Original Paper

Oral Active Vitamin D Treatment and Mortality in Maintenance Hemodialysis Patients

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Key Words

Maintenance hemodialysis · Active vitamin D · Calcitriol · 25(OH)D · All-cause mortality · Cardiovascular mortality

Abstract

Aims: To analyze the relationship between oral active vitamin D treatment and mortality in maintenance hemodialysis (MHD) patients. **Methods:** We examined the association of oral calcitriol treatment with mortality in 156 MHD patients (80 men and 76 women; mean age: 59 ± 15 years). The survival analysis of all-cause and cardiovascular mortality was performed using the Kaplan-Meier survival and Cox proportional-hazards analyses. **Results:** In all, 108 of the 156 patients received active vitamin D treatment. The intact parathyroid hormone level was obviously lower in the patients who received active vitamin D treatment than in those who did not. Throughout the whole follow-up, overall mortality was 16.7% (26 deaths, 13 in each group). The cardiovascular mortality rates were 14.6% (8/48) in the control group and 4.6% (5/108) in the calcitriol group. The crude analysis of all-cause and cardiovascular mortality using the Kaplan-Meier curve showed a significant reduction in mortality risk for patients who received oral active vitamin D compared with those who did not receive it ($p = 0.015$ and 0.026 , respectively). Cox's regression analysis showed that active vitamin D treatment was associated with a significantly lower risk of all-cause mortality ($RR = 0.399$, 95% CI 0.185–0.862, $p = 0.019$) and cardiovascular mortality ($RR = 0.295$, 95% CI 0.094–0.93, $p = 0.037$). However, after adjusting for potential confounding variables, oral active vitamin D therapy was no longer clearly associated with a lower risk of either all-cause or cardiovascular mortality. **Conclusion:** Oral active vitamin D treatment was associated with improved survival in MHD patients. However, this survival benefit was smaller than previously reported, and a large cohort study should be performed.

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Introduction

Vitamin D is a fundamental micronutrient with major implications for human health, and impaired metabolism of vitamin D is one of the most recognized disorders associated with chronic kidney disease (CKD) [1]. In patients with CKD, the production of 1,25-dihydroxy-vitamin D [$1,25(\text{OH})_2\text{D}$], the active form of vitamin D, decreases in concert with declining renal function [2]. Unlike patients without kidney disease, who are able to tightly regulate $1,25(\text{OH})_2\text{D}$ levels within the normal range, patients with kidney disease show profound reductions in $1,25(\text{OH})_2\text{D}$ levels [3].

CKD is associated with a high mortality rate, mainly as a result of cardiovascular disease, the most common cause of death in dialysis patients [4]. A previous study presented evidence suggesting that abnormalities in mineral metabolism may play an important role in cardiovascular disease in patients with CKD [5], and lower levels of $25(\text{OH})\text{D}_3$ [$25(\text{OH})\text{D}$], the substrate of $1,25(\text{OH})_2\text{D}$, is a cardiovascular risk marker in hemodialysis patients [6].

Accumulating evidence supports the view that vitamin D deficiency contributes to the extraordinarily high mortality risk among dialysis patients [7, 8]. The invention of synthetic forms of active vitamin D, also known as vitamin D receptor activators (VDRA), has been considered a turning point in the history of nephrology [9]. Calcitriol is the first synthetic and commercially available VDRA, and it may increase intestinal calcium absorption, effectively suppresses parathyroid hormone (PTH) secretion and prevents skeletal complications [2]. A survival benefit with oral active vitamin D was suggested for hemodialysis patients from six Latin American countries by Naves-Díaz et al. [10]; their results showed that hemodialysis patients receiving oral active vitamin D had significant reductions in overall, cardiovascular, infectious and neoplastic mortality compared with the ones that had not received it, and a survival benefit with oral active vitamin D was seen for those patients receiving mean daily doses of less than $1\text{ }\mu\text{g}$, with the highest reduction associated with the lowest dose. In a male outpatient population with CKD, treatment with low doses ($0.25\text{--}0.5\text{ }\mu\text{g/day}$) of an oral nonselective activated vitamin D analogue (calcitriol) was found to be associated with significantly better survival [11]. However, both vitamin D deficiency and vitamin D toxicity were associated with cardiovascular complications in CKD [12]. Calcitriol administration may also result in an elevation of serum calcium and phosphorus levels, which may, in turn, facilitate vascular calcification and death [13], especially in maintenance hemodialysis (MHD) patients without residual renal function [14]. These less favorable effects of calcitriol therapy have spurred our further investigation of the potential survival effect of oral active vitamin D in a Chinese cohort of MHD patients.

