See corresponding editorial on page 731.

See corresponding CME exam on page 925.

Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial[1–3]

Stefanie S Schleithoff, Armin Zittermann, Gero Tenderich, Heiner K Berthold, Peter Stehle, and Reiner Koerfer

ABSTRACT

Background: Elevated circulating concentrations of proinflammatory cytokines may contribute to the pathogenesis of congestive heart failure (CHF). In vitro studies suggest that vitamin D suppresses proinflammatory cytokines and increases antiinflammatory cytokines.

Objective: We evaluated the effect of vitamin D supplementation on the survival rate and different biochemical variables in patients with CHF.

Design: One hundred twenty-three patients randomly received either 50 μg vitamin D_3/d plus 500 mg Ca/d [D(+) group] or placebo plus 500 mg Ca/d [D(–) group] for 9 mo. Biochemical variables were assessed at baseline and after 9 mo. The survival rate was calculated for a follow-up period of 15 mo.

Results: Ninety-three patients completed the study. Significant treatment effects were observed on logarithmic-transformed serum concentrations of 25-hydroxyvitamin D ($P = 0.001$), parathyroid hormone ($P = 0.007$), tumor necrosis factor α ($P = 0.006$), and interleukin 10 ($P = 0.042$). 25-Hydroxyvitamin D increased by 26.8 ng/mL in the D(+) group but increased only by 3.6 ng/mL in the D(–) group. Compared with baseline, parathyroid hormone was significantly lower and the antiinflammatory cytokine interleukin 10 was significantly higher in the D(+) group after 9 mo. The proinflammatory cytokine tumor necrosis factor α increased in the D(–) group but remained constant in the D(+) group. The survival rate did not differ significantly between the study groups during the follow-up period.

Conclusions: Vitamin D_3 reduces the inflammatory milieu in CHF patients and might serve as a new antiinflammatory agent for the future treatment of the disease. Our data provide evidence for the involvement of an impaired vitamin D–parathyroid hormone axis in the progression of CHF. *Am J Clin Nutr* 2006;83:754–9.

KEY WORDS Congestive heart failure, vitamin D, cytokine, parathyroid hormone

INTRODUCTION

Congestive heart failure (CHF) is a chronic disease that is characterized by dyspnea and fatigue due to a reduced cardiac ejection fraction in association with cardiac hypertrophy. Abnormal cardiac function is responsible for the inability of the heart to supply adequate blood flow, and therefore oxygen delivery, to peripheral tissues and organs or to do so only with elevated filling pressures. Approximately 5 million Americans and 10 million Europeans have CHF (1, 2). Despite evidence-based advances in the treatment of CHF over the past 15 y (2), large observational studies have shown no substantial changes in the prognosis of patients with heart failure. Survival rates 5 y after a first diagnosis of CHF are still only 35–50% (3, 4). Heart transplantation is the ultimate therapeutic measure in patients with end-stage CHF.

The cause of heart failure is not fully understood. In recent years, the pathophysiologic concept of chronic heart failure has changed from an isolated hemodynamic view to a more complex concept involving neurohormonal overactivation and increased concentrations of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin 6 (5, 6). In particular, TNF-α may contribute to the pathogenesis and the progression of CHF (5, 7). Measures to attenuate the deleterious effects of TNF-α on the progression of CHF may thus represent promising therapeutic approaches for its treatment (8, 9). Interestingly, experimental studies have shown that the vitamin D hormone calcitriol can suppress the release of TNF-α (10). Moreover, calcitriol effectively up-regulates the synthesis of the antiinflammatory cytokine interleukin 10 (IL-10) and induces IL-10 receptor expression in vitro (11).

We hypothesized that low vitamin D status may contribute to the pathogenesis and symptoms of CHF (12). Patients with CHF have considerably lower concentrations of the vitamin D metabolites 25-hydroxyvitamin D [25(OH)D] and calcitriol than do age-matched healthy controls (12), and a significant percentage of CHF patients have biochemical signs of hyperparathyroidism (12, 13). Additional strong evidence for the involvement of vitamin D deficiency in the pathogenesis of CHF comes from

[1] From the Institute of Nutrition and Food Science, University of Bonn, Bonn, Germany (SSS and PS); the Heart Center Nordrhein-Westfalen, Department of Cardio-Thoracic Surgery, Bad Oeynhausen, Germany (SSS, AZ, GT, and RK); and the Drug Commission of the German Medical Association, Berlin, Germany (HKB).

