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Effects of Sodium Thiosulfate on Vascular Calcification in End-Stage Renal Disease: A Pilot Study of Feasibility, Safety and Efficacy

Santhosh Jay Mathews[a] Lisa de las Fuentes[a] Prashanth Podaralla[b] Anton Cabellon[b] Sijie Zheng[b] Andrew Bierhals[c] Karen Spence[a] Eduardo Slatopolsky[b] Victor G. Davila-Roman[a] James A. Delmez[b]

[a]Cardiovascular Imaging and Clinical Research Core Laboratory and Cardiovascular Division, [b]Division of Nephrology, and [c]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo., USA

Key Words
Hemodialysis · Sodium thiosulfate · Vascular calcification

Abstract
Background and Objectives: Vascular calcification is a major contributor to morbidity and mortality in hemodialysis. The objective of this pilot study was to determine the feasibility, safety and efficacy of sodium thiosulfate (STS) in the progression of vascular calcification in hemodialysis patients. ***Methods:*** Chronic hemodialysis patients underwent a battery of cardiovascular tests. Those with coronary artery calcium (Agatston scores >50) received intravenous STS after each dialysis for 5 months (n = 22) and the tests were repeated. Changes in MDCT-determined calcification were assessed as the mean annualized rate of change in 3 vascular beds (coronary, thoracic and carotid arteries) and in L1-L2 vertebral bone density. ***Results:*** Although individual analyses showed coronary artery calcification progression in 14/22 subjects, there was no progression in the mean annualized rate of change of vascular calcification in the entire group. The L1-L2 vertebral bone density showed no changes. There were no correlations between rates of progression of vascular calcification and phosphorus, fetuin or C-reactive protein levels. Changes in coronary artery calcification scores correlated with those of the thoracic aorta. ***Conclusion:*** STS treatment is feasible, appears safe and may decrease the rate of progression of vascular calcification in hemodialysis patients. A large, randomized, controlled trial is warranted.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients undergoing chronic hemodialysis (HD) for end-stage renal disease (ESRD) [1]. Vascular calcification, an active and progressive process involving ectopic osteogenesis, has been implicated as an important mediator of the increase cardiovascular morbidity and mortality [2]. Factors promoting vascular calcification include phosphorus accumulation, uremic toxins, oxidative stress and inflammation, which are opposed by inhibitors of calcification such as fetuin-A [3].

Sodium thiosulfate [STS ($Na_2 S_2O_3$)] has been used to treat calcific uremic arteriolopathy (CUA or calciphylax-

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Fax +41 61 306 12 34
E-Mail karger@karger.ch
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James A. Delmez, MD
Division of Nephrology, Washington University School of Medicine
Campus Box 8129, 660 S. Euclid Ave.
St. Louis, MO 63110 (USA)
Tel. +1 314 362 7207, Fax +1 314 747 3743, E-Mail jdelmez@dom.wustl.edu

is), a process that involves medial calcification of small arteries and arterioles of patients with ESRD. Postulated mechanisms of action of STS in CUA are formation of highly soluble calcium thiosulfate complexes and potent antioxidant properties [4, 5].

The purpose of the current study was to determine the feasibility, safety and efficacy of short-term STS treatment of HD patients on calcification in 3 vascular beds (coronary and carotid arteries, and the thoracic aorta) and on L1-L2 vertebral bone density.

Patients and Methods

Study Population

Forty-eight patients undergoing chronic HD treatments at Washington University Medical Center were enrolled. Inclusion criteria were: (1) ESRD on HD, (2) compliance with treatments as subjectively assessed by the investigators, (3) willingness to undergo intravenous STS treatments for 5 months if eligible and (4) ability to give informed consent approved by the Institutional Review Board at Washington University School of Medicine in accordance with the Declaration of Helsinki. Exclusion criteria were: (1) age <18 years, (2) life expectancy <6 months, (3) pregnancy, (4) current or recent (<12 months) treatment with corticosteroids, and (5) weight >350 lbs (due to inability to perform MDCT). After enrollment, all eligible subjects underwent MDCT for measurement of the coronary artery calcium (CAC) score; only those with a CAC score >50 Agatston units were eligible for STS treatment.

