J Korean Med Sci 2009; 24 (Suppl 1): S109-14
ISSN 1011-8934
DOI: 10.3346/jkms.2009.24.S1.S109

Vitamin D Levels and Their Relationship with Cardiac Biomarkers in Chronic Hemodialysis Patients

Vitamin D insufficiency may be associated with cardiovascular (CV) mortality in HD patients. To test this hypothesis, we cross-sectionally measured 25-hydroxyvitamin D (25D), 1,25-dihydroxyvitamin D (1,25D), cardiac troponin T (cTnT), and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) in chronic HD patients. Sixty-five patients (M:F=31:34, age 52.2±13.2 yr, DM 41.5%) were selected. Along with the expected low levels of 1,25D, 59 (90.8%) patients had 25D insufficiency (<30 ng/mL) among whom 15 (23.1%) were 25D deficient (<10 ng/mL). The 25D levels showed a negative correlation with cTnT levels (Spearman's ρ=-0.44, p<0.01) but not with NT-pro-BNP levels (Spearman's ρ=-0.17, p=0.17). The 1,25D levels, however, did not show any relationship with either cTnT or NT-pro-BNP. In multivariate analysis, being male and having low levels of 25D were independent risk factors associated with cTnT elevation (β=0.44, p<0.01 and β=-0.48, p<0.01, respectively). In conclusion, not only 1,25D but also 25D are commonly decreased in HD patients. Lower 25D levels appear to be associated with cTnT elevation, predicting worse CV outcome, and are possible to involve cardiac hypertrophy or coronary artery disease.

Key Words : *Cardiovascular Diseases; Renal Dialysis; Troponin; Vitamin D*

Seong Jae Hur, Dong Min Kim, Kyung Hun Lim, Sun-Hwa Yoon, Hyun Chul Chung, Jong Soo Lee, and Jongha Park

Division of Nephrology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

Received : 22 August 2008
Accepted : 19 December 2008

Address for correspondence
Jongha Park, M.D.
Division of Nephrology, Ulsan University Hospital, University of Ulsan College of Medicine, 290-3 Jeonha-dong, Dong-gu, Ulsan 682-714, Korea
Tel : +82.52-250-8851, Fax : +82.52-251-8235
E-mail : nepholic@yahoo.co.kr

*This work was funded by Ulsan University Hospital (Biomedical Research Centre Promotion Fund, UUH-2007-020).

INTRODUCTION

It is observed that patients with moderate to severe chronic kidney disease (CKD) demonstrate profoundly low levels of 1,25-dihydroxyvitamin D (1,25D) and are also at a high risk of 25-hydroxyvitamin D (25D) deficiency (1, 2). Some observational studies have revealed that active vitamin D therapy is independently associated with improved survival among hemodialysis (HD) patients (3, 4). Moreover, it was recently reported that decreased 25D levels are also associated with increased early overall or cardiovascular (CV) mortality among incident HD patients (5). These results suggest that vitamin D insufficiency is directly related to CV outcome in HD patients. We investigated the relationship of the levels of 25D and 1,25D in the blood with those of cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)-biochemical surrogates of CV outcome in HD patients (6-9).

MATERIALS AND METHODS

Patients

A total of 95 chronic HD patients from our renal unit were screened. The inclusion criteria were: 1) maintenance HD for more than 3 months; 2) no ischemic heart disease (IHD) confirmed by electrocardiography (ECG) or coronary angiography; 3) no recent chest pain or discomfort suggesting IHD; 4) no dyspnea on exertion (New York Heart Association functional class II or above) or orthopnea; 5) no pulmonary edema detected by chest radiography; 6) ejection fraction of at least 40% as indicated by the latest echocardiography; 7) no cerebrovascular, peripheral vascular, chronic obstructive pulmonary, chronic liver or malignant disease; 8) no active vitamin D therapy. After screening, 65 patients were recruited for the study. The study was approved by the local Institutional Review Board and all the subjects provided their informed consent.

