

Special Article - Chronic Kidney Diseases

Impact of Short Daily at Home Hemodialysis on Attenuation of Vascular Calcification

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Received: November 15, 2014; Accepted: January 05, 2015; Published: January 07, 2015

Abstract

Vascular Calcification (VC) has a significant effect in cardiovascular disease on dialysis patients. However no pharmacological interventions have been demonstrated for prevention and/or attenuation of VC. Recent advances with frequent hemodialysis have shown the reduction of hyperphosphatemia. This has led to the idea that there is a strong relation between VC and hyperphosphatemia which suggests therefore, that frequent hemodialysis may reduce VC.

Aim: To examine whether short daily at-home hemodialysis reduces VC.

Method: Using Volume Viewer software with a 16-detector CT scan, the total calcification volume of the aorta was calculated with a cut-of of 130 House field Units. Abdominal CT scans were taken prior to and 3 years after the start of short daily at-home hemodialysis in 37 patients (average age 52 ± 7.0 years, male 33). The underlying kidney diseases were chronic glomerulonephritis (33), diabetic nephropathy (2) and congenital kidney disease (2).

Results: The mean base line calcification score of the abdominal aorta was 7.59 ± 3.49 (cm³), which was reduced by short daily at-home hemodialysis to 6.69 ± 3.57 at the end of the study ($P < 0.05$). Besides, short daily at-home hemodialysis produced normalization of blood pressure, reduction of blood urea nitrogen and serum phosphate, which contribute to vascular calcification.

Conclusion: This is the first demonstration that short daily at-home hemodialysis reduces calcification of the abdominal aorta through attenuation of hyperphosphatemia. (Words: 222).

Keywords: High Dose Hemodialysis; Abdominal Aorta; Hyperphosphatemia; Blood Pressure Control Albumin

Introduction

Cardiovascular disease is the leading cause of death in patients receiving dialysis therapy [1]. This increased risk of cardiovascular disease is usually attributed to traditional risk factors such as blood pressure and volume control, and also non-traditional risk factors such as bone / mineral metabolism, sympathetic nervous system over-activity, retention of uremic toxins, and inflammation. Two of the strongest risk factors for cardiovascular morbidity and mortality are Vascular Calcification (VC), and higher serum phosphate concentration. VC is highly correlated with cardiovascular morbidity and mortality, and linked to aging, diabetes and Chronic Kidney Disease (CKD) [2,3]. Higher serum phosphate has been consistently associated with cardiovascular events and mortality in cohort studies of both CKD patients and those with normal kidney function [4,5]. Higher serum phosphate and VC are thought to lead to be causally related. Disorders of bone and mineral metabolism can result in VC and reduced vascular compliance, thereby resulting in increased myocardial ischemia, cardiac dysfunction, and sudden cardiac death. This causal pathway is supported by several trials with calcium-free phosphate binder, which indicated that phosphate is a modifiable risk factor for mitigating the progression of coronary calcification in hemodialysis patients [6]. Previously only one case report in

which nocturnal Hemodialysis (HD) resolved massive uremic tumoral calcinosis of 44-year-old man in association with reduction of Ca x phosphorus was reported [7]. With this paradigm in mind, it seems logical to test the strength of association between VC and phosphate in other settings. Recent reports have demonstrated that frequent / extended hours (“high-dose”) HD facilitates control of hyperphosphatemia, allowing more liberal dietary intake and freedom from phosphorus binders [8,9]. This study aims to extend those observations, and test the following clinical question: in prevalent HD patients from Japan, does high-dose home HD result in a decrease in VC, prevalent over a 3 year period?

Methods

Study overview and design

This study is a single center, prospective, observational study. The primary objective was to compare abdominal aortic calcification at the inception of high-dose home HD [10] to that after 3 years of follow-up. Ethical clearance and confirmation of scientific validity was provided by the Institutional Review Board of Saitama Medical University.

Setting and participants

The setting for this study is the Kidney Disease Center, Saitama

Medical University, in Moroyama, Japan. At the time of writing, the center had more than 198 dialysis patients, with 90, 60 and 48 on facility HD, home HD, and peritoneal dialysis respectively.