Standard Medications in Dialysis Units

Sevelamer hydrochloride was used to maintain phosphorus levels <5.5 mg/dl. Total elemental calcium did not exceed 1.5 g/day. Ergocalciferol ≥50,000 IU monthly was used to maintain 25-hydroxy vitamin D levels >30 ng/ml. Paricalcitol was used for parathyroid hormone (PTH) levels >300 pg/ml. All patients maintained Kt/V values >1.3 and were treated with high-flux dialyzers; dialysate calcium was 2.5 mEq/l.

STS Treatment Protocol

The study was registered with Clinical Trials (www.clinicaltrial.org), identifier number: NCT00568399. Patients were scheduled to receive a total of 60 STS treatments (intravenous 25% solution; American Reagent Laboratories, Shirley, N.Y., USA) 3 times per week over a 5-month period, starting at a dose of 12.5 g, administered over 30 min after each HD treatment. The dose was increased weekly to 18.75 g and then to 25 g, as tolerated. Since dialysis removes STS, 1 subject who underwent dialysis 4 times a week received a total of 80 treatments over the 5-month period.

Measurements Obtained before and during Treatment

Data on demographics, primary renal disease, comorbid conditions and medications were obtained from hospital and dialysis records at the time of testing. Blood pressure measurements were obtained at the time of the echocardiogram. The calcium, phosphorus, bicarbonate and anion gap values were the mean of each of the monthly levels 4 months prior to treatment and the last 4 months during treatment with STS. Routine laboratory measurements were performed by Spectra Laboratories (Rockleigh, N.J., USA). Serum fetuin-A (Epitope Inc., San Diego, Calif., USA), high-sensitivity C-reactive protein (Life Diagnostics, West Chester, Pa., USA), and PTH (Spectra Laboratories) levels were measured within a month prior to and at the end of STS treatment.

MDCT Imaging for Assessment of Vascular Calcification and Lumbar Bone Density

A 64-slice MDCT scanner (Somatom Sensation 64; Siemens Medical Systems, Forchheim, Germany) measured calcium scores and volumes by the Agatston method [6]. After initial scout imaging, the scan fields were set for the neck, chest and abdomen for measurement of arterial calcification in the carotids (from the arch to 1 mm above the carotid bifurcation), coronary arteries, aortic arch and thoracic aorta (to the top endplate of the T12 vertebral body), and bone density (of L1 and L2 vertebral bodies). The scan parameters included 24 × 1.2 mm collimation, 3-mm slice thickness, 0.37-second rotation time, spiral mode and 120 kVp at 80 mAs with reconstruction at 60% of the R-R interval.

Vascular calcium scores and volumes were measured by use of commercially available software (Vitrea; Vital Images Inc., Minnetonka, Minn., USA) as previously described [6]. All images were randomly evaluated by 2 independent expert observers (S.J.M., A.B.) who were blinded to all clinical characteristics.

Cardiac Structure and Function Evaluation by Echocardiography

Baseline echocardiography to assess cardiac structure and systolic/diastolic function was performed using a commercially-available ultrasound system (Sequoia; Acuson-Siemens, Mountain View, Calif., USA) according to published guidelines [7]. All vascular and cardiac ultrasound studies were analyzed off-line by 2 blinded independent readers using commercially available software (ProSolv CardioVascular; Fujifilm Medical Systems, Stamford, Conn., USA) as previously described by our group [8].

Vascular Structure Evaluation by Carotid Ultrasound

Carotid ultrasound imaging was performed using the ultrasound system described above, with a 15-MHz linear array transducer for measurement of carotid intima-media thickness, as previously described [9].