Clinical and laboratory measurements

This study was conducted in summer (August 2007). We recorded the clinical characteristics, including gender, age, causes of end stage renal disease (ESRD), duration of HD, height, dry weight and pre/post-HD blood pressure (BP). Laboratory analyses were performed prior to the first HD session of the week; they included determination of 25D, 1,25D, cTnT, NT-pro-BNP, hemoglobin, cholesterol, albumin, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, total calcium, phosphate, intact parathyroid hormone (iPTH), and

high-sensitivity C-reactive protein (hs-CRP). Total serum calcium levels were corrected using the serum albumin level. Single pool Kt/V (spKt/V) and normalized protein equivalent of total nitrogen appearance (nPNA) were calculated by the three-point method of the urea kinetic model. Left ventricular hypertrophy (LVH) was estimated by the Sokolow-Lyon voltage (SV1 plus RV5 or V6 in ECG) (10).

The blood samples for 25D, 1,25D, cTnT, and NT-pro-BNP determination were immediately centrifuged and the serum stored at -70℃. The samples were analyzed simultaneously. 25D and 1,25D were estimated using radioimmunoassay (Biosource, Nivelles, Belgium and Immunodiagnostic System Inc., AZ, U.S.A.). The manufacturer's instructions stated the ranges of 25D and 1,25D in healthy controls to be 7.6-75 ng/mL and 20.2-46.2 pg/mL, respectively. NT-pro-BNP was estimated using the Elecsys proBNP immunoassay (Roche Diagnostics, Indianapolis, IN, U.S.A.). cTnT was estimated using a third-generation immunoassay (Elecsys Troponin T STAT immunoassay; Roche Diagnostic, Indianapolis, IN, U.S.A.).

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as the mean±standard deviation (SD). Because 25D, 1,25D, NT-pro-BNP, cTnT, and hs-CRP were positively skewed, they were expressed as medians (interquartile range, IQR). The correlation between these variables was verified by Spearman's correlation analysis. For risk factor analysis, univariate and multivariate regression analyses were performed after log transformation (log_{10}) of the skewed data, as appropriate. A multivariate regression analysis was performed using a stepwise approach, by constructing a model based on covariates ($p<0.10$) related to cTnT as indicated by the univariate analysis. The analyses were conducted using the SPSS software, version 13.0 (SPSS Inc., Chicago, IL, U.S.A.). p value lower than 0.05 was considered statistically significant.

Table 1. Baseline characteristics and laboratory data (n=65)

Age (yr)	52.2±13.2
Gender	M:F=31:34
DM (%)	41.5%
BMI (kg/m^2)	22.8±3.0
HD duration (months)	32±33
Corrected total calcium (mg/dL)	9.0±0.7
Phosphate (mg/dL)	4.6±1.7
Intact PTH (pg/mL)	59 (26-116)
Total cholesterol (mg/dL)	136±34
Albumin (g/dL)	3.9±0.4
Creatinine (mg/dL)	10.2±2.9
hsCRP (mg/dL)	0.04 (0.02-0.14)
spKt/V	1.5±0.3
nPNA (g/kg/day)	1.0±0.3
25D (ng/mL)	14.6 (10.4-21.6)
1,25D (pg/mL)	3.1 (3.0-4.3)

Data are expressed as mean±standard deviation or median (interquatile range) as appropriate.
DM, diabetes mellitus; BMI, body mass index; HD, hemodialysis; PTH, parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; spKt/V, single-pool Kt/V; nPNA, normalized protein equivalent of total nitrogen appearance; 25D, 25-hydroxyvitamin D; 1,25D, 1,25-dihydroxyvitamin D.

RESULTS

25D and 1,25D levels in HD patients

Baseline characteristics and laboratory data of 65 patients are shown in Table 1. The median 25D concentration was 14.6 ng/mL (IQR 10.4-21.6). Thirty (46.1%) patients had 1,25D levels below the detection limit (<3.0 pg/mL), and the median 1,25D concentration was 3.1 pg/mL (IQR 3.0-4.3). The distributions of 25D and 1,25D are shown in Fig. 1. Fifty-nine (90.8%) patients were identified with 25D insufficiency (<30 ng/mL) and 15 (23.1%) with 25D deficiency (<10 ng/mL) (5). Although there is no cutoff value for 1,25D deficiency, our patients had much lower levels compared with the range of 20.2-46.2 pg/mL in healthy controls provided by the manufacturer. The 1,25D concentration was weakly but significantly related to 25D concentration (Spearman's $\rho=0.36$, $p<0.01$).

