Aortic calcification in haemodialysis patients with diabetes mellitus

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Abstract

Background. Certain metabolic disorders, such as hyperphosphatemia, induce vascular calcification in haemodialysis patients; it is unclear, however, whether these disorders contribute to aortic calcification in diabetic haemodialysis patients. This study examined the risk factors of aortic calcification in a large number of haemodialysis patients, and compared risk factors between diabetic and non-diabetic patients.

Methods. The subjects were 667 patients on maintenance haemodialysis: 184 with type 2 diabetes and 483 without. Aortic calcification was measured semi-quantitatively using a plain computed tomography image of the abdominal aorta, and an aortic calcification index (ACI) was calculated.

Results. The ACI of the diabetic subjects was significantly higher than that of those without diabetes (57.3±22.1 vs 44.8±28.3%, P<0.0001), although the dialysis vintage of the former was significantly shorter (P<0.001). Multiple regression analyses showed that diabetes was a significant independent risk factor for increased ACI. Multiple regression analyses, performed separately in diabetics and non-diabetics, revealed that advanced age, higher systolic blood pressure, smoking and longer haemodialysis vintage were common independent risk factors significantly associated with increased ACI in both patient groups (R²=0.296, P<0.0001 for non-diabetics; R²=0.193, P<0.0001 for diabetics). Higher serum phosphate concentration was not significantly associated with increased ACI in diabetic patients (P=0.429), although it was a significant independent factor in non-diabetic patients (β=0.150, P<0.0005).

Conclusion. Aortic calcification in diabetic haemodialysis patients is more advanced, compared with non-diabetic patients, even with short haemodialysis vintage. Since disorders of mineral metabolism are not significantly associated with aortic calcification in diabetic haemodialysis patients, aortic calcification in these patients could be affected by metabolic abnormalities associated with the diabetic state per se, independent of other confounding factors; and aortic calcification may be advanced even before haemodialysis induction.

Keywords: aortic calcification; haemodialysis; phosphate; type 2 diabetes

Introduction

In the general population, diabetes mellitus, the male gender, cigarette smoking, advanced age, hypertension and hyperlipidaemia are the most important risk factors for peripheral vascular disease [1]. Heterotrophic vascular calcification occurs more frequently with advanced age and atherosclerosis, but even more with diabetes mellitus [2]. Vascular calcification, which significantly increases cardiovascular mortality [2,3], is highly prevalent in dialysis patients. Cardiovascular disease and stroke are the leading causes of death in patients with end-stage renal disease (ESRD) dependent on dialysis—where its risk is 10–20 times that in the age- and sex-matched general population [4]. In dialysis patients, disorders of mineral metabolism, particularly hyperphosphataemia, have been emphasized as risk factors for vascular calcification [3,5]. Recently, it was found that vascular calcification was significantly advanced in patients with non-dialysed diabetic nephropathy, when they were compared with diabetic patients without nephropathy or with healthy subjects [6,7]. It is reported that the metabolism of minerals, such as calcium and phosphate, does not affect vascular calcification in non-dialysed patients with diabetic nephropathy [6]. However, the factors affecting vascular calcification in diabetic haemodialysis patients have not yet been analysed. In the present study, in order to determine...
whether disorders of either or both phosphate or calcium metabolism affect vascular calcification in diabetic haemodialysis patients, we studied calcification in the aortas of haemodialysis patients with and without diabetes, and compared the factors affecting aortic calcification in the two groups of patients.

Subjects and methods

Subjects

In January 2002, 791 patients were in haemodialysis treatment for >6 months at the Inoue Hospital Kidney Center (Suita, Japan). Of them, 220 had diabetes and 571 did not. All patients underwent 3-4 h sessions of haemodialysis three times per week. The clinical data of 667 patients (184 with type 2 diabetes and 483 without diabetes) were obtained and examined with their informed consent. Either complete clinical data or informed consent of the remaining 124 patients could not be obtained. The diabetic group consisted of 123 men and 61 women aged from 37 to 79 years (65 ± 9 years; mean ± SD). Of 184 diabetic patients, 36 were being treated with insulin, 18 with oral anti-diabetic agents and 130 with diet only. There was no patient with type 1 diabetes in our cohort, partly due to the small number of type 1 diabetic haemodialysis patients in Japan. The patients without diabetes consisted of 286 men and 197 women aged from 28 to 87 years (59 ± 12 years). This percentage of diabetics (27.5%) was close to their percentage in the entire dialysis population in Japan at the end of 2002 (28.1%, n = 229 538). Blood was drawn before dialysis in a non-fasting condition to measure HbAlc (in the diabetics only) and serum calcium and phosphate (in all patients). The mean value of six measurements during the 6 months before computed tomographic (CT) studies of the aorta was used for the analysis. Serum intact parathyroid hormone (PTH; Allegro Intact PTH; Nichol’s Institute, San Juan Capistrano, CA) was measured once, at the visit when the plain CT was done. This study was approved by the institutional ethics committee of Inoue Hospital.