Vascular Function Assessment

Arterial vascular function was assessed using the SphygmoCor blood pressure analysis system (AtCor Medical, Sydney, N.S.W., Australia) for measurement of the augmentation index and pulse wave velocity as previously described [10].

Statistical Analysis

Variables are expressed as means ± SD. For analysis, progression of vascular calcification by MDCT was defined as the difference between the follow-up and baseline square root-transformed calcium volumes ≥2.5 mm^3 per year. This method has been used previously to assess progression due to the <1% likelihood of being due to variability between MDCT studies [11, 12]. Patients

Table 1. Baseline characteristics of the study population

	Total (n = 22)	Non-progressors (n = 8)	Progressors (n = 14)
Demographics			
Age, years	59 ± 10	60 ± 8	59 ± 11
BMI	30 ± 8	29 ± 4	31 ± 10
Gender, % male	64	88	50
Race and ethnicity			
African American, %	86	88	86
Hemodynamics			
HR, bpm	77 ± 16	75 ± 16	78 ± 16
SBP, mm Hg	129 ± 24	121 ± 20	133 ± 26
DBP, mm Hg	73 ± 12	67 ± 7	76 ± 13
Comorbidity, %			
HTN	95	100	93
Ischemia	77	75	79
CHF	27	25	29
PAD	14	25	7
DM	45	50	43
Statin	59	63	57
Smoking history, %			
Never	41	38	27
Previous	23	25	21
Current	36	38	36
Cause of ESRD, %			
DM	41	50	36
HTN	45	50	43
SLE	9	0	14
PCKD	5	0	5
Hemodialysis			
Vintage, months	67 ± 52	70 ± 68	65 ± 44
Calcium scoring			
Coronary arteries	1,743 ± 1,487	1,622 ± 1,114	1,813 ± 1,700
Thoracic aorta	5,357 ± 4,885	3,231 ± 3,396	6,572 ± 5,289
Carotid arteries	453 ± 479	370 ± 481	501 ± 489
Bone density (L1 and L2)	67,154 ± 16,911	71,045 ± 15,185	64,932 ± 17,978

All p values are nonsignificant. HR = Heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; HTN = hypertension; CHF = congestive heart failure; PAD = peripheral arterial disease; DM = diabetes mellitus; SLE = systemic lupus erythematosus; PCKD = polycystic kidney disease.

Table 2. ESRD-related measures

	Pre-STS	Post-STS
Phosphorus, mg/dl*	5.8 ± 1.2	5.8 ± 1.1
Calcium, mg/dl*	9.0 ± 0.5	9.2 ± 0.5
Bicarbonate, mEq/l**	25.0 ± 2.6	23.4 ± 2.1
Anion gap, mEq/l***	16.2 ± 2.4	21.8 ± 3.2
PTH, pg/ml*	354 ± 296	357 ± 256
Fetuin, g/l*	0.47 ± 0.12	0.44 ± 0.11
hsCRP, ug/ml*	12.4 ± 12.1	19.2 ± 21.6

* p value nonsignificant; ** $p \leq 0.05$; *** $p \leq 0.001$.
hsCRP = High-sensitivity C-reactive protein.

were grouped based on their annualized scores into nonprogressors (<2.5 mm^3/years) and progressors (≥2.5 mm^3/years). Comparisons between the groups were calculated using Wilcoxon-Mann-Whitney tests. Paired tests for differences between pre- and post-treatment were calculated using the Wilcoxon signed-rank test. The correlations between coronary annualized scores and annualized scores for the aorta, carotids and lumbar spine were calculated using Spearman's rank-order coefficients. Statistical analysis was performed using SAS (v. 9.2; SAS Institute, Cary, N.C., USA). All tests were 2-tailed; $p < 0.05$ was considered statistically significant.

Results

Study Population

Forty-eight enrolled subjects underwent the initial cardiovascular tests; 10 were excluded prior to STS treatment due to low CAC scores (<50 Agatston units), and 1 was excluded due to traumatic hip fracture. Of the 37 subjects who were initiated on STS treatment, 2 died (1 each of sepsis and retroperitoneal bleeding), 5 withdrew consent due to nausea and 8 discontinued therapy because of time constraints. Hence, 22 subjects completed the entire protocol.

