Vitamin D Status in Chronic Kidney Disease – UVB Irradiation Is Superior to Oral Supplementation

ROLFDIETER KRAUSE[1,2], HEINZ JÜRGEN ROTH[3], HEINRICH KAASE[4], RAINER STANGE[1] and MICHAEL F. HOLICK[5]

[1]*Department of Natural Medicine, Research Group of Medical Heliotherapy, Charité - University Medicine Berlin and Immanuel Hospital, Berlin, Germany;*
[2]*Nephrological Center Moabit, Curatorium for Dialysis and Kidney Transplantation, Berlin, Germany;*
[3]*Department of Endocrinology, Limbach Laboratory, Heidelberg, Germany;*
[4]*Institute of Lighting Technics, Technical University Berlin, Berlin, Germany;*
[5]*Department of Endocrinology, Vitamin D Research Laboratory, School of Medicine Boston University, Boston, MA, U.S.A.*

Abstract. *Background: In chronic kidney disease (CKD) a deficiency of 1,25-dihydroxyvitamin D is common. The aim of this review was to compare vitamin D status after oral supplementation of vitamin D_3 to that of serial suberythemal irradiation in end-stage kidney disease (ESKD) patients. Patients and Methods: Ninety-five patients, with a mean age of 62 (range=35-82) years, were treated with a mean dose of 35,000 (20,000–60,000) IU vitamin D_3 per week for a period of 18 months. Fourteen patients, with a mean age of 51 (range=41-57) years, were whole-body UVB irradiated for over 6 months. From 3 hemodialysis patients skin biopsies were performed. Results: With oral supplementation 25(OH)D_3 increased by 60%. With UV irradiation 25(OH)D_3 increased by 400%. Gene expression analysis demonstrated an improvement in the vitamin D receptor (VDR) by 0.65 fold, in 1-alpha-hydroxylase (CYP27B1) by 1.0 fold, and in 25-hydroxylase (CYP2R) by 1.2 fold. Conclusion: Serial suberythemal UVB irradiation of patients with CKD on dialysis is capable to improve serum 25(OH)D_3 and 1,25(OH)$_2D_3$ by enhancing the skin's ability to activate vitamin D.*

In the course of chronic kidney disease (CKD) the intracellular uptake of 25(OH)D_3 is reduced and a 1,25-dihydroxyvitamin D deficiency is common. Since the mid 1970s this finding was studied especially in anephric patients (1, 2). After oral treatment of 50,000 and 100,000 IU daily of vitamin D_2, Lambert (3) reported an increase also in 1,25-dihydroxyvitamin D (1,25(OH)$_2D_3$ levels. UVB exposure of the skin is the physiological way to activate vitamin D metabolism (4). The keratinocytes have the enzymes 25-hydroxylase (CYP 2R) and the 1-alpha-hydroxylase (CYP27B1) to hydroxylate vitamin D_3 to 1,25(OH)$_2D_3$ (5). The aim of this review is to compare the blood levels of 25(OH)D_3 after oral supplementation of vitamin D_3 and of serial suberythemal UVB irradiation in dialysis patients.

Correspondence to: Rolfdieter Krause, MD, Research Group Medical Heliotherapy, Department of Natural Medicine, Koenigstr. 63, D-14109 Berlin, Germany. Tel: +49 30 80505 691, Fax: +49 30 80505 692, e-mail: rolfdieter.krause@t-online.de

Key Words: Vitamin D, oral supplementation, UVB irradiation, extra-renal synthesis, 25-hydroxyvitamin D, 1-alpha-hydroxylase, 1,25-dihydroxyvitamin D, vitamin D receptor, chronic kidney disease (CKD), dialysis (ESKD).

Patients and Methods

Oral supplementation. Ninety-five dialysis patients, with a mean age of 62 (range=35-82) years, were treated with a mean dose of 35,000 (20,000-60,000) IU vitamin D3 per week over a period of 18 months. 25(OH)D_3 controls were fixed at start and after each 6 months.