[2] Supported by a grant from the German Heart Foundation.

[3] Reprints not available. Address correspondence to A Zittermann, Department of Cardio-Thoracic Surgery, Heart Center Nordrhein-Westfalen, Georgstrabe 11, 32545 Bad Oeynhausen, Germany. E-mail: azittermann@hdz-nrw.de.

Received July 21, 2005.

Accepted for publication October 12, 2005.

vitamin D receptor knockout mice. Genetic disruption of the vitamin D receptor resulted in overstimulation of the renin-angiotensin system, which leads to high blood pressure, increased concentrations of atrial natriuretic peptide, and cardiac hypertrophy (14). These earlier data encouraged us to perform a controlled clinical trial to clarify whether vitamin D supplementation is able to improve the survival and biochemical variables of patients with CHF.

SUBJECTS AND METHODS

Participants

One hundred twenty-three CHF patients (102 men and 21 women) were recruited at the Heart and Diabetes Center Nordrhein-Westfalen, Germany, between March 2002 and April 2003. The patients were ambulatory and were routinely seen at least twice a year. Only patients with New York Heart Association functional class ≥ II were included. Exclusion criteria were hypercalcemia, serum creatinine concentration >2 mg/dL, nephrolithiasis, sarcoidosis, use of a biventricular pacemaker, acute heart insufficiency, and an actual intake of supplements containing vitamin D and calcium. All patients gave written informed consent to the study procedures, which were approved by the Ethics Committee of the Medical Association Westfalen-Lippe, Germany.

Study design

At study entry, all patients were randomly assigned in a double-blind manner from computer-generated random number lists; 61 patients were assigned to the intervention group [designated as the D(+) group] and 62 patients to the control group [designated as the D(–) group]. The D(+) group received a daily supplement of 50 μg (2000 IU) cholecalciferol (Vigantol Oel; Merck, Darmstadt, Germany), whereas the D(–) group received a placebo (Migliol-Oel; Merck, Darmstadt, Germany). In addition, both groups received a daily supplement of 500 mg Ca to guarantee a calcium intake above the recommended intake for adults of 1000–1200 mg Ca/d (15). The treatment was conducted for a period of 9 mo. The primary study endpoints were survival rates and biochemical variables such as natriuretic peptides and cytokines. Secondary endpoints were those hemodynamic variables, which were assessed routinely during the ambulatory visits, such as left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), the cardiothoracic ratio, maximal oxygen intake (spiroergometry; $\dot{V}O_2$ max), and blood pressure.

We documented patient compliance by controlling the study medication at each visit (bottle counts) and by the analysis of serum 25(OH)D concentrations. The study patients' medical history and medical treatment were assessed with the use of hospital documents. Moreover, the patients had to complete a validated food record (16) on the day before each visit to estimate dietary vitamin D and calcium intakes.

Blood specimens were collected from the antecubital vein of the study subjects after a 12-h overnight fast at baseline and after 9 mo. After centrifugation at room temperature for 20 min (1500 × *g*), aliquots of the serum samples were frozen consecutively and stored at −80 °C until analyzed.

Biochemical analysis

25(OH)D was measured by radioimmunoassay (DiaSorin, Stillwater, MN). As indicated by other data analyses, the reference range for adequate 25(OH)D concentrations should be 33–90 ng/mL (17–20). Serum calcitriol concentrations were measured with the use of a competitive enzyme-linked immunosorbent assay (ELISA; Immundiagnostik, Bensheim, Germany) after solid-phase extraction (reference range: 17–53 pg/mL). The intra- and interassay CVs for the 2 vitamin D metabolites were <7.0% and <9.0%, respectively. Intact parathyroid hormone (PTH; reference range: 16–46 pg/mL), TNF-α, and C-reactive protein were measured by ELISA test kits (DRG Diagnostics, Marburg, Germany) with interassay CVs <10%. IL-10 was measured with a highly sensitive ELISA kit (R&D, Minneapolis, MN). Calcium was assessed with the use of atomic absorption spectrometry (AAS 3030; Perkin Elmer, Ueberlingen, Germany); the CVs were <2.5%. *N*-Terminal propeptide of atrial natriuretic peptide was measured by using a radioimmunoassay kit (Biotop Oy, Oulu, Finland), and *N*-terminal propeptide of brain natriuretic peptide was measured by an electrochemiluminescent-immunoassay (Roche Diagnostics, Mannheim, Germany) with interassay CVs <4%. The concentrations of phosphorus and creatinine were measured enzymatically with the use of routine methods (Wako Chemicals, Neuss, Germany). Albumin was measured with a colorimetric test kit (BioMérieux, Nürtingen, Germany).