The baseline characteristics of the study population (n = 22) and for those grouped by nonprogressor (n = 8) versus progressor (n = 14) status are shown in table 1. The majority of subjects (86%) were African American, 45% were diabetics. At baseline, there were no significant differences for any variable between nonprogressors and progressors, although the progressors tended to have higher vascular calcium and vertebral bone density scores.

Treatment with STS

STS infusions at the dose of 25 g/treatment were associated with nausea and vomiting by all despite antiemetic therapy. This was likely due to the short infusion period and administering the drug after HD treatments, thus eliminating dialytic removal. A lower amount was well tolerated with a maintenance dose of 12.5 g/treat-

Table 3. Vascular ultrasound and echocardiographic measurements pre- versus post-STS

	Pre-STS	Post-STS
Vascular structure		
Carotid IMT, mm	0.91 ± 0.18	0.92 ± 0.24
LV structure		
LVM/Ht$^{2.7}$ (g/m$^{2.7}$)	58 ± 18	58 ± 20
LV systolic function		
LVEF, %	57 ± 13	56 ± 13
S', cm/s	7.6 ± 1.1	7.6 ± 1.3
LV diastolic function		
E/A ratio	1.2 ± 0.5	1.2 ± 0.5
DT, ms	205 ± 40	207 ± 59
IVRT, ms	82 ± 23	72 ± 19
E', cm/s	9.1 ± 2.2	9.4 ± 2.5
PWV, m/s (n = 20)	12 ± 5	13 ± 7
PWA (n=16)		
Augmentation index	23 ± 15	23 ± 12
Augmentation index at HR 75	22 ± 14	23 ± 10

All p values are nonsignificant.

IMT = Intima-media thickness; LV = left ventricle; LVM = left ventricular mass; Ht = height; LVEF = left ventricular ejection fraction; DT = deceleration time; IVRT = isovolumic relaxation time; PWV = pulse wave velocity; PWA = pulse wave analysis.

Table 4. Annualized calcium volumes

	Total (n = 22)	Nonprogressors (n = 8)	Progressors (n = 14)	p
Coronary arteries	6.6 ± 9.7	–3.2 ± 3.7	12.3 ± 7.1	0.001
Thoracic aorta	9.1 ± 9.1	2.9 ± 7.5	12.6 ± 8.2	0.033
Carotid arteries	1.9 ± 8.0	3.2 ± 8.6	0.3 ± 7.4	NS
Bone density (L1 and L2)	1.3 ± 15.9	3.2 ± 19.6	0.3 ± 14.2	NS

NS = Nonsignificant.

Table 5. Annualized volumes and correlation with coronary calcification

	Mean ± SD	r	p
Coronary arteries	6.6 ± 9.7	–	–
Thoracic aorta	9.1 ± 9.1	0.61	0.003
Carotid arteries	1.9 ± 8.0	–0.32	0.48
Bone density (L1 and L2)	1.3 ± 15.9	0.16	0.15

ment in 16 patients and 18.75 g/treatment in 6 patients. There were 12 hospital admissions in the 48 subjects: atypical chest pain (n = 3), gastrointestinal bleeding (n = 1), influenza (n = 1), pneumonia (n = 1), back abscess (n = 1), congestive heart failure exacerbation (n = 2), uncontrolled hypertension (n = 2) and asthma exacerbation (n = 1). None of the hospitalizations or deaths were considered to be related to STS treatment as judged by an independent safety committee.