Serial suberythemal irradiation with UVB. Fourteen hemodialysis patients, with a mean age of 51 (range=41-57) years, were whole-body irradiated three times weekly over 6 months, following an observation period of 9 months without any vitamin D supplementation. The UV lamps had an efficiency of UVB 0.37 mWatts/cm^2, and of UVA 6.4 mWatts/cm^2, with a maximum effective spectrum of 300-320 nm. The serum level of 25(OH)D_3 were measured before start of the UVB irradiation, after 3 months and after 6 months (end) of the irradiation period, and after 3 months and after 9 months of the follow-up time.

Results

Oral supplementation. A continuous increase of the serum level of 25(OH)D_3 was found from a mean of 33 ng/ml to 36 ng/ml

Table I. *Serum level of 25(OH)D_3 during 18 months oral supplementation of a mean dose of 35,000 IU vitamin D_3 per week.*

Start: 33 ng/ml	6 m: 36 ng/ml=+10%	12 m: 44 ng/ml=+29%	18 m: 53 ng/ml=+60%

m, Month.

Table II. *Serum level of 25(OH)D_3 after 3 and 6 months of serial suberythemal UVB irradiation, and after follow-up of 3 months and of 9 months without vitamin D supplementation.*

pre:40 ng/ml	3UVB:120 ng/ml=+300%	6UVB:160 ng/ml=+400%	3mp:100 ng/ml=+150%	9mp:100 ng/ml=+150%

3UVB, 3 months UVB; 6UVB, 6 months UVB; 3mp, 3 months post-UVB; 9mp, 9 months post-UVB.

(+10%) after the first 6 months, and during the following 12 months, 25(OH)D_3 increased further on to 44 ng/ml (+29%) and to 53 ng/ml (+60%) (Table I).

Serial suberythemal UVB irradiation. During the irradiation time 25(OH)D_3 increased continuously from a mean of 40 ng/ml to 120 ng/ml after 3 months (+300%) and to 160 ng/ml after 6 months (+400%). After 3 months stop of the irradiation 25(OH)D_3 decreased to 100 ng/ml (+150%), and remained stable during the follow-up of 9 months without any vitamin D treatment (Table II).

Long-time UVB irradiation. A small number (n=4) of hemodialysis patients was continued on regular UVB irradiation schedule. After an observation period over 10 years with an individual dosing one to three times per week (summer *vs*. winter); there were no adverse events or subjective irritation of the skin. Serum vitamin D_3 remained stable during this 10-year period and serum 25(OH)D_3 remained in the optimal range. Patients with higher serum levels of 25(OH)D_3 also had serum 1,25$(OH)_2D_3$ that were in the normal range (Figure 1).

Gene expression after UVB irradiation. In 3 hemodialysis patients skin biopsies were performed after 6 months of suberythemal UVB irradiation and gene expression was analyzed for the vitamin D receptor (*VDR*), for 1-alpha-hydroxylase (*CYP27B1*), and 25-hydroxylase (*CYP2R*). All genes showed an increased expression, VDR 0.65-fold, 1-alpha 1.0-fold, 25-OHase 1.2-fold (Figure 2).

Discussion

Vitamin D deficiency still is common worldwide (7, 8), also in CKD and ESKD patients (9, 10). The recommendation of the Institute of Medicine (IOM) (11) and of the Endocrine Practice Guidelines Committee (12) are for adults a daily dose of vitamin D_3 of 600 IU per day, up to 4,000 IU per day, and for risk groups 1,500-2,000 IU per day, up to 10,000 IU per day.