Statistics

Statistical evaluations were performed with SPSS version 11 (SPSS Inc, Chicago, IL). Categorical variables were reported by using the number or percent of observations. For comparative evaluations of categorical variables, the Fisher's exact test was used. Continuous variables were expressed as medians with interquartile ranges. Because most biochemical variables were non-normally distributed, as tested by the Kolmogorov-Smirnov test, data were normalized by logarithmic transformation. We then used the unpaired *t* test to compare the values of the study groups at baseline. Results after 9 mo are presented as the change from baseline. We compared changes from baseline between study groups using analysis of covariance with the baseline values as covariate. Moreover, we evaluated time effects within each study group using the paired *t* test. Survival rates were calculated according to the Kaplan-Meier method. The log-rank test was used to test for potential differences in survival rates between the study groups. Because it takes ≥3–6 mo of vitamin D supplementation before a plateau of circulating 25(OH)D concentrations is achieved (17), we calculated survival rate in both groups for a follow-up of 15 mo. *P* values < 0.05 (two-tailed test) were considered statistically significant, and *P* values between 0.05 and 0.10 were considered borderline significant.

RESULTS

The characteristics of the study patients are shown in **Table 1**. Clinical characteristics and medical treatment (except oral anticoagulant treatment) did not differ significantly between the groups. The results of the food records showed a median daily dietary vitamin D intake of 1.35 μg (interquartile range: 0.80–2.50 μg) in the D(+) group and 1.20 μg (0.60, 2.20 μg) in the D(–) group ($P > 0.05$). Median daily dietary calcium intakes of

TABLE 1
Characteristics of the study groups[1]

Characteristics	D(+) group (n = 61)	D(−) group (n = 62)	P^2
Men (n)	52	50	0.500
Age (y)	57 (53, 63)[3]	54 (50, 62)	0.217
Height (m)	1.76 (1.69, 1.82)	1.76 (1.68, 1.82)	0.693
Weight (kg)	83 (72, 91)	79 (71, 89)	0.404
BMI (kg/m^2)	26.0 (23.9, 29.0)	25.4 (24.3, 28.4)	0.756
Smoker (n)	9	7	0.570
Diseases (%)			
Coronary artery disease	47	40	0.422
Dilative cardiomyopathy	53	60	0.422
Hypertension	38	32	0.528
Diabetes	20	23	0.694
Drug therapy (%)			
Diuretics	97	100	0.152
Loop diuretics	84	84	0.968
Thiazide diuretics	26	31	0.589
Aldosterone antagonists	61	68	0.414
Antihypertensive drugs	93	95	0.682
ACE inhibitors	72	86	0.071
Digitalis	71	81	0.192
β-Blockers	92	87	0.398
Anticoagulants	79	61	0.036
Nitrates	51	37	0.127
Potassium supplements	25	23	0.794
Magnesium supplements	23	21	0.791
Uricostatics	39	36	0.660
Lipid-lowering drugs	53	42	0.244
Clinical variables			
LV ejection fraction (%)	31 (27, 37)	33 (28, 40)	0.317
LV end-diastolic diameter (mm)	70 (64, 75)	70 (61, 74)	0.398
Cardiothoracic ratio	0.53 (0.50, 0.56)	0.53 (0.48, 0.58)	0.853
$\dot{V}O_2$ max (ml · kg body wt^{-1} · min^{-1})	15.4 (13.7, 17.1)	14.6 (12.7, 18.0)	0.656
Systolic blood pressure (mm Hg)	120 (110, 130)	125 (111, 140)	0.219
Diastolic blood pressure (mm Hg)	74 (65, 82)	76 (65, 85)	0.489

