ORIGINAL ARTICLE

# Effects of vitamin $D_3$ on selected biochemical parameters of nutritional status, inflammation, and cardiovascular disease in patients undergoing long-term hemodialysis

Anna Bednarek-Skublewska[1], Agata Smoleń[2], Andrzej Jaroszyński[1], Wojciech Załuska[1], Andrzej Książek[1]

1 Department of Nephrology, Medical University of Lublin, Lublin, Poland
2 Department of Mathematics and Biostatistics, Medical University of Lublin, Lublin, Poland

**KEY WORDS**

asymmetric dimethylarginine, hemodialysis, inflammation, vitamin $D_3$

**ABSTRACT**

**INTRODUCTION** Vitamin $D_3$ has diverse biological effects extending beyond the maintenance of calcium and phosphorus homeostasis and ensuring the proper functioning of the body.

**OBJECTIVES** This study evaluated the levels of vitamin $D_3$ and its association with nutritional status, immunological activity, and selected markers of cardiovascular disease in patients on long-term hemodialysis (HD).

**PATIENTS AND METHODS** We measured 25-hydroxyvitamin $D_3$ ($25(OH)D_3$) levels in a group of 84 patients (mean age, 65 years; average time on dialysis, 32.5 months) and investigated correlations between $25(OH)D_3$ levels and the following parameters: albumin, body mass index, hemoglobin (Hb), interleukin 6 (IL-6), interleukin 10, C-reactive protein, asymmetric dimethylarginine (ADMA), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and comorbidity score.

**RESULTS** A mean $25(OH)D_3$ level was 15.4 ±7.2 ng/ml and only 5% of patients had $25(OH)D_3$ levels above the normal value of 30 ng/ml. There was no statistically significant difference in $25(OH)D_3$ levels between women and men ($P = 0.06$). A negative correlation was observed between $25(OH)D_3$ and IL-6 ($R = –0.31$, $P = 0.009$) and ADMA ($R = –0.26$, $P = 0.03$), as well as a positive correlation between $25(OH)D_3$ and Hb ($R = 0.21$, $P = 0.05$). There was no association between $25(OH)D_3$ levels and nutritional status.

**CONCLUSIONS** A significant vitamin $D_3$ deficiency observed in the majority of patients undergoing long-term HD contributes to the development of chronic inflammation, anemia, and indirectly, to endothelial cell injury.

Correspondence to:
Anna Bednarek-Skublewska, MD, PhD, Katedra i Klinika Nefrologii, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-950 Lublin, Poland, phone: +48-817-244-735, fax: +48-817-244-735, e-mail: anna.bednarek@diaverum.com
Received: January 25, 2010.
Revision accepted: April 6, 2010.
Conflict of interests: none declared.
Pol Arch Med Wewn. 2010; 120 (5): 167-174
Translated by Anna Kalińska, MD


**INTRODUCTION** In recent years, both clinical and physiological studies focused on the multidirectional involvement of vitamin $D_3$ in several metabolic pathways of human metabolism.[1-4] Vitamin $D_3$ regulates calcium and phosphorus metabolism and plays a crucial role in maintaining proper bone density.[1,5] Immunomodulatory, cardioprotective, and antiproliferative effects of vitamin $D_3$ have also been described.[1,6-8]

The synthesis of an active form of vitamin $D_3$ is a complex, multistage process, which critically depends on sun exposure and the properly functioning liver and kidneys.[3,9] It is initiated in the cellular membranes of keratinocytes, where UVB radiation of 290–312 nm wavelength induces nonenzymatic photolysis of 7-dehydrocholesterol, a prohormone, into previtamin $D_3$. Previtamin $D_3$ is then converted into vitamin $D_3$ using the body's thermal energy and released into

the skin microvessels, where it is bound by a specific vitamin $D_3$ binding protein and transported to the liver. Hepatic enzymatic hydroxylation at the Carbon 25 position converts the product to 25-hydroxyvitamin $D_3$ ($25(OH)D_3$). The second hydroxylation at Carbon 1, mediated by 1α-hydroxylase, occurs in the proximal tubules of the kidneys and leads to the formation of an active form of vitamin $D_3$, $1,25(OH)_2D_3$ (calcitriol). Various cells containing 1 α-hydroxylase are able to synthesize calcitriol;[1,5] however, an adequate level of $25(OH)D_3$ in the blood is a prerogative for its extrarenal synthesis.

