL,et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006 Feb 16;354(7):684-96. Erratum in: N Engl J Med. 2006 Mar 9;354(10):1102.

Zhu X, Wang B, Zhao G, Gu J, Chen Z, Briantais P, Andres P. An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3mcg/g ointment vs. calcipotriol 50mcg/g ointment in subjects with mild to moderate chronic plaque-type psoriasis. J Eur Acad Dermatol Venereol. 2007 Apr;21(4):46

Questions

1. "Adequate" vitamin D levels are generally considered by the scientific community to be:
A. 25nmol/L or greater
B. 50nmol/L or greater
C. 75nmol/L or greater
D. 220nmol/L or greater

2. According to the dosing algorithm tested by Aloia et al, those with serum levels <80nmol/L had their daily dose of vitamin D increased by how much?
A. 400 IU per day
B. 1,000 IU per day
C. 2,000 IU per day
D. 3,800 IU per day

3. With respect to cancer, vitamin D has:
A. Antiproliferative, proapoptotic, and differentiation inducing effects on tumor cells
B. May 'normalize' the colorectal crypt proliferative zone in sporadic adenoma patients when given at 800 IU per day
C. May 'normalize' the colorectal crypt proliferative zone in sporadic adenoma patients when given at 1,000 IU per day
D. a) and b)
E. a) and c)

4. Vitamin D's antiproliferative effects translate into therapeutic effects in psoriasis. The following are true:
A. Human studies have used calcitriol 3mcg/g as a cream for psoriasis lesions
B. Two of three controlled trials show benefit from use of oral calcitriol for psoriasis
C. Topical calcitriol was superior to tacrolimus for psoriasis
D. All of the above

5. The majority of evidence supporting an anticancer role for vitamin D is observational. The following are true:
A. ≥82nmol/L serum 25(OH)D has been associated with 50% lower risk of colorectal cancer
B. breast cancer patients with serum 25(OH)D levels >72nmol/L at diagnosis have been found to have a 42% lower 15-year death rate compared to those with less than 20ng/ml
C. early stage NSCLC patients (stage IB-IIB) with higher serum 25(OH)D levels had a 75% better chance of overall survival
D. a) and b)
E. a) and c)

6. Lappe et al (2007) found that administration of vitamin D with or without calcium significantly reduced total cancer incidence in postmenopausal women.
A. True
B. False

7. The dose of vitamin D utilized in the Nebraska study was high enough to impact serum levels, raising 25(OH)D from 71nmol/L to an average of 96nmol/L at 12 months.
A. True
B. False

8. The ASCENT trial of DN-101 (a high dose calcitriol preparation) in prostate cancer found significant improvements in overall survival and non-significant improvements in PSA response rates compared to placebo. Median survival was 16 months in the placebo arm, but estimated at 24 months in those receiving calcitriol.
A. True
B. False

9. Which of the following is NOT true? Uncontrolled trials of calcitriol in prostate cancer have found:
A. Prolongation of PSA doubling time
B. Decrease in pain
C. Decreased incidence of hospital-acquired infections
D. Decreased thrombotic events in conjunction with docetaxel chemotherapy

10. A recent public statement issued by a group of scientists and vitamin D researchers recommended raising the minimum serum 25(OH)D level to 100-150nmol/L on the basis that this would prevent approximately 58,000 new cases of breast cancer and 49,000 new cases of colorectal cancer each year.
A. True
B. False

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