25D/1,25D levels and mineral/nutritional parameters

Mineral parameters, including corrected total calcium, phosphate, and iPTH levels correlated poorly with both 25D and 1,25D levels (Table 2). This suggests that although serum levels of calcium, phosphorus, and iPTH are biologically linked with vitamin D metabolism and are traditionally used to identify vitamin D deficiency, this relationship is not apparent in HD patients. Among the nutritional parameters, 25D levels correlated with serum albumin ($\rho=0.47$, $p<0.01$) and creatinine ($\rho=0.42$, $p<0.01$) but 1,25D levels did not.

Table 2. Correlation between 25D/1,25D and mineral/nutritional parameters (n=65)

	25D		1,25D	
	Spearman's ρ	p value	Spearman's ρ	p value
Corrected tCa	-0.08	0.53	0.04	0.74
Phosphate	0.10	0.44	0.09	0.47
iPTH	0.20	0.12	0.13	0.32
Cholesterol	0.05	0.68	-0.21	0.10
Albumin	0.47	<0.01	0.03	0.84
Creatinine	0.42	<0.01	-0.02	0.87
nPNA	0.22	0.10	0.06	0.65

25D, 25-hydroxyvitamin D; 1,25D, 1,25-dihydroxyvitamin D; tCa, total calcium; iPTH, intact parathyroid hormone; nPNA, normalized protein equivalent of total nitrogen appearance.

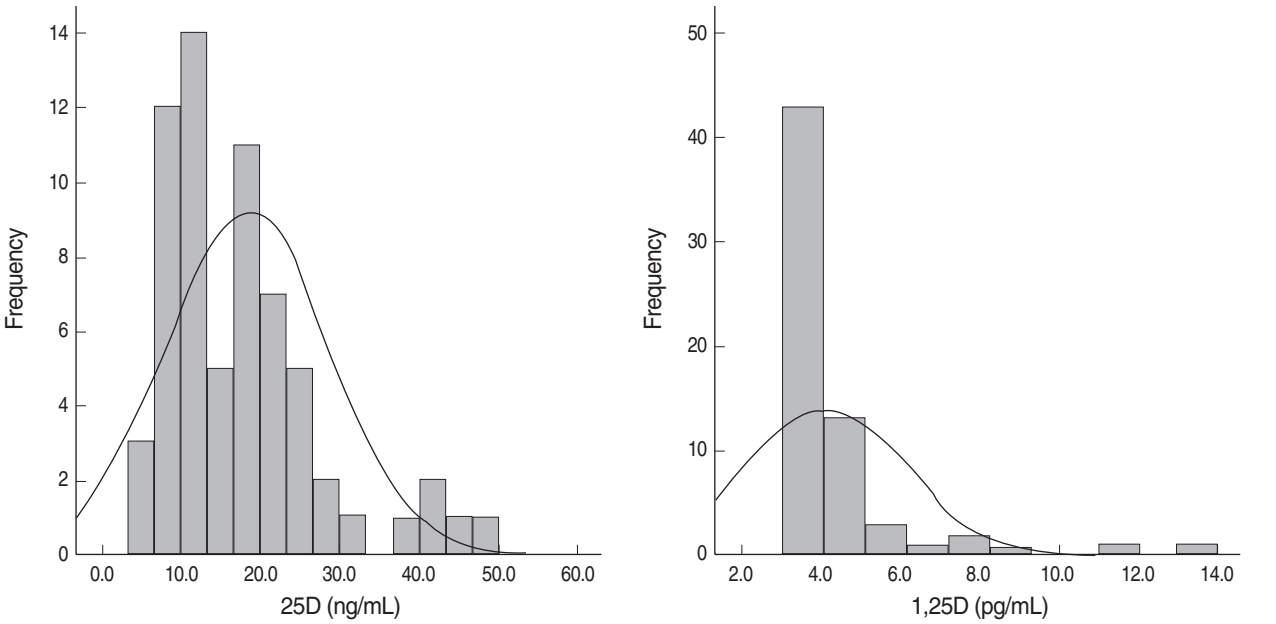

Fig. 1. Distribution of 25D and 1,25D in the study population (n=65). Median 25D concentration was 14.6 ng/mL (IQR 10.4-21.6), and median 1,25D concentration was 3.1 pg/mL (IQR 3.0-4.3).