Thirty-seven HD patients were recruited from hospital HD facilities. Each participant was followed-up for 3 years, with last follow-up completed March 2013. All participants provided informed consent. Key inclusion criteria included: participants were willing and able to perform home HD, aged > 20 years, with duration of dialysis >1 year, and able to provide informed consent. Key exclusion criteria included: those with significant co-morbidity anticipated to reduce life expectancy to <6 months, and those with contraindications to study procedures including CT scanning.

Primary exposure and outcome variables

The primary exposure in the study was high-dose home HD, defined as HD in the home, performed by the patient, with 3-5 hour treatments at a frequency of typically 6 (and no less than 5) times per week. Prior to high-dose home HD, all participants were treated with conventional facility HD in a hospital HD unit, with 4 hour treatments 3 times per week. After study enrollment, all patients underwent home HD training for at least a period of 3 months, transitioning to high dose home HD after completion of training.

HD treatments in the hospital and at home were performed using low flux polysalphose dialyzers (1.5-2.0 m²APS Asahi Medical R Tokyo, Japan), bicarbonate-based dialysate containing 1.25 mmol/L calcium and 134 mmol/ sodium. High-dose home HD was performed using Nikkiso DBB-27 machines (Nikkiso Co., Tokyo, Japan) with the MH-500CX water treatment system (Japan Water System Co., Tokyo, Japan). Typical blood flows were 200 ml/min for both facility and high-dose home HD. Typical dialysate flows were approximately 200 ml/min.

The primary outcome measure in this study was abdominal aortic calcification, measured at baseline and after 3 years follow-up determined by CT. CT scans were performed with a 16-detector CT scan {Prime Purpose MDCT (GE Healthcare, Milwaukee, WI USA)}. Scanning time was 0.5s for two contiguous 1.25 mm sections and 20+5 seconds for the entire zone of interest. Examination was performed during a single, unforced, withheld inspiration. During scanning with the tube rotating at 2 rotations/second and the table moving at 55 mm/s with a 1:1.375 scanning pitch, images were

obtained with an effective section thickness of 10 mm. Scanning was performed with 120 kVp and 350 mAs, standard resolution, and a 28-36 cm field of view. The total duration of the procedure was 5 min. The range of CT scanning is shown in Figure 1 [11]. Volume acquisitions were analyzed using Volume Viewer software (GE Healthcare). The abdominal aorta was segmented manually. In order to reduce errors due to noise, a cut-off of 130 Housefield Units (HU) was applied. The total calcification volume was calculated as the sum of all voxels in the remaining volume [12].

Several pre-specified secondary outcomes were included in the study, measured at baseline and after 3 years follow-up. These included:

- 1) Dialysis efficacy (creatinine and blood urea nitrogen, dry weight)
- 2) Blood pressure (pre- and postdialytic systolic and diastolic blood pressures, antihypertensive drugs)
- 3) Nutrition and inflammation (albumin, body mass index)
- 4) Bone metabolism (calcium, phosphate, intact parathyroid hormone, phosphate binding pharmacotherapy).
- 5) Erythropoiesis (Erythropoietin Resistance Index (ERI), defined as the total weekly erythropoietin dose per kg of body weight, divided by the patient's Hb level, expressed as units per kg per g/dl)

Data measurements and quantitative variables

Data on patient demographics such as age, sex, and etiology and duration of End-Stage Renal Disease (ESRD) and co-morbid conditions were collected from a computerized clinical database, and included as co-variables in multivariate models.

Statistical analysis

Values are expressed as mean + standard deviation. Pre- and post- treatment characteristics were compared using the Wilcoxon rank sum test. Simple regression analysis was carried out among the levels and differences in before and after introduction of HHD and other variables. Multiple regression analysis was performed to obtain adjusted p values. Multiple stepwise models adjusted for age, gender, the presence of DM, serum albumin, calcium, phosphate, creatinine, and dialysis vintage. Multivariate models were limited to only those factors that were significant in univariate analysis to avoid model over fitting. A p-value<0.05 was considered statistically significant. Descriptive and multivariate statistics were carried out using the statistical software JMP ver. 9 (SAS Institute Inc., Cary, NC, USA).