Blood pressure was measured three times before each dialysis session of a 3 month period, and after the subject had rested supine for at least 10 min, using a standard mercury sphygmomanometer, with the cuff applied to the arm that did not have the arteriovenous fistula. The value used for analysis was the mean of the blood pressures measured before dialysis over the three consecutive months.

Information on smoking habits was obtained via a self-administered questionnaire. Lifelong exposure to smoking was estimated as the product of years of smoking and the number of cigarettes smoked daily at the time of the study (cigarette-years).

Measurement and calculation of the aortic calcification index (ACI)

Between January and December 2001, each haemodialysis patient annually had a CT abdominal scan, to rule out renal cancer mostly arising from acquired polycystic kidney disease. Calcification of the abdominal aorta above its bifurcation was evaluated semi-quantitatively in 10 CT slices at 1 cm intervals, with a slight modification of a technique previously reported by others [8,9]. In brief, the cross-section of the abdominal aorta on each slice was divided into 12 sectors, and the number of sectors with calcification was counted in each slice. The number of sectors with calcification was divided by 12. The values thus obtained for the 10 slices were added together. The totals were then divided by 10 (the number of slices inspected) and multiplied by 100 to express the result as a percentage. This value, the aortic calcification index (ACI), was calculated for each patient and was used as the indicator of the extent of aortic calcification. The evaluation of ACI was performed by a single examiner (H.T.), and the coefficient of intra-observer variation was 4.2%.

Statistical analysis

Data were expressed as mean ± SD. An unpaired Student t-test was performed to compare clinical parameters between patients with and without diabetes. Multiple regression analyses were performed to explore the combined impact of factors affecting aortic calcification in all patients, and in diabetic and non-diabetic patients separately. In the model of multiple regression analyses, age, gender (male = 1, female = 0), smoking (cigarette-years), haemodialysis vintage, diabetes (presence = 1, absence = 0), systolic and diastolic blood pressures, total cholesterol, serum calcium, serum phosphate and intact PTH were included as independent variables. Intact PTH values were logarithmically transformed, because of their skewed deviations. All these analyses were performed on personal computers using a statistics software for Windows (Stat View 5) (SAS Institute Inc., Cary, NC).

Results

Clinical characteristics of patients with and without diabetes mellitus

Table 1 shows the clinical characteristics of patients according to the presence or absence of diabetes mellitus. The diabetic patients were significantly older than the non-diabetic ones (P < 0.001). There were no significant differences in the male/female ratio or serum phosphate between diabetic and non-diabetic patients. The haemodialysis vintage of the diabetic patients was significantly shorter than that of the non-diabetics (57.7 ± 46.5 months vs 139 ± 91.5 months, respectively, P < 0.001). The systolic blood pressure and smoking index of the diabetic patients were higher than those of the non-diabetic patients. Blood urea nitrogen (BUN), serum creatinine, serum albumin concentration, serum calcium and intact PTH of the diabetic patients were significantly lower than those of the non-diabetic patients.

Aortic calcification index

The ACI was normally distributed. The ACI of the diabetic haemodialysis patients (57.3 ± 22.1%) was significantly higher (P < 0.001) than that of those
without diabetes (44.8±28.3%). Since there were significant differences in age and haemodialysis vintage between diabetic and non-diabetic patients, the ACI was examined for each 10 year age band and for each 60 month band of haemodialysis vintage, and it was compared between diabetic and non-diabetic patients.

Table 1. Clinical characteristics of diabetic and non-diabetic haemodialysis patients

