UV Irradiation and Pleiotropic Effects of Vitamin D in Chronic Kidney Disease – Benefits on Cardiovascular Comorbidities and Quality of Life

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Abstract. *Background: Vitamin D_3 can be metabolized in the skin to 25(OH)D and 1,25(OH)$_2$D because the skin expresses vitamin D-25-hydroxylase, 25(OH)D-1-alpha-hydroxylase, and the vitamin D receptor. The aim of this review was to discuss the pleiotropic effects after serial suberythemal UVB irradiation with a sun-simulating UV spectrum in end-stage kidney disease patients. Patients and Methods: Fourteen hemodialysis patients, with a mean age of 51 (range 41-57) years, were whole-body UV irradiated over 6 months. Results: Patients demonstrated an increase in their hematocrit and required less erythropoietin. An increase in maximal oxygen uptake and workload capacity was associated with decreased lactic acid production. The patients demonstrated a decreased heart rate and systolic and diastolic blood pressure with an increase in the R-R-interval and the beat-to-beat-differences. Conclusion: Cardiovascular disease is the most important comorbidity. Exposure to simulated sunlight that contains both UVB and UVA reduce cardiovascular risk factors and improve quality of life.*

The goal of this study was to determine whether exposure to simulated sunlight containing UVB radiation which enhances the cutaneous production of vitamin D can have effects on the physical capacity and the cardiovascular system in patients with end-stage kidney disease (ESKD) on dialysis. We have previously shown that compared to oral supplementation, simulated sun exposure for skin type II and III increases the blood levels of 25(OH)D_3 by 4.0-fold and 3.5-fold respectively, and also increases blood levels of 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] (1, 2). In patients with chronic and ESKD the status of 25(OH)D_3 is rated as an independent inverse predictor of disease progression and death (3).

The aim of this review was to discuss the pleiotropic effects after serial suberythemal UVB and UVA irradiation with a sun-simulating UV spectrum in ESKD patients.

Patients and Methods

Serial suberythemal irradiation with UV. Fourteen hemodialysis patients, with a mean age of 51 (range=41-57) years, were whole-body irradiated using a cabin and standing on a rotating platform (one rotation per minute) three times weekly (before start of dialysis procedure) over 6 months (Figure 1) (4). 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 (1).

Results

Serial UV irradiation and erythropoiesis. During the serial suberythemal UV irradiation procedure a continuous increase of the hematocrit was observed from 27.9 Vol% to 28.9 Vol% (+3%) after 7 weeks, and to 29.1 Vol% (+4%) after 14 weeks, and to 29.7 Vol % (+6%) after 26 weeks (Figure 2).

Parallel decrease in the dosage for erythropoietin (rh-EPO) was observed from 4,500 U to 4,000 U (–12%) after 7 weeks, to 3,400 U (–25%) after 14 weeks, and to 3,100 U (–31%) after 26 weeks (Table I).

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Key Words: Sun-simulating suberythemal UVB exposure, vitamin D status, chronic kidney disease, end-stage kidney disease, erythropoiesis, erythropoietin supplementation, oxygen consumption, heart rate variability, cardiovascular comorbidity, quality of life.

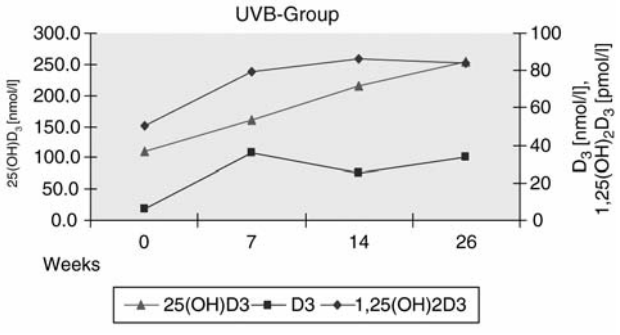

Figure 1. *Time course of vitamin D_3, 25(OH)D_3 (calcidiol), and 1,25(OH)$_2D_3$ (calcitriol) during 6 months of whole-body UV irradiation (with permission from 4).*