Results

All participants achieved full 3 year follow-up, with no drop outs from the study. Abdominal CT scans were obtained in 37 patients (average age 52 + 7.0 years, male 33). The underlying kidney diseases

Table 1: Characteristics of patients.

| | |
|---------------------------|-----------|
| Age(Years) | 52.0±7.0 |
| Dialysis duration(Months) | 66.6±83.8 |
| Gender(Male/female) | 33/4 |
| Diabetes/non diabetes | 33/44 |
| Body mass index(kg/m2) | 22±1.5 |

Abdominal aorta

10 cm from the bifurcation of the aorta



Figure 1: The range of a Computed Tomography (CT) scan is illustrated.

were chronic glomerulonephritis (33), diabetic nephropathy (2) and congenital kidney disease (2). The characteristics of the patients enrolled in this study are shown in Table 1.

Aortic Calcification

There was a statistically significant decrease in aortic calcification volume after high-dose home HD inception (BL: 7.5 ± 3.4; 3 years 6.6 ± 3.5; P<0.05). This change is shown in Figure 2.

Dry weight

Dry weight increased significantly after the inception of high dose home HD to 1.9 + 3.9 % above the baseline (BL) value (p=0.0016).

Blood pressure and antihypertensive drugs

The pre-dialytic systolic blood pressure decreased significantly after the inception of high dose home HD (BL: 146.2 ± 16.5; 3 years: 124.3 ± 16.0 mmHg; p<0.001), as did pre-dialytic diastolic blood pressure (BL: 76.8 ± 6.3; 3 years: 72.3 ± 5.4 mmHg; p<0.01). Similarly, the post-dialytic systolic blood pressure decreased significantly (BL: 132 ± 12.3; 3 years: 124 ± 11.9 mmHg; p<0.001) but without significant corresponding changes in post-dialytic diastolic blood pressure. Over the period of observation, the number and doses of antihypertensive drugs were reduced (not statistically evaluated).

Serum creatinine and blood urea nitrogen

Serum creatinine levels decreased significantly after the inception of high dose home HD (BL: 10.4 ± 1.7; 3 years: 7.6 ± 2.3 mg/dL; p<0.00001), as did blood urea nitrogen (BL: 87.7 ± 13.2; 3 years 36.6 ± 19.6 mg/dL; p<0.001)

Serum albumin and total cholesterol

There was a marked improvement of the levels of serum albumin after the inception of high dose home HD (BL: 3.8 ± 0.5; 3 years: 4.1± 0.4 mg/dL; p<0.005). There was a corresponding trend to increase in total cholesterol, but this change did not achieve statistical significance (BL: 157.2 ± 34.2; 3 years: 178.9 ± 37.9 mg/dL).

Bone mineral metabolism

There was no change serum calcium levels (BL: 9.3 ± 0.6; 3 years: 9.0 ± 0.7 mg/dL) after high dose home HD, although serum phosphate levels declined significantly (BL: 6.3 ± 0.9; 3 years: 4.4 ± 1.4

mg/dL; p=0.025). There was a trend to decrease in intact PTH levels, but this change did not achieve statistical significance (BL: 187 ± 174; 3 years: 143 ± 120 pg/ml).

There was a reduction in the total dose of phosphorus binders being prescribed. At 36 months, 92% (34/37) of participants had their phosphorus binding drug reduced to 0.

Erythropoiesis

There was a statistically significant increase in hemoglobin levels after the inception of high-dose home HD (BL: 10.1 ± 0.6; 3 years: 11.5 ± 1.6 g/dL; p<0.01). Additionally, the need for erythropoiesis-stimulating agents (ESAs) fell significantly (BL: 22,166 ± 15,290; 3 years: 14,555 ± 11,648 IU/week; p<0.01), as did the ESA index (BL: 10.2 ± 3.3 ; 3 years: 2.3 ± 2.1 U/kg per g/dL; P<0.0001)

Multivariate regression analysis

In simple correlational analysis, only changes in serum phosphate were significantly correlated with changes in aortic calcification volume (P<0.05). After multiple regression analysis, the differences in serum creatinine, blood urea nitrogen and systolic blood pressure, difference serum phosphate level were significantly related with the changes in aortic calcification volume (F values; 4.18, P=0.048).