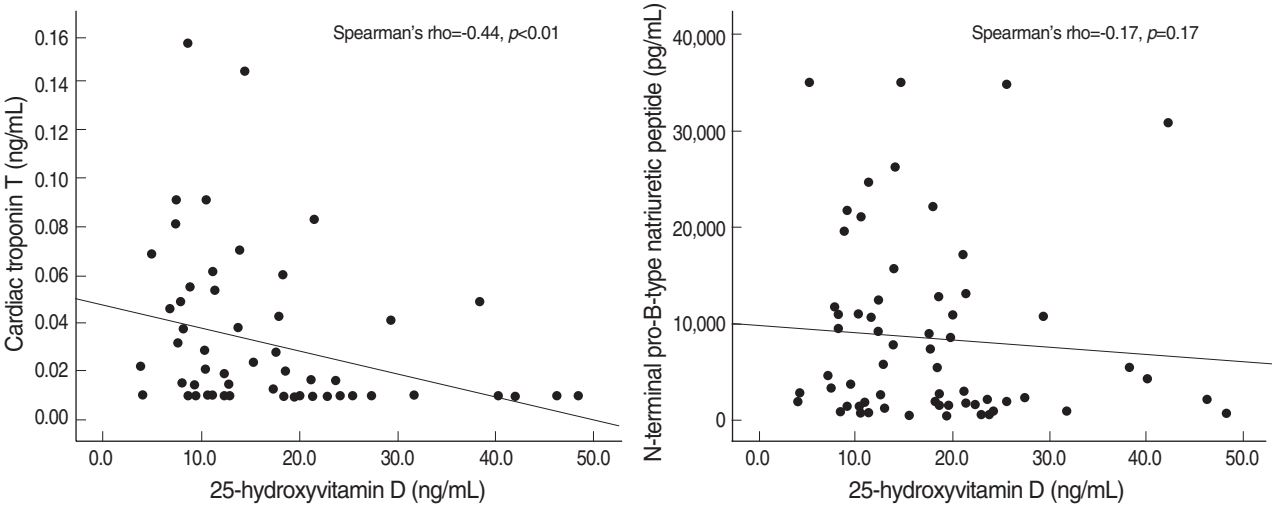

Fig. 2. Relationship between 25D concentration and cTnT/NT-pro-BNP levels (n=65). 25D concentration shows negative correlation with cTnT levels but not with NT-pro-BNP levels.

Relationship between 25D/1,25D and cTnT/NT-pro-BNP

The median cTnT concentration was 0.02 ng/mL (IQR 0.01-0.04), and the median NT-pro-BNP concentration was 4,165 pg/mL (IQR 1,625-11,865). The 25D level was negatively correlated with cTnT levels (ρ=-0.44, p<0.01) but not with NT-pro-BNP levels (ρ=-0.17, p=0.17) (Fig. 2). However, 1,25D levels did not show any relationship with either cTnT or NT-pro-BNP (ρ=-0.14, p=0.27 and ρ=-0.25, p=0.06, respectively). Because pre-HD cTnT and NT-pro-BNP level might have been influenced by a degree of volume overload, we analyzed the effect of ulrafiltration amount/dry weight (UF/DW) on both parameters. If determined DW was optimal, UF/DW could represent excessive fluid accumulation for inter-dialytic period. cTnT or NT-pro-BNP level was not associated with UF/DW (ρ=-0.01, p=0.95 and ρ=0.17, p=0.18, respectively), which meant that the relationship between 25D or 1,25D and cTnT or NT-pro-BNP level was not confounded by UF/DW.

We analyzed the risk factors for elevated cTnT levels, including the following variables: 25D concentration, age, gender, diabetes as a cause of ESRD, HD duration, body mass index (BMI), pre/post-HD systolic and diastolic BP, hemoglobin, cholesterol, albumin, BUN, creatinine, alkaline phosphatase,

Table 3. Univariate and multivariate regression analysis for log cTnT levels (n=65)

Risk factors	β	*p* value
Univariate analysis		
Age	0.16	0.20
Log iPTH	-0.33	<0.01
Log hs-CRP	0.27	0.03
spKt/V	-0.30	0.02
nPNA	-0.28	0.03
Log 25D	-0.36	<0.01
Multivariate analysis		
Male	0.44	<0.01
Log 25D	-0.48	<0.01
γ^2	0.31	
SEE	0.33	