[1] D(+) group, calcium- and vitamin D–supplemented group; D(−) group, calcium-supplemented group; ACE, angiotensin converting enzyme; LV, left ventricular; $\dot{V}O_2$ max, maximum oxygen uptake.
[2] Unpaired t test or Fisher's exact test, as appropriate.
[3] Median; interquartile range in parentheses (all such values).

the D(+) and D(–) group were 983 mg (741, 1275 mg) and 839 mg (656, 1158 mg), respectively ($P > 0.05$). Thus, the dietary calcium intake and the additional calcium supplement led to a total daily calcium intake above the recommended intake value of 1000–1200 mg Ca (15).

Nineteen patients from the D(+) group and 11 patients from the D(–) group did not complete the study ($P > 0.05$). Five patients [4 in the D(+) group and 1 in the D(–) group] had to be excluded due to lack of compliance. Twenty-five patients dropped out of the study prematurely because their health status worsened markedly: 1 patient [from the D(–) group] developed nephrolithiasis, cardiac transplantation was performed in 5 patients, 3 patients had a biventricular pacemaker implanted, and 7 patients could not complete the study because of excessive impairment in health status such as stroke, resuscitation, and high hospitalization rate. Moreover, 9 patients died within the 9 mo, and 13 patients died within the 15 mo follow-up [7 in the D(+) group and 6 in the D(–) group]. Three patients of the D(+) group died within the first 8 wk before a plateau of circulating 25(OH)D was reached (17, 18). Kaplan-Meier estimates showed no significant differences in survival rates in the D(+) and D(–) groups during the 15 mo follow-up (85.7% and 88.2%, respectively; $P = 0.836$).

The 25 patients who dropped out because their health status worsened markedly already had higher serum concentrations of *N*-terminal propeptide of brain natriuretic peptide, *N*-terminal propeptide of atrial natriuretic peptide, and C-reactive protein at baseline than did the patients who completed the study (**Table 2**). Moreover, these dropout patients had relatively high baseline serum concentrations of PTH and calcium, whereas their serum 25(OH)D concentrations were relatively low. In addition, the patients who dropped out had a lower LVEF, a higher LVEDD, and a higher cardiothoracic ratio than did the patients who completed the study.

The biochemical and clinical variables of the 93 study patients who completed the study are summarized in **Table 3**. The values did not differ significantly between the treatment groups at baseline, with the exception of lower IL-10 serum concentrations in the D(+)group than in the D(–) group. In both study groups, baseline 25(OH)D concentrations were below the lower end of the reference range, whereas TNF-α concentrations were

TABLE 2
Biochemical and clinical variables of the study groups and dropout patients at baseline[1]

Variable	Both treatment groups ($n = 93$)	Dropout patients ($n = 25$)	P^2
NT-proBNP (pg/mL)	835 (231, 524)	1719 (928, 2564)	0.003
NT-proANP (nmol/L)	1.00 (0.43, 1.83)	1.93 (1.25, 2.77)	0.002
25-Hydroxyvitamin D (ng/mL)	15.2 (12.0, 22.1)	11.2 (8.8, 19.4)	0.05
Calcitriol (pg/mL)	23.2 (15.3, 37.9)	26.4 (18.0, 31.2)	0.340
Calcium (mg/dL)	9.60 (9.28, 10.0)	10.0 (9.84, 10.5)	0.001
Parathyroid hormone (pg/mL)	37.0 (27.2, 53.0)	45.7 (33.2, 74.7)	0.029
Tumor necrosis factor α (pg/mL)	22.4 (15.8, 31.1)	21.3 (16.1, 24.7)	0.443
C-reactive protein (mg/L)	2.88 (1.16, 7.27)	7.58 (2.53, 21.2)	0.014
Interleukin 10 (pg/mL)	0.74 (0.38, 1.28)	0.56 (0.30, 1.70)	0.694
Phosphate (mg/dL)	3.84 (3.50, 4.00)	3.47 (2.98, 4.12)	0.077
Creatinine (mg/dL)	0.87 (0.64, 1.18)	0.94 (0.68, 1.22)	0.573
Albumin (g/dL)	4.69 (4.46, 5.02)	4.81 (4.55, 5.04)	0.498
LV ejection fraction (%)	33.0 (29.0, 40.0)	29.0 (26.0, 32.5)	0.015
LV end-diastolic diameter (mm)	69.0 (62.0, 74.3)	73.0 (69.5, 81.0)	0.020
Cardiothoracic ratio	0.53 (0.48, 0.56)	0.55 (0.51, 0.61)	0.026
$\dot{V}O_2$max (mL · kg body wt^{-1} · min^{-1})	15.7 (13.1, 17.6)	14.3 (12.3, 16.4)	0.824