Discussion

To our knowledge, this is the first study to assess the effect of high-dose home HD on VC in patients with ESKD. The results suggest that there is attenuation of VC by this modality, and that this attenuation may be causally related to a reduction in serum levels of phosphate. This is an important observation, given the strong relationship between VC and cardiovascular risk in those with ESKD. Our results concur with previous studies showing superior phosphate control with frequent and/or nocturnal HD [8,13]. Only one study has reported less effective phosphate control and an ongoing need for phosphorus binders with this modality [14]. Of note, this study reported on short daily HD where phosphorus removal is primarily dependent on the pre-dialysis phosphorus concentration, session length and frequency, and dietary protein and phosphorus intake. These factors were atypical and important confounders in that previous study, and responsible for its somewhat unusual findings.

High serum levels of calcium, phosphate, and calcium x phosphate product are well established independent risk factors for cardiovascular

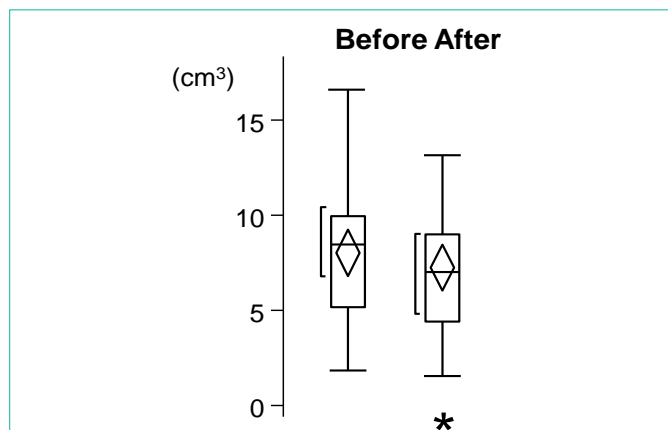


Figure 2: Changes in CT values. The change in the semiquantitative aortic calcification score over three years of high dose home HD, from 7.5 ± 3.4 to 6.6 ± 3.5 (P<0.05).

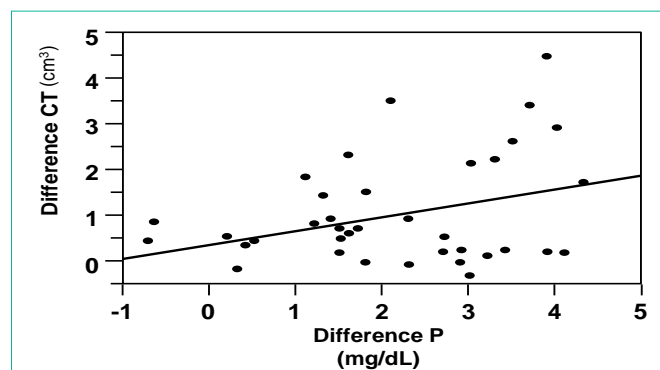


Figure 3: Correlation between differences in serum phosphate and the semiquantitative aortic calcification score over three years of high-dose home HD (P=0.048).

Table 2: Changes in laboratory data before and 3 years after home HD.

| | Before | 3 years |
|---------------------------------|------------|---------------|
| SBP(mm Hg) | 146.2±16.5 | 124.3±16.0*** |
| DBP (mm Hg) | 76.8±6.3 | 72.3±5.04 |
| Creatinine (mg/dL) | 10.4±1.7 | 7.6±2.3**** |
| BUN (mg/dL) | 87.7±13.2 | 36.6±19.6** |
| Calcium (mg/dL) | 9.3±0.6 | 9.0±0.7 |
| Phosphate (mg/dL) | 6.3±0.9 | 4.4±1.4# |
| iPTH (mg/dL) | 187±174 | 143±120 |
| Total cholesterol (mg/dL) | 157.2±34.2 | 178.9±37.9 |
| Albumin (g/dL) | 3.8±0.5 | 4.1±0.4* |
| Hb (g/dL) | 10.1±0.6 | 11.5±1.6* |
| ESA index(U/kg per wk per g/dL) | 10.2±3.3 | 2.3±2.1*** |

SBP Systolic blood pressure; DBP, diastolic blood pressure; BUN blood urea nitrogen; iPTH, intact parathyroid hormone; Hb, hemoglobin; ESA Erythropoietin stimulating agent.

