Sodium thiosulfate and coronary calcification

Background. Coronary artery calcification (CAC) is prevalent among haemodialysis patients and predicts cardiovascular mortality. In addition to modifying traditional cardiovascular risk factors, therapy aimed at lowering serum phosphate and calcium–phosphate product has been advocated. Sodium thiosulfate, through its chelating property, removes calcium from precipitated minerals decreasing calcification burden in calcific uraemic arteriopathy and soft tissue calcification. The effect of sodium thiosulfate on CAC in haemodialysis patients has never been studied.

Methods. Eighty-seven stable chronic haemodialysis patients underwent multi-row spiral computed tomography and bone mineral density (BMD) measurement. Patients with a CAC score $\geq 300$ were included to receive intravenous sodium thiosulfate infusion twice weekly post-haemodialysis for 4 months. CAC and BMD were re-evaluated at the end of the treatment course.

Results. Progression of CAC occurred in 25% and 63% of the patients in the treatment and control group, respectively ($P = 0.03$). CAC score was unchanged in the treatment group but increased significantly in the control group. BMD of the total hip declined significantly in the treat-
ment group. In multivariate analysis adjusted for factors that influenced CAC progression, therapy with sodium thiosulfate was an independent protective factor (odds ratio = 0.05, P = 0.04). Major side effects were persistent anorexia and metabolic acidosis.

Conclusions. The effect of sodium thiosulfate in delaying the progression of CAC is encouraging and will require a larger study. Determination of the safe therapeutic window is necessary in order to avoid bone demineralization.

Keywords: treatment; haemodialysis; bone; sodium thiosulfate; vascular calcification

Introduction

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) [1]. In the general population, the presence of coronary artery calcification (CAC) determined by computed tomography (CT) strongly predicts coronary artery disease (CAD) events [2]. In patients on haemodialysis (HD), the prevalence of CAC ranges from 53% to 92%, and its presence is associated with all-cause and cardiovascular mortality [3–7]. Other than standard cardiovascular risk factors, dialysis vintage, serum phosphate, calcium–phosphate product and amount of elemental calcium intake are among CVD risk factors associated with CAC [8]. In order to decrease the calcification burden, therapy aimed at lowering serum phosphate and calcium–phosphate product such as non-calcium-containing phosphate binders and vitamin D analogues have been advocated.

Sodium thiosulfate (STS) is a chelating and reducing agent. The ability of STS to chelate cations results in its widespread use in cyanide poisoning [9]. STS given intravenously post-HD for several months improved wide-spread skin necrosis associated with calcific uremic arteriolopathy and periarticular and soft tissue calcification [10–13]. Through its chelating and antioxidant properties, STS removes calcium from precipitated minerals into more soluble calcium thiosulfate and improved endothelial function [14,15]. Recently, STS has been shown to prevent vascular calcification in uremic rats [16]. To our knowledge, there is no published study on the treatment effect of STS on CAC.

Materials and methods

Patients

Eighty-seven adult HD patients of Ramathibodi Hospital, Mahidol University, (Bangkok, Thailand), who received regular dialysis at the Ramathibodi Hospital dialysis unit, and eight other satellite dialysis units in Bangkok and agreed to participate in the study underwent CAC screening by multi-row spiral CT and bone mineral density (BMD) measurement. Inclusion criteria included age ≥18 years and dialysis vintage of at least 6 months. Exclusion criteria were missing a dialysis session more than twice per month, acute illness and acute inflammation such as infection and malignancy. Of the 87 patients screened, 49 who had a CAC score ≥300 based on Agatston method and were considered eligible for the interventional study [17]. Twenty patients from four dialysis units where the treatment would be administered and monitored were assigned to the treatment group. Control patients were randomly selected based on the first CAC score that fell within 20% of that of patients in the treatment group (CAC-matched control). We were unable to find the control patient that had a CAC score within 20% of the highest CAC score in the treatment group (3399), therefore, the patient with the highest available CAC score of 2178 was recruited. Most of the patients in the control group were dialysed at different dialysis units from the treatment group but belonged to the same group of nephrologists from Ramathibodi Hospital. All patients regularly received blood tests, X-rays and other medical care at Ramathibodi Hospital. Dialysis units where the treatment would be administered were selected based on convenient location and the ease of travel to and from the units. This study was approved by the ethical committee for research involving human subjects of Ramathibodi Hospital, Mahidol University and the institutional review boards of all health centres where satellite dialysis units were located and conducted according to the Declaration of Helsinki. Informed consent was obtained from all patients.