Subjects and Methods

Patients

This study was approved by the Ethics Review Board for human subjects of the Sichuan Academy of Medical Sciences, Sichuan Provincial People's Hospital. A total of 156 patients undergoing MHD were recruited from the blood purification center of our hospital in July 2010. The inclusion criteria were as follows: (1) being willing to participate and complete a signed consent form; (2) having an age >18 years; (3) not having any plans to move out of the area; (4) being on long-term MHD 3 times a week; (5) following a normal diet and daily activity; (6) being on standard antihypertensive drugs and erythropoietin treatment as well as on regular monitoring of serum marker levels, and (7) not having taken VDRA before joining the study. The exclusion criteria were an age ≥ 80 years, concurrent chronic infectious diseases or cardiovascular events during the previous half year. The patients recruited were prospectively divided into a control group and a calcitriol group according to whether they were willing to receive active vitamin D therapy or not.

Baseline and Clinical Data

Data on baseline characteristics including gender, age, length of dialysis treatment, body mass index (BMI) and prevalence of diabetes were collected at the time of enrollment. Baseline serum samples were collected from the participants at the time of their routine laboratory examinations. The samples were aliquoted and stored over liquid nitrogen until assayed. All laboratory values including blood pressure, serum levels of calcium, phosphate, intact PTH (iPTH), serum hemoglobin, albumin and cholesterol were measured by automated and standardized methods in the clinical laboratory of our hospital. Serum iPTH was determined using the Immulite 1000 ELISA assay (Diagnostic Products Corp., Los Angeles, Calif., USA). Serum 25(OH)D levels were measured at enrollment using an automatic radioimmunoassay method; the radioimmunoassay kits were purchased from Tianjin Concord Medical Technology Co., Ltd.

Follow-Up and Study End Points

The patients were seen regularly, with the frequency dependent on renal function and comorbid conditions, but usually every 3–6 months. Those in the calcitriol group were given the active vitamin D, calcitriol, orally at a daily dose of 0.25–0.5 µg. Vitamin D supplementation or its absence was maintained during the entire follow-up period. The patients were followed up for a period of 40 months (median: 36.8 ± 8.9) until October 2013. Calcium carbonate was prescribed to some of the patients at a dose of 0.6 g per day, or twice a day, as appropriate. The study end points (all-cause and cardiovascular mortality) were accurately recorded.

Statistical Analysis

Statistical analysis was performed using a commercially available statistical software package (SPSS version 17.0; SPSS Inc., Chicago, Ill., USA). Measurement data are presented as arithmetic means and SD, and compared using Student's t test. Enumeration data were analyzed by the χ^2 test. The survival analysis was performed using the Kaplan-Meier survival and Cox proportional-hazards analyses. A p value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Patients with and Those without Oral Active Vitamin D Therapy

A total of 156 MHD patients (80 men and 76 women; mean age: 59 ± 15 years) were recruited for this study. The baseline characteristics of the group that received oral active vitamin D (n = 108) and the group that did not receive it (n = 48) are shown in table 1. There was no statistically significant difference in the distributions of age, gender, length of dialysis treatment, BMI, blood pressure and concurrence of diabetes between the two groups. The serum concentration of iPTH was significantly lower in the calcitriol group than in the control group (348.5 ± 274.5 vs. 438.2 ± 470.7 pg/ml, p < 0.05). The differences in basal blood pressure, concentrations of serum calcium, phosphate, hemoglobin and albumin, C-reactive protein levels as well as Kt/V and cholesterol levels did not reach statistical significance between the two groups (table 1). The utilization of the phosphate binder (calcium carbonate) was significantly different between the two groups (p < 0.05), and about 64.6% of the patients in the control group received calcium carbonate compared with 48.5% of the patients in the calcitriol group.

Mortality of the Patients with and Those without Oral Active Vitamin D Therapy

Throughout the whole follow-up, overall mortality was 16.7% (26 deaths, 13 in each group). The cardiovascular mortality rates were 14.6% (8/48) in the control group and 4.6% (5/108) in the calcitriol group. Overall and cardiovascular mortality rates were consistently higher in the group without active vitamin D treatment than in the group with active vitamin D treatment (p < 0.05).