A multidirectional effect of vitamin $D_3$ on the body is a result of its genomic actions, since binding to its nuclear receptor leads to the formation of a transcriptional factor initiating the synthesis of a specific protein.[2,10] Moreover, calcitriol receptors are expressed on the cell surface, and their binding activates pathways supporting intracellular transcription processes. Such membrane-bound vitamin D receptors can be found not only on intestinal epithelial cells, osteoblasts, and parathyroid gland cells, but also on endothelial cells, cardiomyocytes, skin cells, and T and B lymphocytes.[1,7,11]

The principal form of vitamin $D_3$ found in the body is $25(OH)D_3$, and its levels in serum or plasma are usually measured to assess the overall $D_3$ levels. Levels above 30 ng/ml are generally considered as normal.[2,4] Moderate deficiency is diagnosed when concentration is between 12 and 30 ng/ml, while severe vitamin $D_3$ deficiency is observed when the concentration of $25(OH)D_3$ decreases below 12 ng/ml.

General population studies indicated a strong correlation between $D_3$ deficiency and mortality and morbidity rates.[2,7,12] Such correlation was also confirmed in patients with end-stage kidney failure treated with long-term hemodialysis (HD).[13,14] Lack of 1α-hydroxylase activity in the kidneys contributes to a decreased synthesis of calcitriol in this patient group.[11,15,16] Deficiency of an active form of vitamin $D_3$ leads to disturbances not only in calcium-phosphorus metabolism but also in other functions of the organs and tissues influenced by this multifunctional vitamin.

The aim of the current study was to analyze vitamin $D_3$ status and the factors that influence vitamin $D_3$ levels in patients undergoing a long-term HD treatment. Moreover, we searched for potential correlations between vitamin $D_3$ and selected immunological, nutritional, and cardiovascular parameters.

## PATIENTS AND METHODS

**Patients** The study involved 84 patients (46 men, 38 women; mean age: 65.3 ±14.2 years, median time on HD: 32.5 months [range 3–394]). End-stage renal failure was a result of diabetic nephropathy (23 patients), glomerulonephritis (22 patients), hypertensive nephropathy (15 patients), connective tissue disease (8 patients), and polycystic kidney disease (4 patients). In 12 patients, the underlying cause remained undetected.

Concomitant ischemic heart disease was diagnosed in 25 patients (29%), while 21 patients (25%) were diagnosed with heart failure and qualified as New York Heart Association (NYHA) class II (6 patients, 7%) and NYHA class III (15 patients, 18%).

Patients under 18 years of age, patients on HD for a time period shorter than 3 months, and patients diagnosed with cancer or chronic viral hepatitis B and C were excluded from the study. The study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (KE-0254/190/2006).

**Treatment** **Hemodialysis** All study subjects underwent HD 3 times a week. Each procedure lasted from 3.5 to 4.5 hours. Capillary low-flux dialyzers were used; bicarbonate dialysate contained the calcium concentration of 1.5 mmol/ml in 24 patients (29%), and of 1.25 mmol/ml in the remaining 60 patients. A dialyzer blood flow rate varied between 230 and 400 ml/min (mean 315 ±23 ml/min), while a dialysate flow rate was 500 ml/min.

**Pharmacological treatment** Seventy-five patients (89%) received human recombinant erythropoietin. Seventy-two patients (86%) received hypertension medications: 26 patients (36%) received 1 medication, 34 patients (47%) – 2, and 12 patients (17%) – 3 different medications. The medications included convertase inhibitors (46 patients, 55%), calcium channel blockers (62; 74%), β-adrenergic blockers (35; 42%), and statins (37; 44%).

Fifty-two patients (64%) received a synthetic analog of vitamin $D_3$, 1-α hydroxycholecalciferol (alfacalcidol). The following weekly doses of the medication were used during 3 months before the assay: 8 patients (15%) received 0.25 μg, 12 (23%) – 0.75 μg, 11 (21%) – 1 μg, 14 (27%) – 1.5 μg, and 7 (14%) – 2.75 μg.

Seventy-nine patients (94%) received calcium carbonate, while 30 patients (35%) who had phosphorus levels above 5.5 mg/dl received aluminum hydroxide.

**Biochemical assays** All parameters were analyzed in spring.

Blood samples were obtained from the venous part of vascular access prior to HD and collected in the middle of the week. Samples were centrifuged according to the manufacturers' instructions. Sera were stored in –25°C until the assay.

We measured the concentrations of $25(OH)D_3$, asymmetric dimethylarginine (ADMA), interleukin 6 (IL-6), interleukin (IL-10), human soluble tumor necrosis factor receptor I (sTNF-RI), C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), albumin (alb), hemoglobin (Hb), urea, calcium (Ca), phosphorus (P), and intact parathormone (iPTH).