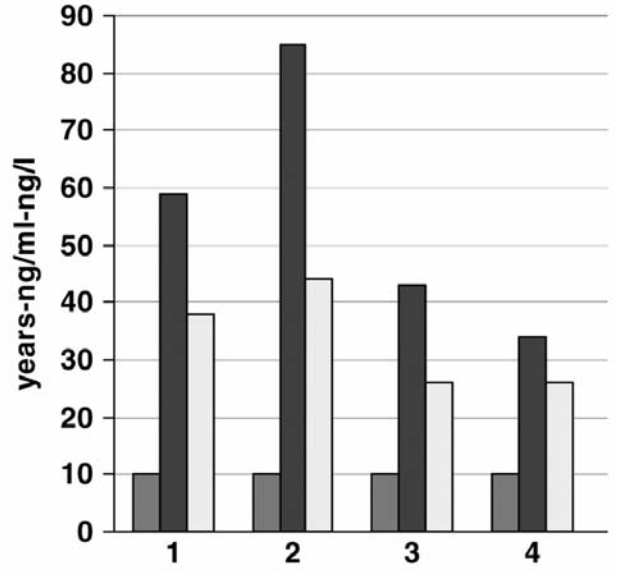

Figure 1. *Vitamin D status of 4 hemodialysis patients over 10 years regularly suberythemal UVB irradiation one to three times weekly (Vit D_3: gray bars; 25(OH)D_3: black bars; 1,25$(OH)_2D_3$: white bars) [from: Krause (6), with permission(Springer Science & Business Media)].*

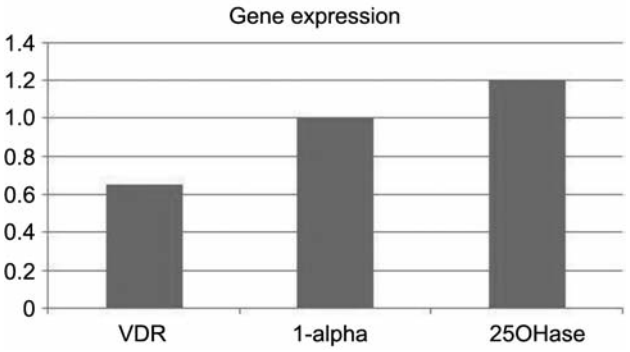

Figure 2. *Gene expression in uremic skin after 6 months of serial suberythemal UVB irradiation.*

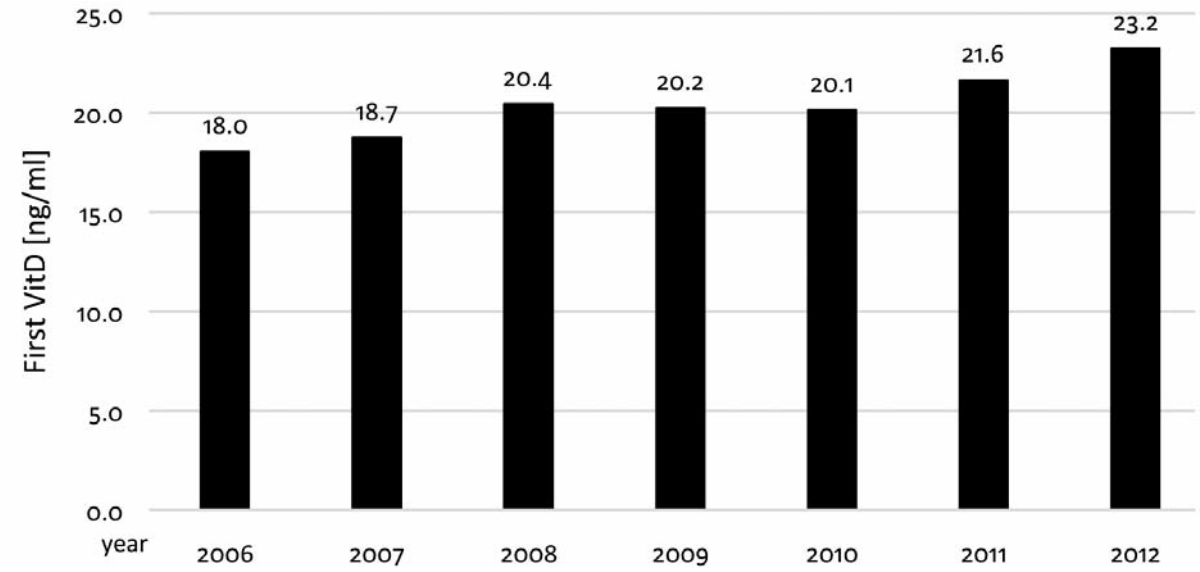

Figure 3. *First 25(OH)D_3 blood levels in patients who initiated hemodialysis in 2006 to 2012. (Marquardt 18; with permission [AntiCancerResearch]).*