<table>
<thead>
<tr>
<th></th>
<th>Diabetic</th>
<th>Non-diabetic</th>
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</thead>
<tbody>
<tr>
<td>Number (males/females)</td>
<td>184 (123/61)</td>
<td>483 (286/197)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65±9***</td>
<td>59±12</td>
</tr>
<tr>
<td>Smoking (cigarette-years)</td>
<td>433±676***</td>
<td>253±414</td>
</tr>
<tr>
<td>Haemodialysis vintage (months)</td>
<td>57.7±46.5***</td>
<td>139.0±91.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>162±17***</td>
<td>151±19</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>74.5±14.8***</td>
<td>79.0±16.4</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>3.6±0.34*</td>
<td>3.69±0.35</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>10.2±2.5***</td>
<td>12.2±3.0</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>163.8±37.3</td>
<td>166.3±35.7</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.0±0.9***</td>
<td>9.4±0.9</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>5.8±1.6</td>
<td>6.1±1.2</td>
</tr>
<tr>
<td>Intact PTH (pg/dl)</td>
<td>144±142**</td>
<td>201±214</td>
</tr>
<tr>
<td>Haemoglobin A1c (%)</td>
<td>6.4±1.3</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.05; **P<0.01; ***P<0.001 vs non-diabetics. **Intact PTH=intact parathyroid hormone. To convert a creatinine value given in mg/dl to μmol/l, multiply by 88.4; to convert cholesterol in mg/dl to mmol/l, multiply by 0.02586; to convert calcium in mg/dl to mmol/l, multiply by 0.2495; to convert phosphate in mg/dl to mmol/l, multiply by 0.32229.

The ACI of diabetic patients aged <50 years and of those aged 61–70 years was significantly higher than those of non-diabetic patients of the same age (61.2±26.7 vs 25.6±26.1%, P<0.001; 58.7±21.6 vs 48.6±29.3%, P<0.01, respectively). There was no significant difference in ACI between diabetic and non-diabetic patients aged 51–60 years and >70 years (47.0±24.5 vs 47.7±26.3%, P=0.8798; and 63.5±16.8 vs 56.4±24.0%, P=0.0801, respectively) (Figure 1).

Significant differences were seen between diabetic and non-diabetic patients with haemodialysis vintages of <60 months and 60–120 months (53.2±22.2 vs 39.2±26.0%, P<0.001; and 63.2±20.5 vs 43.4±27.9%, P<0.001, respectively). There were differences in the ACI between diabetic and non-diabetic patients with haemodialysis vintages of 120–180 months and ≥180 months (63.0±23.0 vs 49.2±28.8%, P=0.1258; and 69.5±20.6 vs 47.3±29.7%, P=0.0522, respectively), although these differences did not reach statistical significance (Figure 2).

Factors associated with increased ACI in all patients

To identify significant factors associated with increased ACI in all patients, multiple regression analyses were performed (Table 2). With model 1, in which the calcium × phosphate product was included as an independent parameter, we demonstrated that age, the male gender, smoking, longer haemodialysis vintage, the presence of diabetes, elevated systolic
blood pressure, total cholesterol and the calcium × phosphate product were significant and independent factors associated with increased ACI ($R^2 = 0.270$, $P < 0.0001$). With model 2, in which serum calcium and phosphate were included as independent parameters (instead of the calcium × phosphate product), we demonstrated that age, the male gender, smoking, longer haemodialysis vintage, the presence of diabetes, elevated systolic blood pressure, total cholesterol and serum phosphate concentration were significant and independent factors associated with increased ACI ($R^2 = 0.273$, $P < 0.0001$). Diastolic blood pressure, serum calcium or intact PTH (with its value logarithmically transformed) were not significantly associated with increased ACI (Table 2). In another analysis, in which pulse pressure was chosen as an independent variable (instead of systolic and diastolic pressures), pulse pressure was a significant and independent factor associated with increased ACI ($\beta = 0.205$, $P < 0.0001$).

Factors associated with increased ACI in diabetic and non-diabetic patients

To assess the factors associated with increased ACI in diabetic and non-diabetic patients, we conducted

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**Table 2.** Factors affecting ACI in all haemodialysis patients (multiple regression analysis)

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
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<th>Model 2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.342</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.349</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Gender (male = 1, female = 0)</td>
<td>0.075</td>
<td>0.0334</td>
<td></td>
<td>0.077</td>
<td>0.0418</td>
<td></td>
</tr>
<tr>
<td>Smoking (cigarette-years)</td>
<td>0.192</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.187</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis vintage (months)</td>
<td>0.222</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.233</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes (presence = 1, absence = 0)</td>
<td>0.144</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.137</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.226</td>
<td>&lt;0.0001</td>
<td></td>
<td>0.240</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>-0.044</td>
<td>0.3121</td>
<td></td>
<td>-0.054</td>
<td>0.2504</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.095</td>
<td>0.0038</td>
<td></td>
<td>0.071</td>
<td>0.0457</td>
<td></td>
</tr>
<tr>
<td>Calcium × phosphate product</td>
<td>0.115</td>
<td>0.0009</td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>-</td>
<td>-</td>
<td></td>
<td>0.025</td>
<td>0.4856</td>
<td></td>
</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td>-</td>
<td>-</td>
<td></td>
<td>0.117</td>
<td>0.0010</td>
<td></td>
</tr>
<tr>
<td>Log (intact PTH)</td>
<td>0.004</td>
<td></td>
<td>0.9011</td>
<td></td>
<td>0.009</td>
<td>0.7903</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.270 ($P &lt; 0.0001$)</td>
<td></td>
<td>0.273 ($P &lt; 0.0001$)</td>
<td></td>
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</tr>
</tbody>
</table>