**TABLE 1** Demographic and biochemical characteristics of patients on long-term dialysis

| Parameter | Standard deviation | Median | Range |
|---|---|---|---|
| age (years) | 65.3 ±14.2 | 68 | 20–92 |
| sex (women/men) | 38/46 | | |
| time on HD (months) | 40 ±43.2 | 32.5 | 3–394 |
| Kt/V | 1.5 ±0.2 | 1.6 | 0.67–2.1 |
| BMI (kg/m$^2$) | 24.8 ±4.2 | 24.4 | 15.8–37.7 |
| nPCR (g/kg/day) | 1 ±0.2 | 1 | 0.5–1.7 |
| MAP (mm/Hg) | 87.2 ±13.3 | 86 | 58–123 |
| 25(OH)$D_3$ (ng/ml) | 15.4 ±7.2 | 14.1 | 2.9–41.1 |
| NT-proBNP (pg/ml) | 15,879.2 ±14,033.3 | 8281 | 402.9–35,000 |
| ADMA ($\mu$mol/l) | 0.5 ±0.3 | 0.5 | 0.009–1.4 |
| IL-6 (pg/ml) | 9.9 ±9 | 6.9 | 1.8–50.4 |
| IL-10 (pg/ml) | 1.5 ±3.1 | 0.8 | 0.004–22 |
| hs-CRP (mg/l) | 7.5 ±6.9 | 5.4 | 0.08–15.5 |
| iPTH (pg/ml) | 429.5 ±401 | 318.5 | 13.0–2100 |
| sTNF-RI (pg/ml) | 184,855.9 ±141,731.9 | 167,889 | 8860–8,928,650 |
| Ca × P (mg$^2$ × mg$^2$) | 41.9 ±11.5 | 41 | 21–68 |
| Ca (mmol/l) | 2.2 ±0.2 | 2.2 | 1.5–2.7 |
| P (mmol/l) | 1.6 ±0.5 | 1.6 | 0.5–2.9 |
| hemoglobin (g/dl) | 10.4 ±1.1 | 10.5 | 7.4–13.8 |
| albumin (g/dl) | 3.8 ±0.4 | 3.8 | 2.7–4.5 |
| CS | 6.3 ±2.5 | 6 | 2–15 |

Abbreviations: ADMA – asymmetric dimethylarginine, BMI – body mass index, Ca – calcium, CS – comorbidity score, HD – hemodialysis, hs-CRP – high-sensitivity C-reactive protein, IL-6 – interleukin 6, IL-10 – interleukin 10, iPTH – intact parathormone, Kt/V – adequacy of hemodialysis, MAP – mean arterial pressure, nPCR – normalized protein catabolic rate, NT-proBNP – N-terminal pro-B-type natriuretic peptide, P – phosphorus, sTNF-RI – human soluble tumor necrosis factor receptor I

Moreover, several scores and parameters were calculated for each patient: comorbidity score (CS) according to the scale published by Charlson et al.,[17] HD adequacy expressed by Kt/V parameter,[18] normalized protein catabolic rate,[19] body mass index (BMI), mean arterial pressure (MAP), and calcium-phosphorus product.

MAP was calculated on the basis of blood pressure measurement taken prior to HD in a horizontal position. The following formula was used: MAP = diastolic pressure + $^1/_3$(systolic pressure – diastolic pressure).

The following biochemical parameters were measured using an enzyme-linked immunosorbent assay: 25(OH)$D_3$ and ADMA (Immundiagnostik AG, Bensheim, Germany), IL-10 (Diaclone, Besancon, France), hs-CRP (IBL International GmbH, Hamburg, Germany),

IL-6 and sTNF-RI (R& D Systems Inc., Abingdon, United Kingdom).

NT-proBNP and iPTH were measured by an electrochemiluminescence immunoassay using Cobas 6000 system with e601 module (Roche Diagnostics, Mannheim, Germany)

The remaining parameters (alb, Hb, Ca, P) were measured using routine laboratory tests.

**Statistical analysis** The obtained results were analyzed using STATISTICA 7.1 (StatSoft, Poland) and presented as mean value ± standard deviation or median with range. Contingency tables as well as the $\chi^2$ test for independence were used to asses the potential differences or correlations between the analyzed parameters.

Because the Shapiro-Wilk test revealed skewed distribution of the analyzed parameters, further analysis of the potential differences between the study groups was conducted using nonparametric tests. The Mann-Whitney U test was used to compare two independent groups. Statistical association between the two variables was analyzed using the Spearman's correlation coefficient R. We adopted an inference error of 5% and a significance level of $P < 0.05$ as an indicator of statistically significant differences or correlations.

All patients signed written informed consent form after being fully informed about treatment options as well as the aims and limitations of the study.

**RESULTS** Patients' demographic and biochemical data are shown in TABLE 1. The mean concentration of 25(OH)$D_3$ in the entire study population was 15.4 ±7.2 ng/ml. Twenty-eight patients (34%) had severe vitamin $D_3$ deficiency, with 25(OH)$D_3$ levels below 12 ng/ml; 52 patients (61%) – moderate deficiency with 25(OH)$D_3$ levels of 12 to 30 ng/ml; finally, only 4 patients (5%) had normal vitamin $D_3$ levels above 30 ng/ml.