Table 1. Baseline data on patients with and those without oral active vitamin D therapy

Characteristics	Without vitamin D (n = 48)	With vitamin D (n = 108)	p value
Age, years	62 ± 15	58 ± 15	>0.05
Male, n (%)	22 (45.8)	58 (53.7)	>0.05
Blood pressure, mm Hg			
Systolic	149 ± 24	140 ± 22	>0.05
Diastolic	81 ± 12	76 ± 12	>0.05
Length of dialysis treatment, months	50 ± 42	50 ± 45	>0.05
Diabetes, n (%)	17 (35.4)	25 (23.1)	>0.05
Calcium carbonate, n (%)	31 (64.6)	50 (48.5)	0.047
C-reactive protein, mg/l	15.1 ± 13.2	10.1 ± 9.5	>0.05
Kt/V	1.28 ± 0.25	1.30 ± 0.35	>0.05
Serum hemoglobin, g/l	99.2 ± 28.1	107.7 ± 27.3	>0.05
Serum albumin, g/l	39.9 ± 4.2	40.0 ± 4.6	>0.05
BMI	23.7 ± 5.0	24.2 ± 8.1	>0.05
Cholesterol, mmol/l	5.0 ± 1.0	4.6 ± 1.2	>0.05
Serum calcium, mmol/l	2.1 ± 0.3	2.2 ± 0.2	>0.05
Serum phosphate, mmol/l	1.7 ± 0.5	1.8 ± 0.5	>0.05
Serum iPTH, pg/ml	438.2 ± 470.7*	348.5 ± 274.5	0.011
25(OH)D, ng/ml	16.1 ± 6.8	25.1 ± 12.2	0.001

Values denote means ± SD unless specified otherwise. * p < 0.05 vs. the calcitriol group (with oral active vitamin D).

Fig. 1. Kaplan-Meier analysis of all-cause mortality. Survival curves for the patients treated with oral active vitamin D (gray line) and for the untreated patients (black line). * p < 0.05 vs. the calcitriol group (with oral active vitamin D).

Survival Analysis of the Patients with and Those without Oral Active Vitamin D Therapy

The crude analysis of all-cause mortality using the Kaplan-Meier curve showed a significant reduction in mortality risk for patients who received oral active vitamin D compared to those who did not receive it (p = 0.015; fig. 1). Cox's regression analysis of oral active vitamin D therapy in relation to the all-cause mortality of patients showed that active vitamin D

Fig. 2. Kaplan-Meier analysis of cardiovascular mortality. Survival curves for the patients treated with oral active vitamin D (gray line) and for the untreated patients (black line). * $p < 0.05$ vs. the calcitriol group (with oral active vitamin D).

treatment was associated with a significantly lower risk of all-cause mortality (RR = 0.399, 95% CI 0.185–0.862, $p = 0.019$). However, after adjusting for potential confounding variables such as age, gender, race, length of dialysis treatment and history of diabetes, oral active vitamin D therapy was no longer clearly associated with a lower risk of all-cause mortality (RR = 0.481, 95% CI 0.207–1.119, $p = 0.089$).

Kaplan-Meier survival curves showed that patients receiving calcitriol are also at a substantially lower risk of cardiovascular mortality ($p = 0.026$; fig. 2). Cardiovascular mortality was significantly lower among patients receiving calcitriol in the unadjusted but not in the adjusted models that included the covariates (RR = 0.295, 95% CI 0.094–0.93, $p = 0.037$ vs. RR = 0.344, 95% CI 0.091–1.300, $p = 0.116$).

Discussion

An adequate vitamin D status is essential for overall health [15]. Increasing clinical evidence supports a high prevalence of vitamin D insufficiency and deficiency in chronic hemodialysis patients [16], and about 81.5% of CKD patients were found to be vitamin D insufficient and deficient [17, 18]. Vitamin D deficiency is not only strongly associated with CKD and cardiovascular disease in humans but may also accelerate disease progression [19]. A retrospective analysis of 325 CKD inpatients in China showed that the mean 25(OH)D level was 18.58 ± 11.7 $\mu\text{g/l}$, which is significantly lower than normal reference values, and the prevalence of vitamin D deficiency and insufficiency was 84.63% and increased with the CKD stage [20]. Most recently, a clinical study indicated that vitamin D insufficiency and deficiency were more common and associated with the level of kidney function in an Asian CKD population, especially in advanced stages of CKD [21].