The anion gap increased from 16.2 ± 2.4 to 21.8 ± 3.2 mEq/l ($p \leq 0.001$) and serum bicarbonate levels decreased from 25.0 ± 2.6 to 23.4 ± 2.1 mEq/l ($p \leq 0.05$), likely due to accumulation of thiosulfate. There were no significant changes in heart rate and blood pressure or serum levels of phosphorus, calcium, PTH, fetuin or high-sensitivity C-reactive protein before and after treatment in the entire group (table 2), or between nonprogressors and progressors for any measure. There were no significant changes (pre- vs. post-STS treatment) in vascular structure (carotid intima-media thickness) and function (augmentation index, pulse wave velocity), or cardiac structure and systolic/diastolic function with STS treatment (table 3).

Table 6. Intra- and interobserver reproducibility of volumes

	Number of studies	Intraclass correlation (ρ)	95% CI
Observer 1			
Coronary	24	0.964	0.987–0.900
Aorta	24	0.999	1.000–0.997
Carotid	23	0.993	0.997–0.973
Bone	22	0.997	0.999–0.991
Observer 1 vs. Observer 2			
Coronary	44	0.993	0.995–0.972
Aorta	44	0.991	0.996–0.976
Carotid	44	0.924	0.967–0.811
Bone	44	0.983	0.991–0.945

Vascular Calcification and Lumbar Bone Density

There were no significant differences in the mean annualized rates of change of the square root-transformed calcium volumes of the coronary, thoracic and carotid arteries or of the L1-L2 vertebral bone density for the entire group (fig. 1; table 4). Although there was consider-