**TABLE 2** Correlations between 25-hydroxyvitamin $D_3$ and the analyzed parameters

| Parameter | Spearman R | *P* |
|---|---|---|
| CS | –0.19 | 0.07 |
| MAP | 0.04 | 0.73 |
| Kt/V | –0.11 | 0.32 |
| NT-proBNP | –0.21 | 0.07 |
| time on HD | 0.06 | 0.81 |
| nPCR | 0.16 | 0.15 |
| hemoglobin | 0.21 | 0.05[a] |
| albumin | 0.13 | 0.23 |
| IL-6 | –0.32 | 0.009[a] |
| IL-10 | –0.05 | 0.66 |
| ADMA | –0.26 | 0.03[a] |
| BMI | –0.19 | 0.11 |
| hs-CRP | –0.09 | 0.39 |
| sTNF-RI | –0.14 | 0.27 |
| alfacalcidol | 0.05 | 0.72 |

a $P < 0.05$

Abbreviations: see TABLE 1

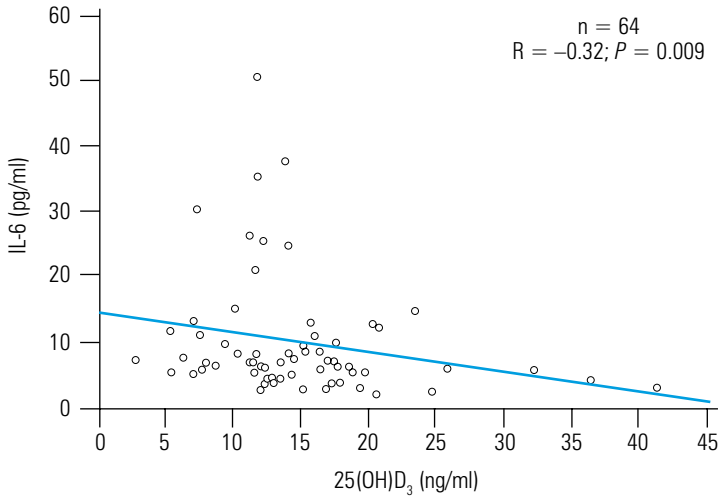


**FIGURE 1** Correlation between the levels of interleukin 6 (IL-6) and 25(OH)$D_3$

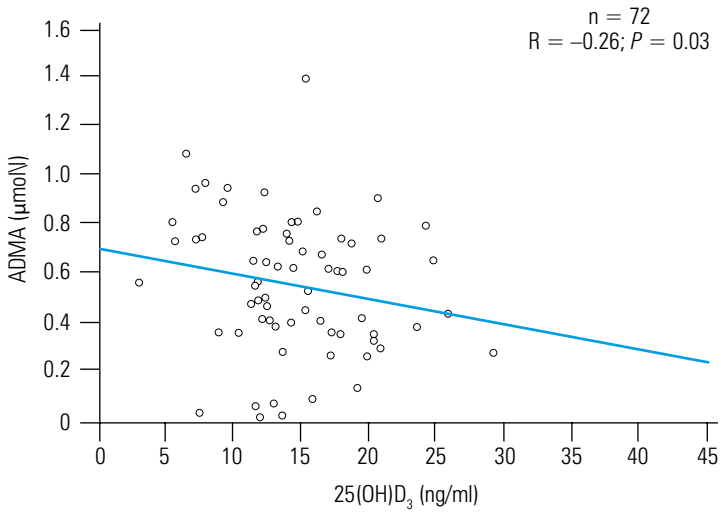


**FIGURE 2** Correlation between the plasma levels of asymmetric dimethylarginine (ADMA) and 25(OH)$D_3$

There was no statistically significant difference between men and women in 25(OH)$D_3$ concentrations (14.4 ±7.4 ng/ml vs. 16.1 ±6.8 ng/ml, respectively; $P = 0.06$).

Similarly, mean 25(OH)$D_3$ values in diabetic patients were similar to those observed in the remaining patient population (13.9 ±6.8 ng/ml vs. 15.9 ±7.3 ng/ml, $P = 0.11$).

Next, we analyzed 25(OH)$D_3$ concentrations in 3 age groups: group 1 – below 50 years of age (5 patients, 6%), group 2 – 50 to 65 years (29 patients, 34.5%), and group 3 – older than 65 (50 patients, 59.5%). Again, there was no statistically significant difference between the groups ($P = 0.81$). Respective values were: 13.9 ±5.1 ng/ml (group 1), 15.9 ±7.4 ng/ml (group 2) and 15.2 ±7.2 ng/ml (group 3).

Correlations between different parameters are presented in TABLE 2. We observed a negative correlation between 25(OH)$D_3$ and IL-6 (R = –0.31, $P = 0.009$; FIGURE 1) and ADMA (R = –0.26, $P = 0.03$; FIGURE 2). A tendency for negative correlation with 25(OH)$D_3$ was also observed for NT-proBNP (R = –0.21, $P = 0.07$) and CS (R = –0.19, $P = 0.06$). Moreover, we noted a positive correlation between 25(OH)$D_3$ and Hb (R = 0.21 $P = 0.05$, FIGURE 3).