Because cTnT, iPTH, hs-CRP, and 25D are positively skewed, a log transformation was performed for them before analysis. β is standardized coefficient of regression.
cTnT, cardiac troponin T; iPTH, intact parathyroid hormone; hs-CRP, high-sensitivity C-reactive protein; spKt/V, single-pool Kt/V; nPNA, normalized protein equivalent of total nitrogen appearance; 25D, 25-hydroxyvitamin D.

corrected total calcium, phosphate, iPTH, hs-CRP, spKt/V, nPNA, the Sokolow-Lyon voltage and UF/DW. It was observed that males had higher cTnT levels than females (0.03 ng/mL [IQR, 0.01-0.05] vs. 0.01 ng/mL [IQR, 0.01-0.02], p=0.01). Diabetic patients had higher cTnT levels than the others (0.04 ng/mL [IQR, 0.01-0.06] vs. 0.01 ng/mL [IQR, 0.01-0.03], p<0.01). In univariate regression analysis, log 25D, log iPTH, log hsCRP, spKt/V, and nPNA showed a correlation with log cTnT (p value<0.1). Furthermore, in a multivariate regression model including age, gender, diabetes, and the above variables, being male and having low log 25D concentration were independent risk factors associated with an increase in the log cTnT value (β=0.44, p<0.01 and β=-0.48, p<0.01, respectively) (Table 3).

DISCUSSION

The present study showed that not only 1,25D but also 25D were profoundly insufficient in Korean HD patients. Lower serum levels of 25D were associated with increased cTnT levels but not with increased NT-pro-BNP levels; this finding was independent of age, diabetes, standard nutritional and inflammatory factors, and mineral parameters. 1,25D, the biologically active form of vitamin D was not related to both cTnT and NT-pro-BNP.

Observations from previous studies suggest that 25D insufficiency or deficiency is common in CKD patients. In the United States, only 29% and 17% of patients with moderate and severe CKD (1), and 22% of incident HD patients had a sufficient 25D level (>30 ng/mL) (5). Our results show that the median 25D concentration was 14.6 ng/mL (IQR 10.4-21.6), and only 9.2% patients showed 25D levels above 30 ng/mL. Comparing the result of incident HD patients in the United States (5) with those in Korea, 25D deficiency seems to be more frequent in our cohort despite the younger age (51.6±12.9 vs. 63±15 yr) and absence of black patients (0 vs. 32%). It should be noted that 25D levels in this study were measured in summer, when sunlight exposure is the highest for the year. Hence, the severity of 25D insufficiency may be more profound in winter. 25D is derived from conversion of calciferol (cholecalciferol or ergocalciferol) in the liver. Cholecalciferol is produced by the skin on exposure to UVB light, and cholecalciferol or ergocalciferol can be obtained from dietary sources such as fortified cereals, dairy products, fish oil, and egg yolk. In CKD patients, decrease in both sunlight exposure and dietary intake may be a main cause of 25D insufficiency. However, it is noteworthy that while 25D production by the liver does not depend on normal renal function, the cutaneous production of cholecalciferol is impaired in uremia (11). As expected, 1,25D level was severely decreased. 1,25D level was partially related with 25D level (ρ=0.36, p<0.01). In ESRD, because 1α-hydroxylase is deficient and is not normally regulated, 1,25D level may be more dependent on the precursor level, 25D.

We demonstrated that 25D levels are negatively associated with cTnT levels, and this finding is independent of other CV risk factors. Usually, cTnT is considered as a marker of ongoing myocardial damage (12) and NT-pro-BNP, a marker of left ventricular overload (13); both have a significant prognostic value in predicting CV mortality in patients with ESRD (6-9). In this regard, our observation is encouraging from 2 viewpoints. First, the 25D insufficiency may be related to high CV mortality in HD patients. Second, the 25D insufficiency may also be partly responsible for myocardial hypertrophy or coronary artery disease in HD patients. It is worth noting that the elevation of cTnT levels was correlated with 25D levels but not with 1,25D (bioactive form of vitamin D) levels. In our opinion, the decrease in 25D may cause more profound 1,25D deficiency as describe above, and then may result in cTnT elevation. The reason that 1,25D level was not associated with cTnT level might be that almost all patients had very low concentration of 1,25D, which was below the limit of detection in a half of the patients. However, it is speculated that 25D itself has important biological effects on the CV system. Although kidney is the major organ that converts 25D to 1,25D by 1α-hydroxylase, many other cells, including vascular smooth muscle and endothelial cells, also express 1α-hydroxylase (14, 15). 1,25D, synthesized from the circulating 25D in these cells, binds the local vitamin D receptor (VDR) in the autocrine/paracrine pathways. 25D circulates at a concentration about 1,000-fold higher than that of 1,25D; this suggests that adequate 25D levels may also be necessary, especially for cells that rely on autocrine/paracrine pathways. However, this aspect will require investigation.