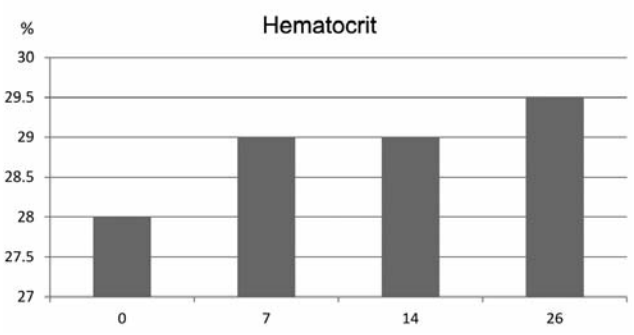

Figure 2. *Increase of hematocrit (Hct) during serial suberythemal UV irradiation. Hct, Hematocrit.*

Table I. *Doses of rh-EPO during serial suberythemal UV irradiation.*

pre: 4,500 U	7 wks.: 4,000 U	14 wks.: 3,400 U	26 wks.: 3,100 U

wks, Weeks.

Table II. *Decrease of lactic acid accumulation during maximum ergometric work load after serial suberythemal UV irradiation.*

pre: 3.9 mmol/l	14 wks.: 2.5 mmol/l	26 wks.:2.6 mmol/l

wks., Weeks.

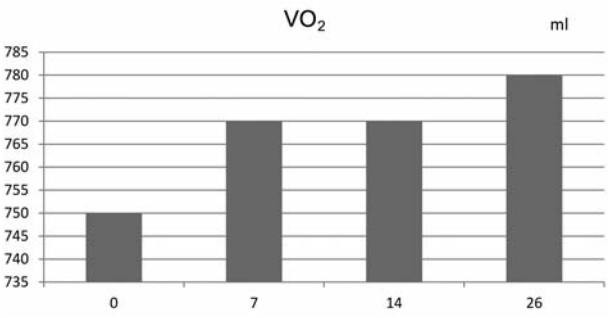

Figure 3. *Increase of oxygen uptake (VO_2) during serial suberythemal UV irradiation. VO_2, Oxygen Uptake.*

Serial UVB and UVA irradiation and cardio-pulmonary capacity. The improvement of erythropoiesis and of hematocrit was accompanied by an increase of the maximal oxygen uptake capacity from 710 ml O_2/min to 795 ml O_2/min (+11%) (Figure 3).

Serial UVB and UVA irradiation on work-load capacity. The maximal increase of the work-load capacity by bicycle ergometry in sitting positon was found after 7 weeks of UV irradiation from 74 Watts to 80 Watts, corresponding from 1.15 Watts/kg body weight (kgBW) to 1.25 Watts/kgBW (+8%); after 14 weeks and 26 weeks UV irradiation, respectively, the maximal workload capacity stabilized on a level of 76 Watts (1.20 Watts/kgBW) (+3%) (Figure 4).

Serial UV irradiation and muscle metabolism. The improvement of the oxygen consumption also was associated with a decrease in lactic acid production during maximal workload; the production of lactic acid during maximal ergometric workload decreased by 33% from 3.9 mmol/l to 2.5 mmol/l after 14 weeks, and was stable with 2.6 mmol/l after 26 weeks of UV irradiation (Table II).

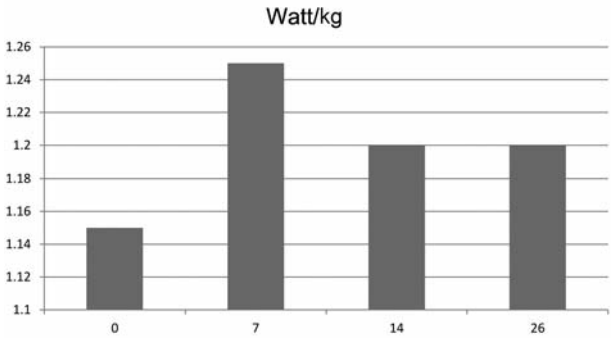

Figure 4. *Increase in maximum work load (Watt/kg) during serial suberythemal UV irradiation.*