In our study, the duration of long-term HD treatment did not influence the concentrations of 25(OH)$D_3$ ($P = 0.81$). Furthermore, we were unable to find any correlation between vitamin $D_3$ and MAP ($P = 0.73$) or any of the tested nutritional parameters. A weekly dose of alfacalcidiol did not correlate with vitamin $D_3$ status ($P = 0.72$). Likewise, no significant differences in the mean concentration of 25(OH)$D_3$ were found between the groups of patients who received and who did not receive alfacalcidiol (15.3 ±7.2 ng/ml vs. 15.5 ±7.23 ng/ml, respectively; $P = 0.85$).

**DISCUSSION** Our study showed that 95% of patients undergoing long-term HD were affected by various degrees of vitamin $D_3$ deficiency. Severe deficiency was detected in 34% of patients. Vitamin $D_3$ deficiency affected both short- and long-term dialysis patients to the same extent. Additionally, women were characterized by a tendency for lower 25(OH)$D_3$ concentrations than men, although the observed differences were not statistically significant (14.4 ±7.4 ng/ml vs. 16.1 ±6.8 ng/ml, $P = 0.06$). In contrast to these findings, significantly lower $D_3$ levels were detected in hemodialyzed women as reported by Erkal et al.[20] A similar tendency has been observed in the general population of women, with $D_3$ deficiency being more strongly pronounced in elderly women than in men.[12,21]

Our study did not show any significant relationship of $D_3$ status with morbidity; however, we observed that patients with a higher CS score calculated according to the scale published by Charlson et al.[17] had lower vitamin $D_3$ levels, although the reported differences were not statistically significant. Likewise, the mean concentration of

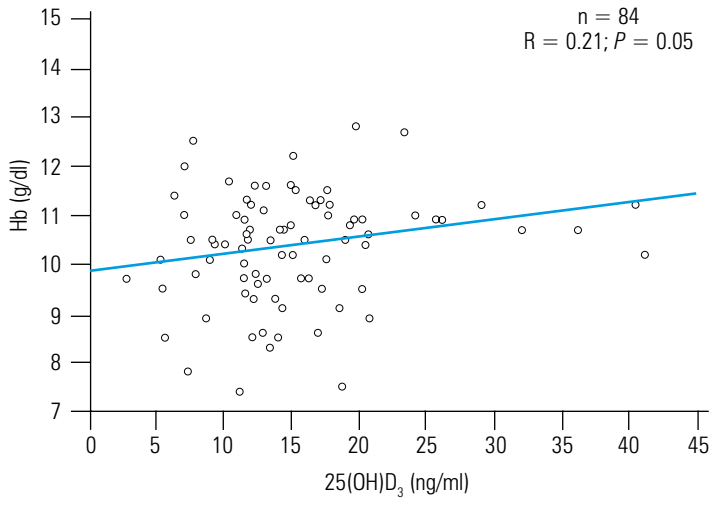


**FIGURE 3** Correlation between hemoglobin (Hb) and 25(OH)$D_3$

25(OH)$D_3$ in diabetic subjects did not differ significantly from the remaining patients. Interestingly, in contrast to our study, Matias et al.[14] reported that among patients treated with HD, diabetic subpopulation is characterized by significantly lower vitamin $D_3$ values as compared with nondiabetic counterparts.

Numerous factors may lead to decreased levels of vitamin $D_3$ in patients on long-term HD. Such deficiency may result from a decreased synthesis of vitamin $D_3$ in keratinocytes, since it is difficult to achieve an adequate sun exposure in these chronically ill patients.[22,23] Del Vaale et al.[22] noted that a particularly severe deficiency of vitamin $D_3$ in HD patients occurs in the fall and winter, when the levels of UVB are markedly reduced.

An age-related decrease in the concentration of keratinocyte cell membrane-derived 7-dehydrocholesterol is also an important contributor to vitamin $D_3$ deficiency in elderly patients.[24,25] It is even more relevant in the population of patients on HD, in which there is an increasing number of patients older than 65 years. Indeed, such patients constituted a majority in our study, while only 5% of our patients were younger than 55 years. Nevertheless, we were not able to detect any correlation between vitamin $D_3$ levels and patients' age. Our observation is in agreement with the previously reported study by Del Valle et al.[22] On the other hand, such correlation between age and depleted vitamin $D_3$ supply exists in the general population.[26,27]

Vitamin $D_3$ deficiency observed in patients on long-term HD is also a result of poor absorption of this fat-soluble vitamin in the digestive system, resulting from the lack of nutritional fat necessary for proper absorption.[2,3] Moreover, inadequate consumption of products rich in vitamin $D_3$ might have similar consequences. Generally, such products (e.g., fish and eggs) should be consumed 3 to 4 times a week to maintain proper vitamin $D_3$ levels.[2,4] However, intake of these products should be limited in patients with end-stage renal failure due to high phosphorus content.