[1] All values are medians; interquartile range in parentheses. NT-proBNP, *N*-terminal propeptide of brain natriuretic peptide; NT-proANP, *N*-terminal propeptide of atrial natriuretic peptide; LV, left ventricular; $\dot{V}O_2$max, maximum oxygen uptake.
[2] Unpaired *t* test.

markedly higher than the generally accepted mean normal concentration of 6 pg/mL for healthy middle-aged subjects.

Significant treatment effects on logarithmic transformed serum concentrations of 25(OH)D ($P = 0.001$), PTH ($P = 0.007$), TNF-α ($P = 0.006$), and IL-10 ($P = 0.042$) were observed. Other biochemical variables, including calcitriol concentrations and natriuretic peptides, were not significantly affected by vitamin D supplementation.

In detail, vitamin D supplementation increased median 25(OH)D concentrations by 26.8 ng/mL ($P = 0.001$; paired *t* test), whereas placebo treatment was associated with an increase of only 3.6 ng/mL ($P = 0.045$; paired *t* test). Moreover, median

TABLE 3
Biochemical and clinical variables of the patients who finished the study[1]

	Baseline		Change from baseline		
Variable	D(+) group ($n = 42$)	D (−) group ($n = 51$)	D(+) group ($n = 42$)	D(−) group ($n = 51$)	P for change between groups[2]
25-Hydroxyvitamin D (ng/mL)	14.4 (11.5, 22.1)	15.3 (12.7, 22.8)	26.8 (9.2, 35.1)[3]	3.6 (−2.8, 8.5)[3]	0.001
Calcitriol (pg/mL)	23.1 (14.0, 35.3)	23.6 (16.2, 39.0)	7.5 (−9.2, 14.8)	0.9 (−7.8, 8.0)	0.112
Calcium (mg/dL)	9.52 (9.24, 10.0)	9.72 (9.28, 10.1)	0.08 (−0.1, 0.17)	−0.12 (−0.09, 0.12)	0.869
Parathyroid hormone (pg/mL)	34.6 (26.7, 48.0)	39.2 (28.9, 63.9)	−4.9 (−14.3, 3.3)[3]	−4.4 (−10.3, 13.1)	0.007
Tumor necrosis factor α (pg/mL)	20.9 (14.1, 25.1)	23.0 (16.5, 32.7)	−2.0 (−4.3, 5.5)	2.7 (19.6, −32.8)[3]	0.006
C-reactive protein (mg/L)	2.50 (0.98, 6.60)	3.43 (1.57, 12.1)	0.0 (−1.37, 1.71)	−0.05 (−2.8, 2.2)	0.246
Interleukin 10 (pg/mL)	0.56 (0.31, 1.27)	0.91 (0.53, 1.35)	0.24 (−0.11, 0.41)[3]	−0.20 (−0.39, 0.41)	0.042
NT-proBNP (pg/mL)	721 (444, 1140)	859 (180, 1869)	9 (−99, 277)	50 (−111, 436)	0.457
NT-proANP (nmol/L)	0.99 (0.52, 1.84)	1.00 (0.43, 1.81)	0.05 (−0.24, 0.73)	0.03 (−0.94, 0.88)	0.384
Phosphate (mg/dL)	3.81 (3.69, 4.00)	3.84 (3.44, 4.00)	0.09 (−0.05, 0.05)	−0.03 (−0.06, 0.06)	0.354
Creatinine (mg/dL)	0.83 (0.65, 1.27)	0.90 (0.60, 1.15)	0.00 (−0.12, 0.14)	−0.02 (−0.16, 0.16)	0.844
Albumin (g/dL)	4.62 (4.40, 5.01)	4.76 (4.48, 5.05)	−0.02 (−0.44, 0.49)	−0.12 (−0.44, 0.50)	0.607
Systolic blood pressure (mm Hg)	123 (114, 133)	128 (111, 142)	−3 (−14, 8)	−4 (−13, 8)	0.865
Diastolic blood pressure (mm Hg)	75.0 (68.0, 84.0)	77.0 (65.0, 85.0)	−3 (−9, 3)	−2 (−7, 8)	0.376
LV ejection fraction (%)[4]	32.5 (26.8, 38.5)	33.0 (29.8, 40.0)	2 (−2, 7)	3 (0, 9)	0.643
LV end-diastolic diameter (mm)[4]	69.0 (63.0, 75.0)	69.0 (61.0, 73.5)	−3 (−5.8, 1.0)	−2.5 (−5.8, 0)	0.768
Cardiothoracic ratio	0.53(0.50, 0.56)	0.52 (0.48, 0.57)	0.0 (−0.02, 0.02)	0.0 (−0.02, 0.03)	0.788
$\dot{V}O_2$max (mL · kg body wt^{-1} · min^{-1})	16.1 (13.8, 17.4)	14.6 (12.8, 18.1)	−0.2 (−1.8, 2.0)	0.9 (−1.4, 2.6)	0.429