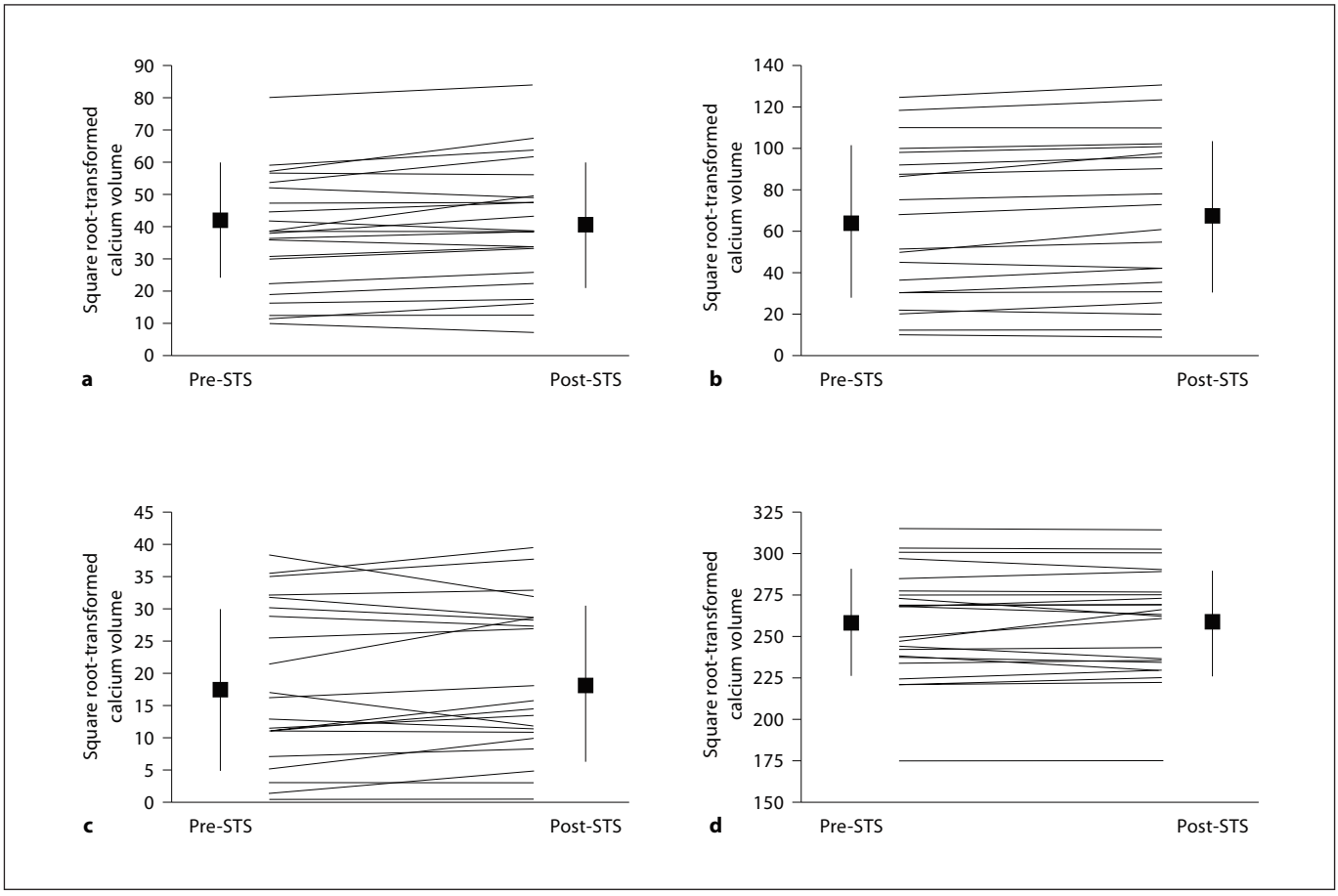

Fig. 1. Individual measurements of vascular calcification volume pre- and post-STS. **a** Coronary arteries. **b** Thoracic aorta. **c** Carotid arteries. **d** Bone density.

able interindividual variability in the calcium scores, for the entire group the coronary artery calcification-transformed annualized rate was 6.6 ± 9.7.

The mean and median coronary artery percentage increase in calcium scores were 17 and 14%, respectively, in the entire group. However, in the 8 patients who showed no evidence of progression, there was a nonsignificant decrease in calcium volumes (mean 9.6%; median 6.1%). Interestingly, those in whom the coronary artery calcification did not progress also had a slower rate of thoracic aortic calcification ($p < 0.05$) compared to those in whom the coronary calcification progressed. The annualized CAC volumes exhibited a modest correlation with the annualized thoracic aorta volumes ($r = 0.61$, $p = 0.003$), but not with those of the carotid arteries or L1-L2 vertebral bone density (table 5). There was excellent intra- and interobserver reproducibility in the determination of MDCT vascular calcium volumes and lumbar bone density (table 6).

Discussion

The present pilot study shows that short-term (60 doses over 5 months) intravenous STS (12.5–18.75 g/treatment 3 times/week) is feasible and fairly well tolerated (with the exception of nausea and vomiting which was controlled by decreasing or avoiding the higher doses). STS treatment showed no overall statistically significant progression of vascular calcification of the coronary and carotid arteries, or of the thoracic aorta. Changes in thoracic aorta calcification, but not carotid arteries, correlated with those of the coronary arteries. There were no adverse effects of treatment on vascular or cardiac structure and function. Furthermore, L1-L2 vertebral bone density remained unchanged with STS treatment in the entire group. However, subgroup analysis revealed progression in 14 of 22 patients. No baseline or treatment variables were associated with progression.

The use of STS for reduction of vascular calcification is supported by studies reporting efficacy in calcific uremic arteriopathy (CUA), urolithiasis and tumoral calcinosis [13]. Disruption of normal calcium-phosphate homeostasis is considered a primary cause for calcium-phosphate deposition in CUA, but this entity can be seen in the presence of normal calcium, phosphate and serum PTH levels [4]. Therefore, other factors can lead to ectopic osteogenesis in the absence of direct calcium/phosphate deposition. STS was first described as an antidote for cyanide poisoning over 110 years ago. It is also used as a dechlorinator, a modifier of platinum-based treatment toxicity, and a topical treatment for acne and pityriasis versicolor [4, 14]. In uremic patients, STS may reduce vascular calcification by forming a soluble complex with calcium that lowers free calcium ions, and/or by antioxidant effects (with improved endothelial function and vasodilatation) [14]. STS has unpaired electrons that may scavenge free radicals to stimulate glutathione production (an antioxidant). Moreover, STS may generate hydrogen sulfide which is a vasodilator and has anti-inflammatory properties and analgesic effects.