Vitamin $D_3$ is synthesized in the skin and subsequently stored in the adipose tissue; excess body fat can hamper its release. Studies on the general population revealed decreased $D_3$ levels in individuals with BMI >30 kg/m$^2$ as compared to those with lower BMI values,[28] and a significant negative correlation between BMI and vitamin $D_3$ levels in the general population was reported by Melamed et al.[12] However, our study as well as studies published by other authors[16,29] do not support the correlation of vitamin $D_3$ levels with BMI and other nutritional parameters in the population of hemodialyzed patients. Interestingly, Matias et al.[14] reported that lower levels of albumin in hemodialyzed patients corresponded with lower levels of 25(OH)$D_3$.

Vitamin $D_3$ deficiency is often diagnosed in patients with congestive heart failure.[1,2,6] Such deficiency can lead to intracellular calcium depletion, and defective sarcomere shortening.[30] Cardiomyocytes express receptors for both vitamin $D_3$ and calbindin, a vitamin D-dependent calcium binding protein, which mediates transport of calcium ions into the cell.[31] Zittermann et al.[30] demonstrated that 25(OH)$D_3$ negatively correlated with N-terminal natriuretic peptide. In our study, we analyzed a possible correlation between vitamin $D_3$ and another natriuretic peptide, NT-proBNP, because its increased levels have been reported in patients with increased preload and with heart failure.[32,33] However, in our study, vitamin $D_3$ did not play any significant role in NT-proBNP release from cardiomyocytic granules.

Because vitamin $D_3$ protects endothelial cells by suppressing the proliferation and calcification, and by inhibiting the development of inflammation,[11,30,34] we analyzed the influence of 25(OH)$D_3$ on selected parameters of immune system activation. Although most of the results did not reach the significance level, a negative correlation of 25(OH)$D_3$ with IL-6 was observed. Interestingly, IL-6 is a potent initiator and regulator of acute inflammatory responses and supports the transformation of acute phase into chronic inflammatory state; its role in stimulating the development of atherosclerosis has also been described.[35] One of the possible proatherogenic mechanisms of IL-6 relies on its ability to upregulate the expression of adhesion molecules on endothelial cells, and therefore facilitating adhesion of leukocytes to the vascular wall and subsequent endothelial cell damage. Moreover, IL-6 as well as other proinflammatory cytokines are able to adversely affect blood vessel relaxation by suppressing the production of endothelial nitric oxide (NO) synthase.

An active form of vitamin $D_3$ has also been reported to affect the Th1/Th2 balance and increase the population of Th2 lymphocytes. IL-10 is one of the several cytokines produced by Th2 cells and can act not only as a potent anti-inflammatory but also antiatherogenic factor.[36] Nevertheless,

we did not find evidence for immunomodulatory function of vitamin $D_3$ in the population of hemodialyzed patients through the IL-10-related anti-inflammatory pathway.

Anemia affecting the HD population constitutes an independent risk factor for developing heart failure, as well as for increased cardiovascular mortality.[37] A study by Sim et al.[38] showed a negative correlation between vitamin $D_3$ deficiency and risk of anemia and increased requirement for erythropoietic factors, although the background of these correlations was not elucidated. Similarly, Patel et al.[39] observed a positive correlation between vitamin $D_3$ and Hb concentration in patients with chronic kidney disease. Our study confirmed these results.

ADMA is a prognostic marker of cardiovascular complications both in the general population and in a population of patients with progressive kidney disease.[40,41] ADMA is an endogenous inhibitor of NO synthase, and NO deficiency can manifest itself clinically as an increased total peripheral resistance leading to endothelial cell damage and subsequent progression to atherosclerosis.[42]

In our study, vitamin $D_3$ deficiency in hemodialyzed patients was accompanied by an increase in ADMA concentrations. To our knowledge, we have been the first to report this statistically significant correlation.

Interestingly, London et al.[43] studied a group of patients on long-term HD and noted that vitamin $D_3$ deficiency in these patients correlated with vascular stiffness and increased pulse pressure – symptoms possibly caused by ADMA affecting endothelial cells.

The current study extends the analysis of vitamin $D_3$ function beyond the field of calcium-phosphorus homeostasis. In our analysis, we included a broad panel of biochemical markers of immune system activation, nutritional status, and disease. The obtained results allow us to conclude that significant vitamin $D_3$ deficiency diagnosed in the majority of patients on long-term HD contributes to the development of chronic inflammation, decreased immunity, and anemia, setting the stage for endothelial damage. In our study, vitamin $D_3$ deficiency was not influenced by the duration of long-term HD therapy, patients' age or nutritional status.