Dialysis patients are able to achieve a serum level of 25(OH)D_3 >30 ng/ml when treated with high oral doses of vitamin D. Marckmann *et al*. gave 40,000 IU vitamin D_3 per week over 2 months, and there was an mean increase of 25(OH)D_3 by 40 ng/ml (from 8 ng/ml to 48 ng/ml) in the dialysis patients (13). Bhan *et al*. used oral supplementation of 50,000 IU vitamin D_2 either weekly or monthly over 12 weeks; and comparable to vitamin D_3 there was an increase of 28 ng/ml (from 22 ng/ml to 50 ng/ml) with weekly, and of 16 ng/ml (to 38 ng/ml) with monthly dosing (14). Armas *et al*. gave 1,500 IU vitamin D3 per day over 15 weeks to CKD stage 5 patients, and reported a mean increase of 25(OH)D3 by only 9 ng/ml (from 15 ng/ml to 24 ng/ml) (15). Zitt *et al*. treated dialysis patients with a mean dose of 7,600 IU vitamin D_3 (proportionately 100 IU/kg body weight, with a mean body weight of 76 kg) once weekly over a period of 6 months; and they found a mean increase of 25(OH)D3 by 16 ng/ml (from 10 ng/ml to 26 ng/ml) (16). An additional modality is to substitute modified release MR-calcidiol; daily doses between 30 μg to 90 μg are safe and effective to increase also the serum levels of 1,25(OH)2D (17).

By our regime the mean dose was 35,000 IU per week, equalling a mean dose of 5,000 IU per day over the period of 18 months. The regime was dosed individually between 20,000 IU and 60,000 IU per week, proportionally 2,850 IU/day up to 8,600 IU/day. Dialysis patients, being people at risk, need a minimal supplementation dose between 3,000 IU to 8,500 IU per day respectively, between 35,000 IU to 50,000 IU per week over a period of two months minimum, to increase the serum level of 25(OH)D_3 over 30 ng/ml. This is in accordance with the recommendation of the Endocrine Practice Guidelines Committee (12).

The vitamin D status of the majority of the German hemodialysis patients had a mean serum level of 25(OH)D_3 of 23 ng/ml (18) (Figure 3). That is considered to be vitamin D deficiency by the guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) (19). Only 29% of the German dialysis patients had a sufficient vitamin D status (25(OH)D_3 >30 ng/ml (Figure 4).

From the data of Holick (20) 1 MED (minimal erythema dose) is equivalent to an oral dose between 10,000-25,000 IU, and 1 MED is equivalent to 20 mJ/cm^2 UVB. We always used suberythemal UV doses, starting with 13 mJ/cm^2 (equal to 0.65 MED), and we increased the dose based on the individuals' sensitivity, by approximately 10% every week. This is equivalent an oral dose of vitamin D_3 of 5,000 IU–12,000 IU per UV irradiation, or 15,000 IU-36,000 IU per week. After 3 months the increase of 25(OH)D_3 was 300% (from 40 ng/ml to 120 ng/ml) and after 6 months until 160 ng/ml (400% incrrease). This is consistent with the serum levels of 25(OH)D_3 by Lambert (3) and Dusso (21) who had reported that in CKD and ESKD patients a high normal level of 25(OH)D_3 between 60-100 ng/ml, or higher, was needed for the extrarenal production of 1,25$(OH)_2$D. This is also in accordance with recommendation for risk groups of the US Endocrine Society (12) for a daily supplementation between 4,000 IU-10,000 IU vitamin D_3. By our experience suberythemal UVB irradiation can be used over a longer time, and the serum level of 25(OH)D_3 can be stabilized to sufficient levels of >30 ng/ml and up to 80 ng/ml. With these serum