Initially, 20 patients were included to receive STS infusion; however, four patients were excluded due to the following reasons: Two patients requested to discontinue the study during the first 2 weeks due to persistent anorexia despite half the original dose of STS. One patient did not receive the correct dosage of STS, and the other patient had follow-up CAC examination at a different hospital because the CT machine at Ramathibodi Hospital was temporarily unavailable. Thus, 16 patients in the treatment group and their matched controls were analysed. The patients were followed prospectively, and follow-up CAC and BMD examinations were repeated at the same interval. One patient in the control group did not complete the BMD study, therefore, BMD results of the control group were from 15 patients.

Treatment protocol

Twenty-five percent STS (Merck, Darmstadt, Germany), 12.5 g, was given intravenously over 15–20 minutes after HD treatment was completed twice a week for a period of at least 4 months. The STS dose was chosen based on the previously reported studies on the treatment of calcific uremic arteriolopathy which ranged from 5 to 25 g after each HD treatment [10–12]. Two months into the treatment period, one patient with severe CAD and aortic regurgitation developed frequent hypotension during HD, and the dose of STS was decreased by half to avoid precipitating hypotension. Another two patients complained of anorexia and poor appetite that persisted for 24–48 hours after STS administration, and the dose was decreased by half towards the last 2 months of the treatment. STS was discontinued after follow-up CAC and BMD examinations were completed.

Biochemical data

The presence of CAD was defined by a history of myocardial infarction, unstable angina and positive coronary angiography or myocardial perfusion scan. Laboratory data reported at baseline were prior 6-month average values up to the date of first CAC examination. Serum calcium was corrected based on the following equation—corrected calcium = serum calcium + [(40 – serum albumin) / 10 × 0.8]. Routine pre-dialysis blood chemistries were collected prior to the 4-month course of STS therapy and during the treatment course. Post-dialysis blood chemistries were obtained a few minutes post-HD (prior to STS infusion) and immediately after STS infusion was completed. Blood chemistries were analysed by Technicon Auto Analyzer (Dimension RXL, DE). Serum intact PTH was measured by immunoradiometric assay (ELISA-PTH, CIS bio international, France).
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Results

Analysis of CAC progression and BMD changes

Baseline characteristics of the progressors and non-progressors are shown in Table 2. CAD was more prevalent among progressors. Patients with CAC progression received higher elemental calcium intake. A significantly greater number of patients in the non-progressor group received STS therapy. Linear regression analysis demonstrated significant correlation between annualized changes of square root-transformed CAC volume score with log-transformed initial CAC score \( (r = 0.44, P < 0.01) \), baseline phosphate \( (r = 0.42, P = 0.02) \) and calcium–phosphate product \( (r = 0.41, P = 0.02) \). Univariate analysis for factors predicting CAC progression revealed CAD (odds ratio \( \text{OR} = 9, P = 0.009 \) ), log-transformed initial CAC score \( (\text{OR} = 34.9, P = 0.02) \) and STS therapy \( (\text{OR} = 0.2, P = 0.04) \) to be significant predictors. No associations were identified with other baseline data including sex, age, diabetes mellitus, dialysis vintage, dialysis frequency, dialysate calcium, cholesterol, albumin, PTH and elemental calcium and active vitamin D intake. Multivariate analysis adjusted for the relevant factors revealed STS therapy to be the only significant protective factor for CAC progression (Table 3). As for BMD, there was no correlation with any of the baseline factors as well as STS therapy.