**Acknowledgements** The study was supported by the Medical University of Lublin, Poland, Grant No. PW 449/2009.

## REFERENCES

1 Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune disease, cancers and cardiovascular disease. Am J Clin Nutr. 2004; 80 (6 Suppl): 1678S- 1688S.

2 Heaney RP. Vitamin D in health and disease. Clin J Am Soc Nephrol. 2008; 3: 1535-1541.

3 Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008; 88: 491S-499S.

4 Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol. 2009; 19: 73-78.

5 Jones G. Expanding role for vitamin D in chronic kidney disease: impotence of blood 25-(OH)-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha, 25-dihydroxyvitamin $D_3$. Semin Dial. 2007; 20: 316-324.

6 Zittermann A, Schleithoff SS, Tenderach G, et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure. J Am Coll Cardiol. 2003; 41: 105- 112.

7 Holick MF. Vitamin D: importance in prevention of cancers, type I diabetes, heart disease and osteoporosis. Am J Clin Nutr. 2004; 79: 362-371.

8 Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006; 38: 754-759.

9 Fournier A, Fardellone P, Achard JM, et al. Importance of vitamin D repletion in uraemia. Nephrol Dial Transplant. 1999; 14: 819-823.

10 Stumpf WE, Sar M, Reid FA, et al. Target cells for 1,25-dihydroxyvitamin $D_3$ in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. Science. 1979; 206: 1188-1190.

11 Bhalla AK, Clemens T, Amento E, et al. Specific high-affinity receptors for 1,25- dihydroxyvitamin $D_3$ in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab. 1983: 57: 13008-13110.

12 Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and risk of mortality in the general population. Arch Intern Med. 2008; 11; 168: 1629-1637.

13 Wolf M, Shah A, Gutierrez O, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007; 72: 1004-1013.

14 Matias PJ, Ferreira C, Jorge C, et al. 25-Hydroxyvitamin D3, arterial calcifications and cardiovascular risk markers in hemodialysis patients. Nephrol Dial Transplant. 2009; 24: 611-618.

15 Coen G. Vitamin D: an old prohormone with an emergent role in chronic kidney disease. J Nephrol. 2008: 21: 313-323.

16 González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol 2004; 24: 503-510.

17 Charlson ME, Popei P, Ales KL, et al. A new method of classifying comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-83.

18 Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V an analysis of error. J Am Soc Nephrol. 1993; 4: 1205-1213.

19 NKF-K/DOQI. Nutrition Work Group Clinical Practice Guidelines for nutrition in chronic renal failure. National Kidney Foundation. New York; 2001: 75-80.

20 Erkal MZ, Wilde J, Bilgin Y, et al. High prevalence of vitamin D deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: identification of risk factors. Osteoporos Int. 2006; 17: 1133-1140.

21 Napiórkowska L, Budlewski T, Jakubas-Kwiatkowska W, et al. Prevalence of low serum vitamin D concentration in an urban population of elderly women in Poland. Pol Arch Med Wewn. 2009; 119: 699-703.

22 Del Valle E, Negri AL, Aguirre C, et al. Prevalence of 25 (OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. Hemodial Int. 2007; 11: 315-321.

23 Pecovnik-Balon B, Jakopin E, Bevc S. Vitamin D as a novel non-traditional risk factor for mortality in hemodialysis patients. Ther Apher Dial. 2009; 13: 268-72.

24 MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin $D_3$. J Clin Invest. 1985; 76: 1536-1538.

25 Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. Lancet. 1989; 1: 1104-1105.

26 Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001; 22; 477-501.

27 Visser M, Deeg DJ, Puts MT, et al. Low serum concentration of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. Am J Clin Nutr. 2006; 86: 616-622.

28 Bell NH, Epstein S, Greene A, et al. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest. 1985; 76: 370-373.

29 Jean G, Charra B, Chazot C. Vitamin D deficiency and associated factors in hemodialysis patients. J Ren Nutr. 2008; 18: 395-399.

30 Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr. 2005; 94: 483-92.

31 Bronner F. Recent developments in intestinal calcium absorption. Nutr Rev. 2009; 62: 109-113.

**32** Hammerer-Lercher A, Puschendorf B, Mair J. Cardiac natriuretic peptides: new laboratory parameters in heart failure patients. Clin Lab. 2001; 47: 265-277.

**33** Hunt PJ, Richards AM, Nicholls MG, et al. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin Endocrinol (Oxf). 1997; 47: 287-296.

**34** Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs – a brief overview. Mol Cell Biochem. 2003; 253: 247-254.

**35** Łukaszewicz M, Mroczko B, Szmitkowski M. [Clinical relevance of interleukin 6 (IL-6) as a prognostic factor in cancer]. Pol Arch Med Wewn. 2007; 117: 247-251. Polish.