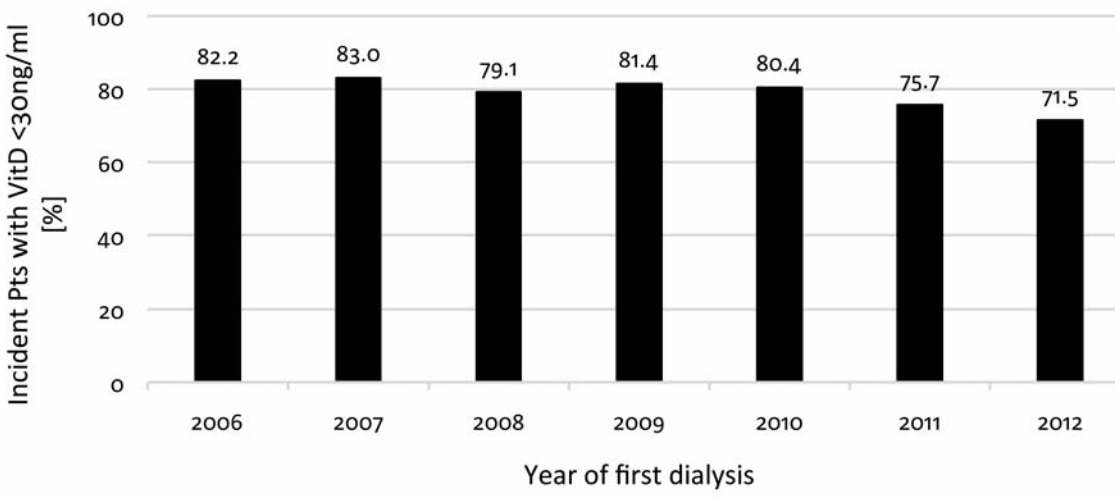

Figure 4. *Percentage of incident HD patients 2006-2012 with first 25(OH)D_3 level <30 ng/ml [with permission (18)].*

levels of 25(OH)D_3 it was also possible to achieve a normal serum level of 1,25$(OH)_2$D in these dialysis patients. No hypercalcemia nor hyperphosphatemia were observed.

Moreover, UVB irradiation of the skin activated gene expression of the vitamin D receptor (*VDR*), 1-alpha-hydroxylase (*CYP27B*) and of the 25-hydroxykase (*CYP2R*) confirming the observation of Ala-Houhala *et al.* (22). The increase in expression of the 25-hydroxylase can potentially improve the local capacity in the skin to convert vitamin D3 to 25(OH)D_3. The increase in expression of the 1-alpha-hydroxylase in the skin can potentially improve the skin's ability to convert 25(OH)D_3 to 1,25$(OH)_2$D.

In conclusion, our results showed that a serial suberythemal UVB irradiation in patients with chronic kidney disease on dialysis were able to substantially raise their blood levels of 25(OH)D_3. This increase was also associated with an increase in circulating levels of 1,25$(OH)_2$D. In addition the UVB irradiation has the expression of enzymes in the skin that could potentially convert cutaneously produced vitamin D3 to 25(OH)D and 1,25$(OH)_2$D. Therefore, suberythemal UVB irradiation of the skin seems to be superior to oral supplementation in CKD and ESKD patients for maintaining their vitamin D status.

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References

1 Gray RW, Weber HP, Dominquez JH and Lemann J Jr.: The metabolism of vitamin D3 and 25 hydroxyvitamin D_3 in normal and anephric humans. J Clin Endocrinol Metab *32*: 1045-1056, 1974.

2 Horst RL, Littledike ET, Gray RW and Napoli JL: Impaired 24,25-dihydroxyvitamin D production in anephric human and pig. J Clin Invest *67*: 274-280, 1981.

3 Lambert PW, Stern PH, Avioli RC, Brackett NC, Turner RT, Greene A and Fu IY: Evidence of extrarenal production of 1,25-dihydroxivitamin D in man. J Clin Invest *69*: 722-725, 1982.

4 Morrone LF and Cozzolino M: The beneficial impact of vitamin D treatment in CKD patients: what's next? Clin Kidney J *8*: 38-40, 2014.