Serial UV irradiation and blood pressure (BP). At rest a decrease of the systolic BP from 142 mmHg to 136 mmHg (–5%), and of the diastolic BP from 88 mmHg to 81 mmHg (–8%) was registered. Although the maximal workload was

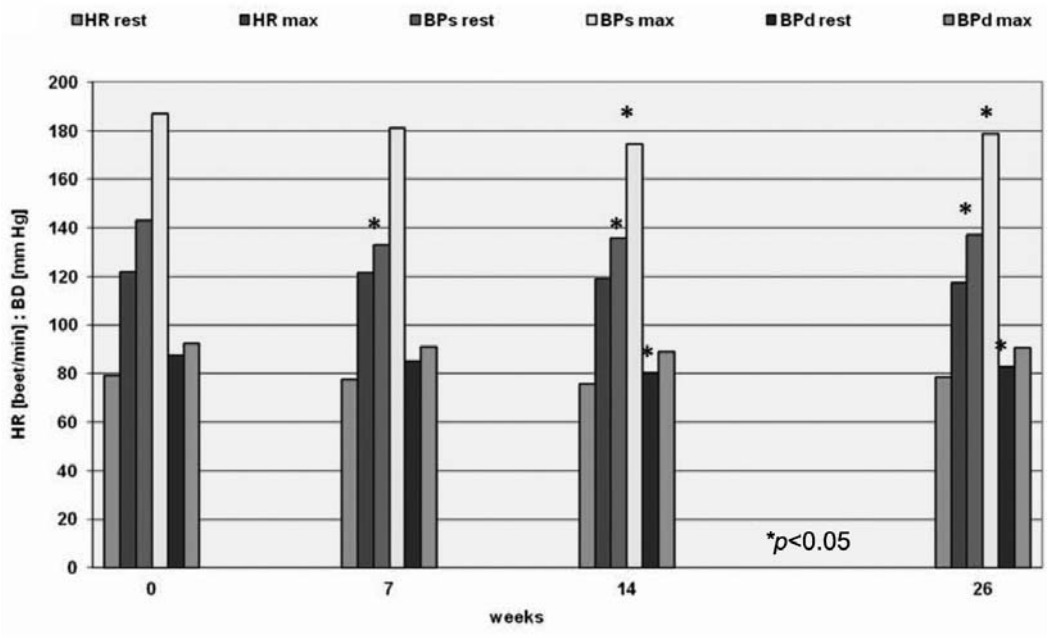

Figure 5. *Decrease of heart rate and of systolic and diastolic blood pressure at rest and at maximum work load during serial suberythemal UV irradiation. HR, Heart rate; BPs, systolic blood pressure; BPd. Diastolic blood pressure; max, maximum workload (with permission from 5).*

increased by 8% a decrease was registered of the systolic BP from 186 mmHg to 175 mmHg (–6%), and also a decrease of the diastolic BP from 92 mmHg to 89 mmHg (–4%) (Figure 5).

Serial UV irradiation and heart rate variability (HVR). The cardio-circulatory adaptation was associated with a reduction in the heart rate at rest and during maximal work load, with ECG demonstrating an increase of the mean R-R-interval from 795 msec to 828 msec (+14%), and increase of the beat-to-beat differences from 6.7 msec to 9.8 msec (+32%) during UV irradiation (Figure 6).