$\beta =$ standard regression coefficient; $R^2 =$ multiple coefficient of determination.
Factors associated with increased ACI in shorter and longer haemodialysis vintages

To examine the association of diabetes and serum phosphate with ACI, multiple regression analyses were performed according to the length of haemodialysis vintage, in which the same independent variables as in model 2 (Table 2) were chosen. In an analysis of patients with a haemodialysis vintage <60 months (118 non-diabetics and 112 diabetics), diabetes was a significant factor associated with increased ACI (β = 0.174, P = 0.0019), but phosphate was not (P = 0.3628). In patients with a haemodialysis vintage <120 months (231 non-diabetics and 166 diabetics), diabetes was a significant factor (β = 0.195, P < 0.0001), and phosphate was of borderline significance (β = 0.160, P = 0.058). In patients with a haemodialysis vintage >60 months (365 non-diabetics and 72 diabetics), both diabetes and phosphate were significant factors (β = 0.157, P = 0.0006 and β = 0.151, P = 0.0004, respectively). In patients with a haemodialysis vintage >120 months (252 non-diabetics and 18 diabetics), phosphate was a significant factor (β = 0.167, P = 0.0015) and diabetes was of borderline significance (β = 0.089, P = 0.0847).

Discussion

In this study, we examined aortic calcification and measured the ACI of a large number of haemodialysis patients. Our method of measuring ACI has some limitations for the quantitative evaluation of aortic calcification, compared with other quantitative methods, such as electron beam CT. However, our method does not need special equipment, and can semi-quantitatively measure aortic calcification by inspecting multiple aortic slices 10 cm above the bifurcation [8,9]. Although some methodological limitations of measuring ACI may be present in this study, our observations indicated that diabetes was a significant and independent risk factor for aortic calcification in ESRD patients, after adjustment for other confounding factors. Although there were several common risk factors for increased ACI in both diabetic and non-diabetic patients, higher serum phosphate was a significant risk factor for increased ACI in non-diabetic haemodialysis patients, but it was not in type 2 diabetic haemodialysis patients.

The results of the present study—which showed that type 2 diabetes was a factor, among other significant, independent factors, significantly and independently associated with aortic calcification—are consistent with previous studies that examined various sites of vascular calcification [3,5,10]. Although there have been a few reports of studies of the relationship between aortic calcification and diabetes in dialysis patients [9,11,12], those studies examined a relatively small number of patients, and their findings on the effect of diabetes on aortic calcification were not adjusted for age,
haemodialysis vintage or other confounding clinical factors. The present study examined a large number of haemodialysis patients \( (n = 667) \), and clearly demonstrated that diabetes was a significant risk factor for increased ACI, independent of advanced age, derangement of calcium-phosphate metabolism, smoking, blood pressure, cholesterol levels and longer haemodialysis vintage. In diabetic patients, aortic calcification was significantly more advanced than in non-diabetic ones, even though haemodialysis vintage was significantly shorter in the diabetics.

Disordered mineral metabolism, particularly hyperphosphataemia or hypercaleaemia, or both, is one of the factors most frequently quoted in association with vascular calcification in ESRD patients [5,13]. It has been reported that the strict control of serum calcium and phosphate attenuates vascular calcification in animals [14] and in humans on haemodialysis [15]. Serum phosphate was predictive of cardiovascular disease and vascular calcification in haemodialysis patients [10,12,16]. Our study, which showed that a higher serum phosphate level is a significant independent risk factor for aortic calcification, as is the calcium \( \times \) phosphate product (particularly in non-diabetic patients), also emphasizes the importance of strictly controlling serum phosphate in haemodialysis patients, particularly in those without diabetes. In patients with shorter haemodialysis vintages, diabetes was a significant, independent factor associated with increased ACI. In patients with longer haemodialysis vintages, higher serum phosphate was a significant independent factor associated with increased ACI. This result perhaps is partly due to the small number of diabetics with longer haemodialysis vintages in our cohort. However, strict control of phosphate should be considered, particularly in patients with longer haemodialysis vintages.