5 Lehmann B and Meurer M: Vitamin D metabolism. Dermatol Ther *23*: 2-12, 2010.

6 Krause R: Role of Vitamin D and Ultraviolet Radiation in Chronic Kidney Disease. *In*: Vitamin D – Physiology, Molecular Biology, and Clinical Applications (MF Holick, ed.) 2.Ed. New York Springer/Humana Press. pg.967-983, 2010.

7 Hinzpeter B: Vitamin D Status in Germany. Tönning/Lübeck/ Marburg, Der Andere Verlag, 2008.

8 Holick MFand Chen TC: Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr *87*: 1080S-1086S, 2008.

9 Drechsler C, Verduijn M, Pilz S, Dekker FW, Krediet RT, Ritz E, Wanner C, Boeschoten EW, Brandernburg V and Group NS: Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. Nephrol Dial Transplant *26*: 1024-1032, 2011.

10 Krause R, Schober-Halstenberg HJ, Edenharter G, Haas K, Roth HJ and Frei U: Vitamin D status and Mortality of German hemodialysis patients. Antican Res *32*: 391-396, 2012.

11 IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. Committee to Review Dietary Reference Intakes for Calcium and Vitamin D. Washington DC: The National Academies Press, 2011.
12 Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CN, Hanley DA, Heeney RP, Murad MH and Weaver CM: Endocrine Society: Evaluation, treatment, and prevention of vitamin D deficiency: Endocrine Society clinical practice guideline. J Clin Endocrinol Metab *96*: 1911-1930, 2011.
13 Marckmann P, Agerskov H, Thineshkumar S, Bladbjerg EM, Sidelmann JJ, Jespersen J, Nybo M, Rasmussen LM, Hansen D and Scholze A: Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. Nephrol Dial Transplant *27*: 3523-3531, 2012.
14 Bhan I, Dobens D, Tamez H, Deferio JJ, Li YC, Warren HS, Ankers E, Wenger J, Tucker JK, Trottier C, Pathan F, Kalim S, Nigwekar SU and Thadahani R: Nutritional Vitamin D Supplementation in Dialysis: A Randomized Trial. Clin J Am Soc Nephrol *10*: 611-619, 2015.
15 Armas LA, Andukuri R, Barger-Lux J, Heaney RP and Lund R: 25-Hydroxyvitamin D Response to Cholecalciferol Supplementation in Hemodialysis. Clin J Am Soc Nephrol *7*: 1428-1434, 2012.
16 Zitt E; Sprenger-Mähr H, Mündle M and Lhotta K: Efficacy and safety of body weight-adapted oral cholecalciferol substitution in dialysis patients with vitamin D deficiency. BMC Nephrology *16*: 128-135, 2015.
17 Sprague SM, Silva L, Al-Saghir F, Damle R, Tabash SP, PetkovichM Messner EJ, White AJ, Melnick JZ and Bishop CW: Modified-Release Calcifediol Effectively Controls Secondary Hyperparathyroidism Associated with Vitamin D Insufficiency in Chronic Kidney Disease. Am J Nephrol *40*: 535-545, 2014.
18 Marquardt P, Krause R, Schaller M, Bach D and Gersdorff G: Vitamin D starus and cancer prevalence of hemodialysis patients in Germany. AntiCancer Research *35*: 1181-1188, 2015.
19 KDIGO Guideline for Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD). Kidney Intern *76(Suppl 113)*: S1-S130, 2009.
20 Holick MF: Sunlight, UV-Radiation, Vitamin D and Skin Cancer: How much sunlight do we need ? In: Sunlight, Vitamin D and Skin Cancer. (J.Reichrath, ed.). New York, Springer, pg. 1-15, 2008.
21 Dusso A, Lopez-Hilker S, Rapp N and Slatopolsky E: Extra-renal production of calcitriol in chronic renal failure. Kidney Int *34(3)*: 368-375, 1988.
22 Ala-Houhala MJ, Vähävihou K, Hasan T, Kautiainen H, Snellman E, Karisola P, Dombrowski Y, Schauber J, Saha H and Reunala T: Narrow-band ultraviolet B exposure increases serum vitamin D levels in hemodialysis patients. Nephrol Dial Transplant *27*: 2435-2440, 2012.

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