Factors associated with CAC progression and BMD changes

Baseline characteristics of the patients are shown in Table 1. There was no significant difference in the baseline characteristics except the treatment group had lower serum albumin and PTH. The mean interscan periods from initial to follow-up CAC examination were 36.8 ± 5.5 and 35.9 ± 6.1 weeks in the treatment and control group, respectively \((P = 0.68)\). The average interval from the first CAC examination to the start of STS treatment was 15.7 ± 4.9 weeks. STS was administered for an average of 21.1 ± 2.6 weeks. To analyse CAC progression, CAC scores were calculated using the volumetric method, which is more reproducible than the traditional area-based Agatston method [21]. The progression was defined as the difference between the follow-up and baseline square root-transformed CAC volume score of ≥2.5 mm³ per year as described previously since this has <1% likelihood of being a result of interscan variability [22,23]. In the treatment group, progression occurred in 4 (25%) patients compared to 10 (63%) patients in the control group \((P = 0.03)\). The changes of CAC volume score were shown in Figure 1. CAC score did not change significantly in the treatment group but increased substantially in the control group. The average rate of rise of CAC score was 13% per year in the treatment and 37% per year in the control group. Two of the four patients that had CAC progression in the treatment group received a half dose of STS infusion during the last 2 months (see Treatment protocol section). Initial and follow-up CAC scores analysed by traditional area-based Agatston method were 904 (range 307–3399) and 1020 mm³ (range 296–4512) \((P = 0.28)\) for the treatment group and 1014 (range 317–2178) and 1275 mm³ (range 429–3367) \((P = 0.004)\) for the control group. BMD of the hip and lumbar spine are shown in Figure 2. In the treatment group, a significant decline in the BMD of total hip was observed.

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment n = 16</th>
<th>Control n = 16*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n/%)</td>
<td>11 (69)</td>
<td>8 (50)</td>
<td>0.28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.6 ± 14.4</td>
<td>65.2 ± 12.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.6 ± 13.5</td>
<td>62.5 ± 12.7</td>
<td>0.29</td>
</tr>
<tr>
<td>DM (n/%)</td>
<td>7 (44)</td>
<td>10 (63)</td>
<td>1.00</td>
</tr>
<tr>
<td>CAD (n/%)</td>
<td>6 (38)</td>
<td>6 (38)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>44.7 ± 33.7</td>
<td>47.2 ± 28.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Dialysis frequency</td>
<td>6 (38)</td>
<td>8 (50)</td>
<td>0.48</td>
</tr>
<tr>
<td>twice/week (n/%)</td>
<td>2.6 ± 0.4</td>
<td>2.6 ± 0.5</td>
<td>0.89</td>
</tr>
<tr>
<td>Baseline laboratory dataa</td>
<td></td>
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<tr>
<td>Cholesterol (mg/dL)</td>
<td>157.3 ± 36.5</td>
<td>176.9 ± 28.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>34.8 ± 2.8</td>
<td>36.8 ± 2.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>9.9 ± 0.5</td>
<td>10 ± 0.8</td>
<td>0.78</td>
</tr>
<tr>
<td>PO4 (mg/dL)</td>
<td>4.9 ± 1.2</td>
<td>5 ± 1.2</td>
<td>0.73</td>
</tr>
<tr>
<td>CaPO4 (mg/dL)</td>
<td>48.9 ± 13.5</td>
<td>50.5 ± 12.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)c</td>
<td>239 (50–966)</td>
<td>390 (132–842)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Elemental</td>
<td>850 (0–3000)</td>
<td>757 (0–2625)</td>
<td>0.66</td>
</tr>
<tr>
<td>calcium (mg/day)d</td>
<td>1.6 ± 2.4</td>
<td>1.8 ± 1.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Active vitamin D (mcg/week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agatston methodc</td>
<td>904 (307–3399)</td>
<td>1014 (317–2178)</td>
<td>0.82</td>
</tr>
<tr>
<td>Volume methodc</td>
<td>771 (236–2701)</td>
<td>840 (292–1826)</td>
<td>0.85</td>
</tr>
<tr>
<td>BMD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lumbar spine (g/cm²)</td>
<td>0.914 ± 0.152</td>
<td>0.937 ± 0.121</td>
<td>0.64</td>
</tr>
<tr>
<td>Hip (g/cm²)</td>
<td>0.773 ± 0.14</td>
<td>0.717 ± 0.084</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Except for BMD which is an average of 15 patients.