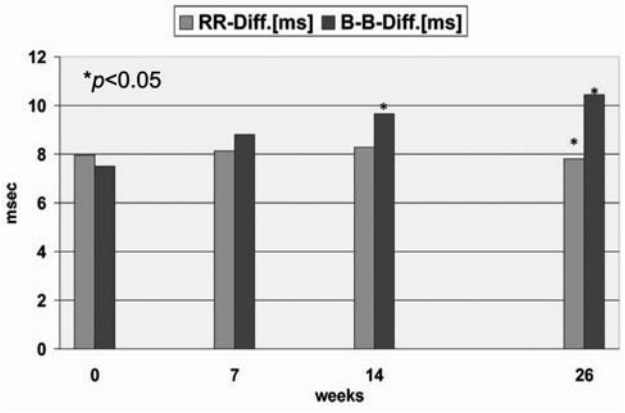

Figure 6. *Increase of RR-interval and beat-to-beat-differences: decrease of sympathetic and increase of parasympathetic tonus. RR-Diff, RR-Interval; B-B-Diff, Beat-to-Beat-Differences (with permission from 5).*

Discussion

Vitamin D deficiency is a risk of early death also for the general population, and this risk increased up to 39% until 46% for the lowest *versus* the highest quartiles of the 25(OH)D serum levels (6, 7). This is in accordance with the results for a representative cohort of the German hemodialysis patients that for a serum level of 25(OH)D between 30-21 ng/ml the risk for all-cause mortality was 19% higher than 25(OH)D >30 ng/ml, for 25(OH)D between 20-13 was 50% higher, for 25(OH)D <12.5 ng/ml even 167% higher than 25(OH)D >30 ng/ml (8) (Figure 7). The progression of renal anemia is an important problem in the course of CKD. The availability of recombinant erythropoietin since end of the 1980's was a milestone in the treatment of CKD the patients. A serum level of 25(OH)D >30 ng/ml has been reported to help maintain bone marrow production of red blood cells. A retrospective study by Lac *et al*. (9) reported that a reduction of 25(OH)D <30 ng/ml during an observation time of 4 months required that these patients increase their dose rh-EPO by 22% per week. This observation was confirmed by Naini *et al*. (10) who found that patients who were treated with vitamin D_3 and raised their blood levels of 25(OH)D up to a mean serum level of

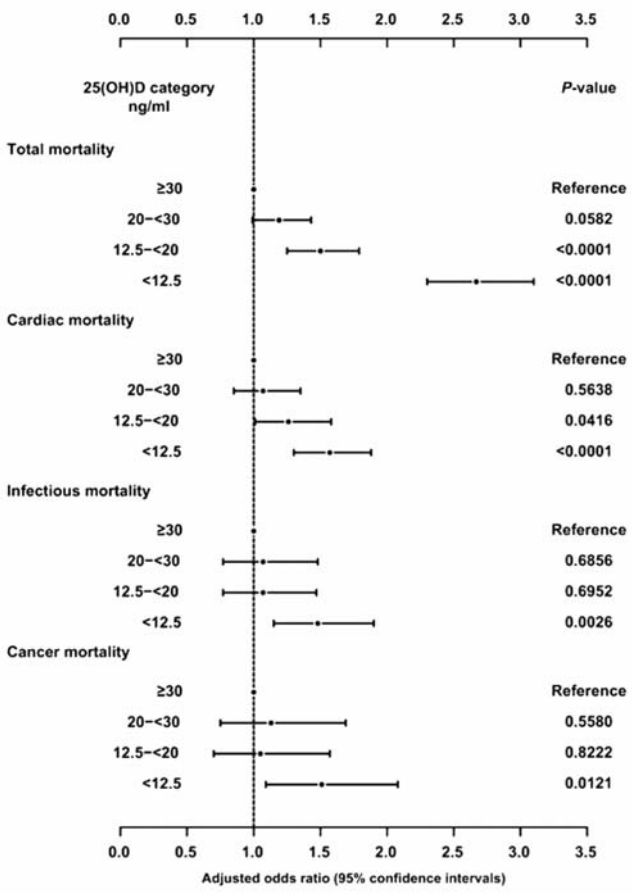

Figure 7. *Adjusted odds ratio (with 95% confidence intervals) for mortality according to 25(OH)D serum levels (with permission from 8).*

79 ng/ml resulted in a reduction in their rh-EPO dosage. The vitamin D receptor (VDR) seems to be an important modulator for hematopoiesis in the bone marrow (11). We had previously reported that serial exposure to suberythemal doses of simulated sunlight containing UVB increases circulating levels vitamin D, 25(OH)D and $1,25(OH)_2D$ (1). The present study demonstrated there was also improvement in the hematocrit and following a reduction of the dose of rh-EPO. The reduction shall also prevent from possible complications using this medication *i.e.* polycythemia. The improvement in the hematocrit of our patients resulted in an increase in oxygen uptake and promoted better physical working capacity.