Significance between before and 3 years ** P<0.01 *** P<0.001**** P<0.0001 **** P<0.00001 * P<0.005 # p=0.025

events in those with ESKD [15]. However, it has also been shown by some investigators that these factors directly promote vascular remodelling and VC [16,17]. Not all investigators have shown this to be the case. For instance, Arad et al. did not find associations of serum concentrations of calcium, 1,25-Vit D, and PTH with the presence of arterial calcification [18]. On balance, however, the weight of evidence does suggest that higher concentrations of serum phosphorus and calcium are associated with more extensive VC among patients on HD. In recent years, the underlying mechanisms responsible for this effect have been characterized at the cellular and molecular level, and include the transformation of vascular smooth muscle cells to an osteochondrogenic phenotype in response to increases in phosphorus concentration in the culture medium [19].

Calcification of the abdominal aorta is a well-accepted measure of VC, and a recognized risk factor for cardiovascular morbidity and mortality in patients on HD [20]. As discussed by Hanada et al. [12], the section of the aorta that is best for measuring calcification is that which was used in this study. This section is a site with turbulent flow that is therefore susceptible to development of atheroma. The section is also simple to investigate since it is in a radiologically accessible part of the aorta.

Of note, our results also suggested better control of blood pressure with high-dose home HD, and that this improvement was also independently associated with the decrease in aortic calcification. The improvement in blood pressure control concurs with the findings of others, such as Chan et al. [21] who reported in a retrospective review that 75% of such patients had normal blood pressure values without the concomitant use of antihypertensive agents. In a prospective crossover trial, Fagugli et al. [22] also reported that high-dose home HD improved blood pressure control and decreased antihypertensive requirements. Further both studies included extracellular fluid volume and were able to associate the decrease in blood pressure to a concomitant decrease in extracellular fluid volume. The association between improved blood pressure and aortic calcification in our

study reflects that VC is a multi factorial process. Potentially differing factors may exert maximum influence at either the predisposition, initiation and continuation phases of the process. Knowledge of all the mechanisms responsible for VC is incomplete, as is knowledge of all the measures that might lead to its attenuation. Immutable factors that have been shown to predict VC include older age, longer dialysis vintage, and diabetes. The current study suggests that these mutable factors such as Ca x P product, blood pressure, and uraemic toxemia that might be altered to change the clinical course of patients through high dose home HD.

Lastly, it is well known that malnutrition and inflammation impact survival of ESKD patients. Many investigators have shown that serum albumin levels are depressed in patients on maintenance HD who manifest other signs of malnutrition [23]. In addition, serum albumin levels usually improve as nutrition is replenished [24]. This study shows that these factors improve with high-dose home HD, probably through better control of the uraemic state.

There are several limitations to the current study that need to be highlighted. The CT imaging methods used did not distinguish the two types of VC (patchy calcification of the intimal and calcification of the media). As is known, disturbances of mineral metabolism link specifically with medial rather than intimal calcification, which in turn associates with atherosclerosis. Second, our study was cross-sectional, and does not relate the detection of VC in various vessels to cardiovascular events in a longitudinal fashion. Third, VC represents the result of long-standing atherosclerotic and calcification processes. It is unclear whether the steady-state of serum chemistry such as calcium, phosphate, and intact PTH concentrations measured in this study accurately represents pathological processes that occurred during the development of VC. Fourthly, serum phosphate cannot be taken as an solitary biomarker of VC, and should be interpreted along with full information on other factors regulating mineral balance such as fibroblast growth factor 23 (FGF23). Although FGF-23 was not measured in our study, it is less likely that FGF-23 plays a major role for attenuation of VC considering there have been no reports demonstrating vascular toxicity of FGF-23.

Lastly, we are aware that the sample size of our cohort was small, as well as the limited time of the follow-up to 36 months. This obviously restricts the strength of our conclusions. These limitations only allow for the evaluation of surrogate end-points instead of cardiovascular events. Moreover, the observational nature of the study design did not allow for a direct parallel-group comparison between conventional facility HD and high-dose home HD, and cannot be used to prove causality.

In conclusion, this is the first demonstration that high-dose home HD reduces calcification of the abdominal aorta through attenuation of hyperphosphatemia. Our study has confirmed that selected patients may benefit from this modality, which offers an attractive treatment alternative with benefits that may ultimately have an impact up on patient survival.

Acknowledgements

Professor Mark Marshall, an Associate Professor and the University of Auckland, reviewed our manuscript and gave us precious suggestions.

Disclosure

The first author was provided by Baxter Healthcare Corporation (20110 Renal Discoveries Extramural Grant Program).

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