Although no large, prospective, randomized trials examining the role of STS in reducing vascular calcification have been published, one small nonrandomized study has studied this in HD patients [15]. In this study, 49 patients with a CAC Agatston score $\geq$300 were enrolled; of these, 16 were selected to receive STS and another 15 comprised a concurrent nonrandomized control group. Patients in the treatment group received 12 g of STS twice a week after dialysis for 4 months. The authors found that STS treatment was associated with no overall progression of CAC. Only 4 of 16 in the STS group were 'progressors' versus 10 of 15 in the control group. The sole predictor of CAC progression was STS treatment. Similarities between the present and the previous study include the lack of a significant increase in the CAC with STS treatment. In addition, the present study also showed no increase in calcium scores of the thoracic aorta and carotid arteries. Furthermore, vascular and cardiac structure and function were evaluated in the present study and found to not change with treatment. Thus, taken together, the results of these 2 pilot studies provide preliminary data supporting the hypothesis that STS treatment may be effective in decreasing progression of vascular calcification in HD patients.

The effects of STS on bone density are different in the 2 studies. The present study showed no change in calcium score in the L1-L2 vertebrae, but the hip was not evaluated. In contrast, hip bone mineral density was decreased, but the vertebral spine was not evaluated in the in the previous study. A recent animal study showed that those treated with STS exhibited decreased bone strength compared to placebo [5]. Thus, the effects of STS on bone density are a potentially serious complication that requires further evaluation.

Several other differences between these 2 studies are worth discussing. First, the patient populations are different: a predominantly African-American population in the present study versus a Thai population in the previous. Second, STS treatment in the present study occurred 3 times/week for 5 months versus 2 times/week for 4 months in the previous study. The doses were similar, with STS 12.5 g/treatment being the predominant dose used in both studies. However, the optimal STS dose and treatment duration remains to be determined.

Studies evaluating progression of established CAC in ESRD patients report annualized increases of 6–104% [16–22]. Variability in progression with these studies may be due to heterogeneity in design, differences in CT scanner type and scoring systems, dialysis vintage, comorbidities (e.g. diabetes and age), and variation in baseline levels of calcium, phosphorus and PTH. Renal transplantation seems to slow the progression of CAC in the ESRD population, but uremia alone does not explain ongoing vascular calcification [20, 23]. Prior studies have demonstrated the effectiveness of statin therapy on reducing CAC progression in those without renal failure: 25–39% annual progression in the untreated versus 8–15% in the treated group [24, 25]. Moreover diabetic status (33% greater annual progression over nondiabetic subjects) and abdominal obesity are predictive of progression [25].

This work may have important implications for vascular calcification in dialysis patients. First, vascular calcification is associated with high cardiovascular morbidity and mortality. Second, vascular calcification tends to be rapidly progressive. Finally, other than noncalcium-containing phosphate binders, treatment options are currently limited for reducing the rate of vascular calcification.

Limitations

Neither this study nor the previous one enrolled a prospective, randomized, placebo-controlled, double-blind control group; therefore, a conclusive statement about the risks and benefits of STS treatment cannot be made. Furthermore, the sample size for both studies was small. The randomization of several hundred HD patients to receive prolonged treatment with STS or placebo likely would be

necessary to attain adequate power in determining STS benefits and risks. Unfortunately, this was beyond our capacity.

Conclusions

This study shows a statistical overall lack of progression in CAC volumes in patients treated with STS, independent of phosphorus, calcium, fetuin or high-sensitivity C-reactive protein levels, and a significant correlation of CAC score changes with aortic calcium scores. Furthermore, STS treatment is feasible, appears safe and may decrease the progression of vascular calcification in HD patients. A large multicenter randomized controlled study to test this possibility is warranted.

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Disclosure Statement

The authors report no conflict of interest relevant to this work.

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