In a prospective cohort of HD patients, vitamin D insufficiency was associated with an increased rate of early CV mortality (5). Observational studies have indicated that CV outcomes associated with active vitamin D therapy have a significant advantage (3, 4). On the other hand, the recent meta-analysis of 76 randomized trials found no good evidence that vitamin D compounds reduced risk for death, bone pain, vascular calcification, or need for parathyroidectomy in patients with CKD (16). Hence, the available evidences are debatable, and it is difficult to conclude whether there exists a definite relationship between vitamin D insufficiency and CV mortality, and whether active vitamin D therapy would be favourable for reducing CV mortality. However, some mechanisms may explain the link between vitamin D insufficiency and elevated cTnT levels. First, vitamin D may suppress myocardial hypertrophy; calcitriol was shown to antagonize endothelin-stimulated hypertrophy in neonatal rat cardiomyocytes (17). Clinical studies have revealed that intravenous calcitriol produces a significant regression of the left ventricular mass index and concomitant reductions in plasma iPTH, angiotensin II, and arterial natriuretic peptide (18). However, it is unclear whether vitamin D reduces cardiac hypertrophy by itself via VDR or by reducing iPTH. Second, vitamin D may affect arterial cells. As mentioned above, vascular smooth muscle cells and endothelial cells have 1α-hydroxylase and express VDR (14, 15). Putative vascular effects of vitamin D are wide-ranging, including modulation of smooth muscle cell proliferation (19, 20), inflammation (21), and thrombosis (22). Hence, vitamin D insufficiency may be involved in the progression of coronary artery disease. In this study, unlike the cTnT level, 25D or 1,25D did not related to NT-pro-BNP level. cTnT is more sensitive and specific to myocardial injury than NT-pro-BNP. NT-pro-BNP is dependent on volume state rather than direct myocardial damage. If vitamin D deficiency causes myocardial injury via above mechanisms, it could be related more closely to cTnT level than to NT-pro-BNP level. However, it could not be excluded that the statistical power of our study might be weak to elucidate the relationship between vitamin D and NT-pro-BNP level.

There are several limitations to this study. First, this is a cross-sectional study using cardiac biomarkers as surrogates of CV outcome. Selection bias and residual confounding may also have contributed to the results. It is possible that the more malnourished patient had lower vitamin D levels, and that the increased cTnT levels were associated with antecedent inflammation-malnutrition syndrome in HD patients. We measured biochemical parameters only one time. The intra- and inter-assay coefficient of variation of cTnT were 1.1-3.4% and 1.7-5.6%, respectively. But the reproducibility of the observed relationship is still doubtful. Second, we did not evaluate echocardiographic parameters such as left ventricular mass index and transmitral flow velocity to mitral annular velocity ratio (E/E′) which reflects left ventricular end diastolic pressure at the time of study. This is major limitation of the study. If this had been done, understanding the role of vitamin D in the CV system would have become clearer. Third, we did not evaluate residual renal function in all participants. Because cTnT and NT-pro-BNP level may be affected by residual renal function, the possibility of confounding by it should be noted. However, the strength of this study is in the meticulous patient selection: we included only ambulatory patients without documented IHD, CHF, or co-morbidities. Therefore, confounding of vitamin D or cardiac biomarker levels by underlying heart disease already existed and other chronic illness may have been minimal within this study.

In conclusion, the levels of 25D as well as those of 1,25D are commonly low and correlate poorly with serum calcium, phosphate, and iPTH in HD patients. The lower 25D levels appear to be associated with cTnT elevation, predicting worse CV outcome, and is possible to involve cardiac hypertrophy or coronary artery disease. The impact of vitamin D insufficiency on the CV system is important issue in CKD and further investigation should be required in this regard.