**36** Li AC, Glass CK. The macrophage foam cell as a target of therapeutic intervention. Nat Med. 2002; 8: 1235-1242.

**37** Foley RN, Parfrey PS, Harnett JD, et al. The impact of anemia on cardiomyopathy morbidity, and mortality in end stage renal disease. Am J Kidney Dis. 1996; 28: 53-61.

**38** Sim JJ, Lac PT, Liu IL, et al. Vitamin D deficiency and anemia: a cross-sectional study. Ann Hematol. 2009; 89: 447-452.

**39** Patel NM, Gutierrez OM, Andress DL, et al. Vitamin D deficiency and anemia in early chronic kidney disease. Kidney Int. 2010; 77: 715-720.

**40** Böger RH, Zoccalli C. ADMA – a novel risk factor that explains excess cardiovascular event rate in patients with end-stage renal disease. Atherosclerosis. 2003; 4: 23-28.

**41** Kielstein J T, Zoccali C. Asymmetric dimethylarginine: a cardiovascular risk factor and a uremic toxin coming of age? Am J Kidney Dis. 2005; 46: 186-191.

**42** Cooke JP. Asymmetrical dimethylarginine. The Uber marker? Circulation. 2004; 109: 1813-1818.

**43** London GM, Guérin AP, Verbeke FH, et al. Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. J Am Soc Nephrol. 2007; 18: 613-620.

ARTYKUŁ ORYGINALNY

# Wpływ witaminy $D_3$ na wybrane parametry biochemiczne stanu odżywienia, zapalenia oraz uszkodzenia układu sercowo-naczyniowego u pacjentów przewlekle hemodializowanych

Anna Bednarek-Skublewska[1], Agata Smoleń[2], Andrzej Jaroszyński[1], Wojciech Załuska[1], Andrzej Książek[1]

1 Katedra i Klinika Nefrologii, Uniwersytet Medyczny w Lublinie, Lublin
2 Zakład Matematyki i Biostatystyki Medycznej, Uniwersytet Medyczny w Lublinie, Lublin

**SŁOWA KLUCZOWE**

asymetryczna dimetylarginina, hemodializa, witamina $D_3$, zapalenie

**STRESZCZENIE**

**WPROWADZENIE** Witamina $D_3$ ma różnorodne działanie biologiczne, wykraczające poza obszar homeostazy wapnia i fosforu, które przyczyniają się do prawidłowego funkcjonowania organizmu.

**CELE** Celem badania była ocena zasobów witaminy $D_3$ oraz analiza ich związku ze stanem odżywienia, aktywnością immunologiczną i wybranymi parametrami uszkodzenia układu sercowo-naczyniowego u pacjentów przewlekle hemodializowanych.

**PACJENCI I METODY** W grupie 84 pacjentów (średni wiek 65 lat, czas leczenia hemodializami 32,5 miesiąca) oznaczono 25 hydroksywitaminę $D_3$ ($25(OH)D_3$) i badano jej związek z następującymi parametrami: albuminą, wskaźnikiem masy ciała, hemoglobiną (Hb), interleukiną 6 (IL-6), interleukiną 10, białkiem C-reaktywnym, asymetryczną dimetylargininą (ADMA), N-końcowym mózgowym peptydem natriuretycznym (NT-proBNP), oraz z punktacją chorobowości (*comorbidity score*).

**WYNIKI** Średnie stężenie $25(OH)D_3$ wynosiło 15,4 ±7,2 ng/ml i tylko u 5% pacjentów stężenie $25(OH)D_3$ przekraczało 30 ng/ml, wartość uznaną za prawidłową. Nie zaobserwowano istotnych różnic w średnich wartościach stężeń $25(OH)D_3$ między kobietami i mężczyznami ($P = 0,06$). Odnotowano ujemne zależności $25(OH)D_3$ z IL-6 ($R = –0,31$; $P = 0,009$) i ADMA ($R = –0,26$; $P = 0,03$) oraz dodatnią korelację z Hb ($R = 0,21$; $P = 0,05$). Nie wykazano związku witaminy $D_3$ ze stanem odżywienia.

**WNIOSKI** Stwierdzany u większości pacjentów przewlekle hemodializowanych znaczny niedobór zasobów witaminy $D_3$ przyczynia się do rozwoju przewlekłego zapalenia, niedokrwistości oraz pośrednio do uszkodzenia śródbłonka.

Adres do korespondencji:
dr med. Anna Bednarek-Skublewska, Katedra i Klinika Nefrologii, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-950 Lublin, tel.: 12-81-724-47-35, fax: 12-81-724-47-35, e-mail: anna.bednarek@diaverum.com
**Praca wpłynęła:** 25.01.2010.
**Przyjęta do druku:** 06.04.2010.
**Nie zgłoszono sprzeczności interesów.**
Pol Arch Med Wewn. 2010; 120 (5): 167-174