aPrior 6-month average values up to the date of first CAC examination.

bMedian (range).

*p < 0.05.

Imaging procedure

Multi-slice CT was performed with the 64-slice technique of 3-mm thickness and programmed calcium scoring (Somaton Sensation Cardiac-64, Siemens, Germany). The CAC score was determined based on Agatston and volume score method as described previously [17,21]. Agatston score was determined by multiplication of the pixel area and the density score whereas the volume score was calculated by multiplying the pixel area by the section thickness. Initial and follow-up CAC scores were reviewed by single observer who was blinded to the treatment protocol. BMD was determined by dual energy X-ray absorptiometry (Hologic, Bedford, MA, USA).

Statistical analysis

Data is presented as mean ± SD unless specified otherwise. The differences between the mean of two groups were analysed by Student’s t-test. In non-normal distribution data, Mann–Whitney U-test and Wilcoxon signed-rank test were applied. Categorical variables were compared using chi-square test. Linear regression analysis was applied to demonstrate the relationship between two continuous variables. Univariate and multivariate logistic regression analyses were used to assess important factors associated with CAC progression. \( P < 0.05 \) is considered to be statistically significant.
resulted in an increase in serum sodium and chloride, a decline in serum bicarbonate and calcium and an elevated anion gap. Pre-dialysis blood chemistries obtained before the start of 4-month STS treatment course and during the treatment course are shown in Table 5. Persistent elevation of serum sodium as well as anion gap into the
next dialysis session was observed. Overall, the reported side effects included anorexia and poor appetite in 15 of 20 patients (75%) resulting in two patients requesting to discontinue the study. Another two patients who complained of persistent anorexia and poor appetite up to 48 hours post-infusion, so the STS dose was decreased by half towards the last 2 months with symptomatic improvement. Other side effects included sneezing in three patients (19%), two episodes of transient hypotension in two patients and one episode of dizziness.

**Discussion**

The present study demonstrated for the first time the possibility of delayed CAC progression by intravenous STS in HD patients. Only 25% of the patients that received STS for at least 4 months showed CAC progression, whereas over 60% that did not receive STS exhibited significant progression. CAC score did not change significantly in the treatment group but increased substantially in the control group. When adjusted for relevant risk factors, the administration of STS retained the significance as protective factor for CAC progression. BMD of the hip declined in the group of patients that received STS therapy.

**The effect of STS in delaying the progression of CAC**

The finding of delayed CAC progression by STS therapy is in agreement with the recently published animal study that reported a protective effect of intraperitoneal STS on vascular calcification in uraemic rats [16]. STS is a chelating and reducing agent. The ability of STS to chelate cations results in its widespread use in cyanide poisoning. STS is normally cleared by the kidney with the half-life of 15 minutes [9]. Half-life was drastically prolonged in drastically in HD patients and was reported to be up to 478 minutes [10]. STS has been used successfully in conditions with increased calcification burden such as nephro lithiasis, calcific uraemic arteriolopathy and soft tissue calcification both in normal and reduced kidney function [10,13,14,24,25]. When STS was given to uraemic rats, enhanced urinary calcium excretion was observed [16]. Therefore, in HD patients, it is likely that precipitated calcium in the coronary arteries was prevented or removed attenuating the calcification burden. Whether this was due to STS removal of calcium from precipitated minerals or the accompanying metabolic acidosis will require further study considering the protective effect of metabolic acidosis on vascular and soft tissue calcification has also been documented [26].