The risk factors for vascular calcification in diabetic haemodialysis patients have not been reported previously. It is not known whether or not the risk factors for vascular calcification are the same in diabetic and non-diabetic haemodialysis patients. In our previous study, in which we examined the calcification of an artery of the hand (medial calcification), we found that risk factors differed between diabetic and non-diabetic haemodialysis patients: serum phosphate concentration was a significant risk factor for peripheral artery calcification in non-diabetic haemodialysis patients, but not in their diabetic counterparts [17]. In the present study, although higher serum phosphate was identified as a significant independent risk factor for aortic calcification (considered to be mostly intimal calcification) in non-diabetic haemodialysis patients, serum phosphate concentration did not turn out to be a significant risk factor for aortic calcification in diabetic haemodialysis patients \( (P = 0.4219) \). Analysing non-dialysed diabetic patients with nephropathy and serum creatinine in the 2.7 \( \pm \) 0.2 mg/dl range, Mehrotra et al. demonstrated that disorders of mineral metabolism that included calcium, phosphate, intact PTH and 1,25-dihydroxyvitamin D were not significantly associated with the coronary calcification score [6]. Considering their results together with ours, hyperphosphataemia may not be a significant major risk factor for vascular calcification in either non-dialysed or dialysed diabetic patients with chronic renal failure—although hyperphosphataemia is a significant independent risk factor for both medial and intimal arterial calcification in non-diabetic haemodialysis patients.

The present study did not determine the reason why serum phosphate was not a significant risk factor in diabetic haemodialysis patients. One reason might be that arteriosclerosis in non-uraemic diabetic patients is more advanced than in non-diabetics [18], possibly leading to a higher degree of vascular calcification in the former even before dialysis [19]. Atherosclerotic plaque disease with calcification is reported to be highly prevalent in non-uraemic patients with diabetes [20]. It has been reported that diabetic patients with nephropathy have more coronary artery calcification than diabetic patients without nephropathy [6,7]. Reporting on their study of non-dialysed diabetic patients with chronic renal failure (serum creatinine 2.7 \( \pm \) 0.2 mg/dl), Merjanian et al. emphasized that vascular calcification is present, and often severe, long before progression to ESRD [7]. In the present study, in patients with haemodialysis vintages < 60 months and 60–120 months, ACI in the diabetic patients was significantly higher than that in the non-diabetics. This result also suggests that aortic calcification in diabetic patients may be advanced even before they start haemodialysis. Factors other than derangement of phosphate metabolism (as yet unproven) may contribute to vascular calcification in diabetic haemodialysis patients. In the present study, using a multiple regression analysis model, the multiple coefficient of determination \( (R^2) \) in diabetic haemodialysis patients was 0.193, indicating a 19.3% correlation between the ACI risk factors and the condition, while the multiple coefficient of determination \( (R^2) \) in non-diabetic haemodialysis patients was as high as 0.293. The multiple coefficient of determination \( (R^2) \) in the analysis of diabetic haemodialysis patients was smaller than that of non-diabetic haemodialysis patients. This result also suggests that other unknown risk factors for vascular calcification, which were not included in our analyses, may contribute to aortic calcification in diabetic haemodialysis patients. Diabetes is known to be a disease complicated by heterogeneous metabolic risk factors such as hyperglycaemia, hyperlipidaemia, insulin resistance, glycation, oxidative and carbonic stress, and tissue hypoxia [21,22]. In our previous study, poor glycaemic control represented by higher haemoglobin A1c was a significant risk factor of peripheral artery calcification in diabetic haemodialysis patients [17]; however, we did not show the same in our present study, which examined aortic calcification. In a report of a recent study that demonstrated the presence of carboxymethyl-lysine at the site of arterial calcification, Sakata et al. stated that in diabetic patients glycoxidation is associated with calcification of the internal...
Thoracic artery [23]. It is suggested that hypoxia under hyperglycaemia leads to diabetic arteriosclerosis and calcification [22]. Further studies are required to identify the metabolic factors that are related to diabetes, *per se*, that contribute to aortic calcification in diabetic haemodialysis patients.

In conclusion, our study of a large number of haemodialysis patients clearly demonstrated that diabetes is a significant independent risk factor for increased aortic calcification, and that phosphate concentration is a significant independent risk factor for aortic calcification in non-diabetic haemodialysis patients, but not in those with diabetes. This suggests that factors related to the diabetic state, *per se*, which is independent of other confounding factors, may influence aortic calcification in diabetic haemodialysis patients, contributing to significantly greater aortic calcification, even before the onset of ESRD.

Conflict of interest statement. None declared.

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