REFERENCES

1. LaClair RE, Hellman RN, Karp SL, Kraus M, Ofner S, Li Q, Graves KL, Moe SM. *Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States*. *Am J Kidney Dis 2005; 45: 1026-33*.
2. Ishimura E, Nishizawa Y, Inaba M, Matsumoto N, Emoto M, Kawagishi T, Shoji S, Okuno S, Kim M, Miki T, Morii H. *Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure*. *Kidney Int 1999; 55: 1019-27*.
3. Shoji T, Shinohara K, Kimoto E, Emoto M, Tahara H, Koyama H, Inaba M, Fukumoto S, Ishimura E, Miki T, Tabata T, Nishizawa Y. *Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population*. *Nephrol Dial Transplant 2004; 19: 179-84*.
4. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo CA Jr, Thadhani R. *Activated injectable vitamin D and hemodialysis survival: a historical cohort study*. *J Am Soc Nephrol 2005; 16: 1115-25*.
5. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R. *Vitamin D levels and early mortality among incident hemodialysis patients*. *Kidney Int 2007; 72: 1004-13*.
6. Mallamaci F, Zoccali C, Parlongo S, Tripepi G, Benedetto FA, Cutrupi S, Bonanno G, Fatuzzo P, Rapisarda F, Seminara G, Stancanelli B, Bellanuova I, Cataliotti A, Malatino LS. *Troponin is related to left ventricular mass and predicts all-cause and cardiovascular mortality in hemodialysis patients*. *Am J Kidney Dis 2002; 40: 68-75*.
7. deFilippi C, Wasserman S, Rosanio S, Tiblier E, Sperger H, Tocchi M, Christenson R, Uretsky B, Smiley M, Gold J, Muniz H, Badalamenti J, Herzog C, Henrich W. *Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and car-*

diomyopathy in patients undergoing long-term hemodialysis. JAMA 2003; 290: 353-9.

8. Iliou MC, Fumeron C, Benoit MO, Tuppin P, Calonge VM, Moatti N, Buisson C, Jacquot C. *Prognostic value of cardiac markers in ESRD: Chronic Hemodialysis and New Cardiac Markers Evaluation (CHANCE) study. Am J Kidney Dis 2003; 42: 513-23.*
9. Satyan S, Light RP, Agarwal R. *Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. Am J Kidney Dis 2007; 50: 1009-19.*
10. Sokolow M, Lyon TP. *The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949; 37: 161-86.*
11. Jacob AI, Sallman A, Santiz Z, Hollis BW. *Defective photoproduction of cholecalciferol in normal and uremic humans. J Nutr 1984; 114: 1313-9.*
12. Setsuta K, Seino Y, Ogawa T, Arao M, Miyatake Y, Takano T. *Use of cytosolic and myofibril markers in the detection of ongoing myocardial damage in patients with chronic heart failure. Am J Med 2002; 113: 717-22.*
13. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. *Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135: 825-32.*
14. Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M. *Extrarenal expression of 25-hydroxyvitamin d (3)-1 alpha-hydroxylase. J Clin Endocrinol Metab 2001; 86: 888-94.*
15. Somjen D, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. *25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation 2005; 111: 1666-71.*
16. Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GF. *Meta-analysis: vitamin D compounds in chronic kidney disease. Ann Intern Med 2007; 147: 840-53.*
17. Wu J, Garami M, Cheng T, Gardner DG. *1,25 (OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. J Clin Invest 1996; 97: 1577-88.*
18. Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK. *Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. Am J Kidney Dis 1999; 33: 73-81.*
19. Carthy EP, Yamashita W, Hsu A, Ooi BS. *1,25-Dihydroxyvitamin D3 and rat vascular smooth muscle cell growth. Hypertension 1989; 13: 954-9.*
20. Mitsuhashi T, Morris Jr RC, Ives HE. *1,25-dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. J Clin Invest 1991; 87: 1889-95.*
21. Rigby WF, Denome S, Fanger MW. *Regulation of lymphokine production and human T lymphocyte activation by 1, 25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. J Clin Invest 1987; 79: 1659-64.*
22. Aihara K, Azuma H, Akaike M, Ikeda Y, Yamashita M, Sudo T, Hayashi H, Yamada Y, Endoh F, Fujimura M, Yoshida T, Yamaguchi H, Hashizume S, Kato M, Yoshimura K, Yamamoto Y, Kato S, Matsumoto T. *Disruption of nuclear vitamin D receptor gene causes enhanced thrombogenicity in mice. J Biol Chem 2004; 279: 35798-802.*