[1] All values are medians; interquartile range in parentheses. D(+) group, calcium- and vitamin D–supplemented group; D(−) group, calcium supplemented group; NT-proBNP, *N*-terminal propeptide of brain natriuretic peptide; NT -proANP, *N*-terminal propeptide of atrial natriuretic peptide; LV, left ventricular; $\dot{V}O_2$max, maximum oxygen uptake. Significant differences between the 2 groups at baseline were only observed for serum interleukin 10 concentrations ($P = 0.044$).
[2] Analysis of covariance with baseline value as covariate.
[3] Change is significantly different from baseline within a subgroup (paired *t* test).
[4] Significant change over time with both groups combined (main effect of time).

PTH concentrations fell significantly by 14% in the D(+) group ($P = 0.034$; paired t test), but only tended to decrease by 11% in the D(–) group ($P = 0.092$; paired t test). Compared with baseline values, median IL-10 concentrations increased by 43% in the D(+) group ($P = 0.035$; paired t test) during treatment but did not significantly change in the D(–) group during that time interval (−22%, $P = 0.579$; paired t test). Median concentrations of TNF-α did not differ significantly in the D(+) group after 9 mo of vitamin D supplementation compared with baseline values ($P = 0.812$; paired t test), but increased by 12% in the D(–) group during that time interval ($P = 0.017$; paired t test).

After 9 mo of intervention, the D(+) group as well as the D(–) group showed improvements in LVEF values and also in LVEDD values. However, the extent of change from baseline did not differ significantly between the study groups (Table 3). Dietary calcium and vitamin D intake, as well as type and dosage of medications, did not change significantly during intervention in either the D(+) or the D(–) groups (data not shown).

DISCUSSION

In the present clinical study, we showed for the first time that a daily supplement of 50 μg vitamin D for 9 mo is able to increase serum concentrations of the antiinflammatory cytokine IL-10 and to prevent an increase in serum concentrations of the proinflammatory cytokine TNF-α in CHF patients. Moreover, the suppression in serum PTH concentrations was more pronounced in the D(+) group (calcium and vitamin D supplemented) than in the D(–) group (only calcium supplemented). Hemodynamic variables improved in both study groups, whereas natriuretic peptides did not significantly change. The survival rate during 15 mo of follow-up was similar in both groups.