**Baseline factors and CAC progression**

Higher PTH and albumin were observed at baseline in the control group. Studies that demonstrated the association of high PTH with CAC progression are lacking. On the contrary, several groups reported the association of vascular calcification progression with hypoparathyroidism and low bone turnover [27–31]. Others failed to demonstrate
Table 5. Predialysis blood chemistries before and during STS therapy

<table>
<thead>
<tr>
<th></th>
<th>Beforea</th>
<th>Duringb</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/L)</td>
<td>138 ± 2.6</td>
<td>139.8 ± 2.1</td>
<td>0.02*</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>4.5 ± 0.5</td>
<td>4.5 ± 0.6</td>
<td>0.59</td>
</tr>
<tr>
<td>HCO₃ (mmol/L)</td>
<td>98.3 ± 3.9</td>
<td>98 ± 3.2</td>
<td>0.78</td>
</tr>
<tr>
<td>Anion gap</td>
<td>14.9 ± 4.6</td>
<td>17.4 ± 4.6</td>
<td>0.007*</td>
</tr>
<tr>
<td>PO₄ (mg/dL)</td>
<td>4.4 ± 1.5</td>
<td>4.2 ± 1.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>10 ± 0.6</td>
<td>9.7 ± 1.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>34.3 ± 4.2</td>
<td>35 ± 4.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Intact PTH (pg/mL)c</td>
<td>182 (4–791)</td>
<td>182 (10–553)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*aObtained twice predialysis before the start of 4-month STS treatment course.
*bObtained twice predialysis during the 4-month period of STS treatment.
*Median (range).

The increased sodium load and widened anion gap metabolic acidosis during STS therapy has been reported previously [10,11]. The accumulation of thiosulfuric acid was thought to be responsible for the anion gap [10]. The immediate decline in serum calcium was likely the result of chelation property of STS. The reduction in serum calcium appeared to be transient and did not persist into the next dialysis session which could explain the absence of changes in PTH in the long term. Side effects related to anorexia, nausea and vomiting have also been observed by others [10–12,39]. However, in the present study, persistent anorexia resulted in 10% discontinuation and another 10% necessitated dosage reduction. The dose of STS in the present study is relatively low at 12.5 g twice weekly when compared to other reports that administered as high as 25 g three times per week [11,12]. The optimum dose of STS in this regard is yet to be determined, and further studies will be necessary. Other reported reactions such as hypotension and dizziness were transient and disappeared with subsequent dose.

Limitation of the study
The present study is non-randomized and limited by small number of patients. Most of the patients in the control group were dialysed at different dialysis units from the treatment group. Nevertheless, they were from the same population cohort of one hospital centre and belonged to the same group of nephrologists. Baseline characteristics of patients from both groups were comparable. Multivariate analysis was performed to adjust for these potential confounders. The reduction of CAC score after STS therapy could not be demonstrated possibly owing to the average lag time of 3 months before STS was initiated after initial CAC examination. Beneficial effect may be more evident in the patients with lower CAC score. More frequent administration of longer than 4-month duration may be required especially in patients with high initial CAC score.

In conclusion, STS has the potential to delay the progression of CAC in HD patients. Further study is required to determine the safe therapeutic window in order to avoid bone demineralization.

Acknowledgements. We would like to thank the staffs of Pharmacology Department of Rajavithi Hospital and Wichan Prasertsilpakul and Dr. Sutipong Jongjirasiri of Radiology Department of Ramathibodi Hospital for assisting in the project. This work was supported by the Kidney Foundation of Thailand, Faculty of Medicine Ramathibodi Hospital, Mahidol University grant no. 51056/2008 and Vejdusit Foundation under the royal patronage of H.R.H. Princess Galayanivadhana.

Conflict of interest statement. None declared.

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Received for publication: 1.9.09; Accepted in revised form: 14.12.09