Vitamin D deficiency in dialysis patients is associated with an adverse health outcome [22]. In a previous prospective study on German hemodialysis patients, Krause et al. [18] found that the all-cause mortality risk had more than doubled in patients with severe deficiency [25(OH)D < 12.5 ng/ml], and comparable data were obtained for mortality from cardi-

ac disease, highlighting the need to primarily ensure adequate 25(OH)D levels in dialysis patients to achieve an advantage in survival. A survival benefit with oral active vitamin D was determined by Naves-Díaz et al. [10] in a large cohort of hemodialysis patients from six Latin American countries, as mentioned earlier, and this advantage was inversely related to the vitamin dose. Consistent with the results of previous studies, our study demonstrated that oral active vitamin D therapy reduced the risks of all-cause and cardiovascular mortality in MHD patients. However, these survival advantages were no longer statistically significant after adjusting for potential confounding variables.

The most important finding of the present study is that, for MHD patients, the advantage in survival with calcitriol may be significantly smaller than previously reported [10]. Although the mortality risk was decreased among patients receiving calcitriol versus controls in the unadjusted models, these differences diminished and were not statistically significant in the models adjusted for important covariates such as age, gender, race, length of dialysis treatment and history of diabetes. These results suggest that differences in mortality between patients receiving oral active vitamin D and controls may be smaller than previously reported. Several factors such as variations in practice patterns, racial differences, the sample size and the level of kidney function in the populations included as well as varying study inclusion criteria may have contributed to the smaller differences observed in the current study. Cardiovascular disease is the most common cause of death of dialysis patients [4]. In this study, MHD patients with concurrent chronic infectious diseases and/or cardiovascular events during the previous half year were excluded. An analysis by Tentori et al. [23] suggested that the larger size of samples may have something to do with the higher mortality rates in hemodialysis patients. Dissimilarities in practice patterns by clinic – and possibly by physician within each clinic – may have contributed to the observed differences in mortality, as may have racial and ethnic differences [24]. Moreover, there was a study which indicated that in patients treated with VDRA, the detected 25(OH)D deficiency did not have any bearing on survival, and measuring serum levels of 25(OH)D may not be necessary, at least not in MHD patients [25].

Abnormalities in serum calcium, phosphate and PTH levels have been associated with increased all-cause and arteriosclerotic cardiovascular disease morbidity [5, 26]. High serum calcium concentrations per se have been associated with increased mortality, and they also contribute to arterial calcifications and the subsequent increase in mortality [27]. High levels of phosphate both at baseline and during follow-up are associated with mortality in incident dialysis patients [26]. One of the major actions of vitamin D is to maintain calcium and phosphate serum concentrations in the normal range and to allow for the mineralization of newly synthesized bone [28]. Higher serum calcium and lower phosphorus levels were detected in hemodialysis patients who did not receive vitamin D therapy when compared with patients who received any vitamin D analog [23], while Teng et al. [29] found that both calcium and phosphorus levels were increased after calcitriol therapy. However, in a cross-sectional analysis of 825 consecutive patients from a prospective cohort of US incident hemodialysis patients, Wolf et al. [25] found that calcium, phosphorus and PTH levels correlated poorly with 25(OH)D and 1,25(OH)₂D concentrations. Unlike the results of those studies, our data showed no significant difference in serum levels of calcium and phosphorus between the patients who received vitamin D and those who did not, while the serum level of iPTH was significantly downregulated by oral vitamin D therapy.

In kidney disease, the progressive loss of the renal capacity to produce calcitriol is a key contributor to PTH elevations [30]; the elevated serum PTH may cause skeletal abnormalities and disturbances in calcium and phosphate homeostasis, predisposing to renal and cardiovascular damage, ectopic calcifications and high mortality rates [31]. The safe correction of calcitriol deficiency to suppress PTH levels has, therefore, been suggested as the treatment of choice for decades. However, after 14 years of prospective observation, Avram et al. [32]

found that low serum PTH was associated with increased mortality risk in hemodialysis and peritoneal dialysis patients. The findings of our present study showed that the correction of calcitriol deficiency by oral vitamin D therapy suppressed iPTH levels in MHD patients. It is still difficult to say whether the low iPTH concentration observed among calcitriol-treated patients contributed to an increase or a decrease in mortality risk, and future studies are still needed.

In summary, our study indicated that oral active vitamin D was associated with improved survival in MHD patients. However, this survival benefit was smaller than previously reported, and a large cohort study is needed.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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