Our results agree with experimental data showing that vitamin D is able to suppress the release of TNF-α and to enhance IL-10 synthesis (10, 11). Moreover, earlier epidemiologic data indicated that high blood concentrations of 25(OH)D were associated with high IL-10 concentrations (21). Because IL-10 is able to suppress the production of proinflammatory cytokines, this antiinflammatory cytokine seems to have important cardioprotective actions (22). In addition, experimental studies have shown that IL-10 deficiency leads to severe atherosclerosis (23). In contrast to the protective effects of high IL-10 concentrations, evidence that high TNF-α concentrations contribute to the pathogenesis and progression of CHF is increasing (24). In vitro studies showed that the release of TNF-α can be suppressed by calcitriol in a dose-dependent fashion (25). It should be mentioned that several tissues, such as cytokine-producing immune cells, express 1-α-hydroxylase (26) and are thus able to make calcitriol for themselves from circulating 25(OH)D. Although serum calcitriol concentrations are usually homeostatically regulated, local calcitriol production depends on the concentration of circulating 25(OH)D (27).

The potential utility of an anti-TNF-α therapy in the management of heart failure is currently an area of great interest (8, 9). Consequently, our data on serum TNF-α as well as on serum IL-10 concentrations suggest that a vitamin D supplement can improve the cytokine profile of CHF patients. Our results may therefore offer interesting therapeutic options for diseases such as CHF, which are associated with up-regulated proinflammatory cytokines.

Men with left ventricular hypertrophy have higher PTH concentrations than do men without left ventricular hypertrophy (44.1 ± 26.2 pg/mL compared with 29.4 ± 13.9 pg/mL) (28). Moreover, excess PTH concentrations have adverse effects on cardiac function and lead to cardiomyocyte hypertrophy and interstitial fibrosis (29). In our study, the vitamin D- and calcium-supplemented D(+) group showed a significantly more pronounced decrease of serum PTH concentrations than did the only calcium-supplemented D(–) group (Table 3). Calcium supplementation may also increase the amount of extracellular activator calcium that is necessary for the first step in myocardial contractions (12). Although we cannot rule out that the significant increase of LVEF and decrease of LVEDD in both study groups was due to study bias, it may be that the calcium supplementation of both groups led to an improvement of left ventricular function, either directly or indirectly, through the decrease in serum PTH concentrations.

Another important finding of our study was that, compared with the patients who completed the study, the patients who dropped out prematurely because their health status worsened markedly had higher serum PTH concentrations and lower 25(OH)D concentrations at baseline, whereas their hemodynamic variables were more impaired at baseline. Data support the assumption that a disturbed vitamin D-PTH-calcium axis may be involved in the pathogenesis of CHF. The elevated PTH concentrations of the patients who dropped out may have caused calcium release from bone and may thus be responsible for the slightly enhanced fasting serum calcium concentrations of these patients at baseline (Table 2).

Our study has some limitations. First, the increase of 26.8 ng 25(OH)D/mL in the D(+) group [median 25(OH)D concentration after 9 mo: 42 ng/mL] was probably too low to optimize all vitamin D–dependent functions. It has only become clear in the past few years that serum 25(OH)D concentrations of >33 ng/mL and ≤90 ng/mL (80–225 nmol/L) are considered adequate (17–20). Vitamin D dosages >50 μg/d and circulating 25(OH)D concentrations higher than the median concentration of 42 ng/mL (105 nmol/L), which was reached after 9 mo of vitamin D supplementation, may probably result in an additional improvement of the cytokine profile in CHF patients. Second, the number of dropouts was relatively high in our study. However, note that the patients in our study were severely ill. The high number of dropouts supports the general observation that CHF patients with New York Heart Association class ≥II have high complication and mortality rates. Third, calcium supplementation may have influenced cardiac function in both study groups (*see* above). However, dietary calcium intake in Western countries is often below the calcium recommendation of 1000–1200 mg/d (30). This was also the case in our study groups (*see* Results, above). Therefore, we believe that it would have been unethical to not supplement both study groups with calcium.

In conclusion, the results of our study indicate that vitamin D can serve as an antiinflammatory agent and may therefore be useful for the management of CHF. Moreover, vitamin D was able to suppress serum concentrations of PTH, a hormone that may contribute to impaired cardiac function. Calcium supplementation may result in a slight improvement of hemodynamic variables. Our data provide additional evidence for the involvement of an impaired vitamin D-PTH-calcium axis in the progression of CHF.

We thank Dr. E. Murray for his assistance in writing the manuscript.