It is well documented for the past several decades that physical performance increased with UV exposure (12-14). The physical capacity is higher in summer than during winter time, and the level of physical performance reaches its peak with the highest serum levels of 25(OH)D, with an optimum of 50 ng/ml (15). Endurance-specific type II muscle fibers are sensitive to vitamin D deficiency. Therefore, the status of 25(OH)D plays an important role in muscle structure and function due, in part, to the role of vitamin D interacting with its receptor in skeletal muscle tissue (16). Because older age is associated with falls (17) and also with decreased VDR expression (18) improvement in vitamin D status by exposure to sunlight may be of benefit in reducing risk of falls.

A low physical capacity in hemodialysis patients with vitamin deficiency (<10 ng/ml) was found by Kim (19) with a decreased capacity for the 6-min-Walking-Test, for the Hand-Grip-Dynamometry, and for the Timed-up-and-Go-Test. This is consistent with our results that the physical capacity during maximal exercising using a bicycle ergometer increased by a maximum 8%. Additionally the maximum accumulation of lactic acid was lower. These observations support the data from Schuh (20) who reported that increase of physical capacity especially in elderly and sick people feel better, and the health-related quality of life improves (21, 22). It is well-known that there is an association of improvement of endurance capacity and a reduction of heart rate and also blood pressure (23, 24). One of the most important factors is the balance between sympathetic and parasympathetic tone of the cardiovascular regulation. This results in an enhanced heart rate variability (HRV), and also to a lowered respiratory rate which enhanced the effects on HRV (25, 26). This is also true after exercise training with CKD and dialysis patients (27); vitamin D deficiency is associated with suppression of resting vagal tone, and this results in suppression of the sympatho-vagal balance, following a withdrawal of the cardio-protective vagal tone (28). Also HRV differences were reported to be associated with the seasonal vitamin D status (29). This is in line with our data that after the UVB-mediated increase of 25(OH)D an increase of the R-R-intervals of the ECG and of the beat-to-beat differences (reduction of the heart rate) was found.

The normalization of the serum 25(OH)D levels in our patients resulted in a decrease in the heart rate at rest and during exercise. The same effects were reported from our group after different exercise training regimes with dialysis patients (30, 31).

The interaction of ultraviolet radiation, latitude and arterial hypertension is well-known (32, 33). Our group has demonstrated a significant reduction of systolic and diastolic blood pressure (–6/–6 mmHg) in patients with mild essential hypertension that after serial suberythemal UVB irradiation two times weekly over 6 weeks at end of winter time (February and March) (34). This supports our data that in dialysis patients at rest and also during maximal ergometric workload a reduction of the blood pressure was found. In a Mendalian randomization study Vimaleswaran (35) reported that an increased 25(OH)D concentration was associated with reduced risk of hypertension. Vitamin D deficiency is associated with a higher risk of left ventricular hypertrophy, of coronary heart disease and myocardial infarction, of stroke,

peripheral vascular disease, and metabolic syndrome (36). Mann *et al*. conducted a meta-analysis and reported the advantage of vitamin D and their analogs on cardiovascular outcome and mortality (37).

In conclusion, cardiovascular disease is one of the most important comorbidities in chronic and end-stage kidney disease. Disorders in vitamin D metabolism has negative health consequences on many risk factors. Thus, improvement of vitamin D status by serial suberythemal doses of ultraviolet radiation can reduce the risk, and can increase the health-related quality of life status in these patients with a better physical and mental condition (38).

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