SSS was responsible for the study design, recruitment of patients, data collection, data analysis, and writing of the manuscript. AZ was responsible for the study design, data analysis, and writing of the manuscript. GT participated in the review of the original data and their compilation. HKB participated in the design of the study. PS and RK were responsible for revising the manuscript critically for important intellectual content and for final approval of the manuscript. The authors had no conflicts of interest.

REFERENCES

1. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
2. Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007–18.
3. Bleumink GS, Knetsch AM, Sturkenboom MC, et al Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 2004;25:1614–9.
4. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397–402.
5. Rauchhaus M, Doehner W, Francis DP, et al. Plasma cytokine parameters and mortality in patients with chronic heart failure. Circulation 2000;102:3060–7.
6. Swedberg K, Eneroth P, Kjekshus J, Snapinn S. Effects of enalapril and neuroendocrine activation on prognosis in severe congestive heart failure (follow-up of the CONSENSUS trial). CONSENSUS Trial Study Group. Am J Cardiol 1990;66:40D–4D.
7. Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. Circulation 1996;93:704–11.
8. Deswal A, Bozkurt B, Seta Y, et al. Safety and efficacy of a soluble P75 tumor necrosis factor receptor (Enbrel, etanercept) in patients with advanced heart failure. Circulation 1999;99:3224–6.
9. Kubota T, Bounoutas GS, Miyagishima M, et al. Soluble tumor necrosis factor receptor abrogates myocardial inflammation but not hypertrophy in cytokine-induced cardiomyopathy. Circulation 2000;101:2518–25.
10. Zhu Y, Mahon BD, Froicu M, Cantorna MT. Calcium and 1alpha,25-dihydroxyvitamin D3 target the TNF-alpha pathway to suppress experimental inflammatory bowel disease. Eur J Immunol 2005;35:217–24.
11. Canning MO, Grotenhuis K, de Wit H, Ruwhof C, Drexhage HA. 1-alpha,25-Dihydroxyvitamin D3 (1,25(OH)(2)D(3)) hampers the maturation of fully active immature dendritic cells from monocytes. Eur J Endocrinol 2001;145:351–7.
12. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 2003;41:105–12.
13. Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med 1997;103:197–207.
14. Xiang W, Kong J, Chen S, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab 2005;288:E125–32.
15. Standing committee on the scientific evaluation of dietary reference intakes, Food and Nutrition Board, Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington DC: National Academy Press, 1997.
16. Zittermann A, Schwarz I, Scheld K, et al. Physiologic fluctuations of serum estradiol levels influence biochemical markers of bone resorption in young women. J Clin Endocrinol Metab 2000;85:95–101.
17. Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J 2004;3:8.
18. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999;69:842–56.
19. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003;89:552–72.
20. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 2005;10:94–111.
21. Zittermann A, Dembinski J, Stehle P. Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. Pediatr Allergy Immunol 2004;15:242–6.
22. Ohtsuka T, Hamada M, Hiasa G, et al. Effect of beta-blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. J Am Coll Cardiol 2001;37:412–7.
23. Mallat Z, Besnard S, Duriez M, et al. Protective role of interleukin-10 in atherosclerosis. Circ Res 1999;85:E17–24.
24. Koller-Strametz J, Pacher R, Frey B, Kos T, Woloszczuk W, Stanek B. Circulating tumor necrosis factor-alpha levels in chronic heart failure: relation to its soluble receptor II, interleukin-6, and neurohumoral variables. J Heart Lung Transplant 1998;17:356–62.
25. Muller K, Haahr PM, Diamant M, Rieneck K, Kharazmi A, Bendtzen K. 1,25-Dihydroxyvitamin D3 inhibits cytokine production by human blood monocytes at the post-transcriptional level. Cytokine 1992;4:506–12.
26. Hewison M, Zehnder D, Chakraverty R, Adams JS. Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. Mol Cell Endocrinol 2004;215:31–8.
27. Holick MF. Vitamin D. The underappreciated D-lightful hormone that is important for skeletal and cellular health. Curr Opin Endocrinol Diabetes 2002;9: 87–98.
28. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J 2003;24:2054–60.
29. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int 1999;56:383–92.
30. Ervin RB, Kennedy-Stephenson J. Mineral intakes of elderly adult supplement and non-supplement users in the third national health and nutrition examination survey. J Nutr 2002;132:3422–7.