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Original article

Serum phosphate is an independent predictor of the total aortic calcification volume in non-hemodialysis patients undergoing cardiovascular surgery

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ABSTRACT

Background: A high serum phosphate level is a well-known risk factor for vascular calcification (VC) in patients on hemodialysis (HD). However, the association between the serum phosphate level and VC in non-HD patients is unclear. Our aim was to assess the impact of serum phosphate level on aortic calcification (AC) volume in non-HD patients undergoing cardiovascular surgery.

Methods: A total of 117 patients who underwent thoracoabdominal computed tomography as a preoperative general evaluation before cardiovascular surgery were enrolled. The total AC volume was quantified using the volume-rendering method by extracting the area ≥130 HU within the entire aorta. The total AC volume index (AC-VI) was estimated as the total AC volume divided by the body surface area.

Results: In the 117 patients (64.7 ± 13.1 years, 39% women), the median total AC-VI was 1.23 mL/m^2. The mean estimated glomerular filtration rate (eGFR), adjusted serum calcium levels, and serum phosphate levels were 63.8 ± 19.9 mL/min/1.73 m^2, 9.1 ± 0.4 mg/dL, and 3.6 ± 0.6 mg/dL, respectively. When the patients were classified into four quartiles based on their total AC-VI value, the serum phosphate level showed a positive correlation with a probability of being in the highest AC-VI quartile (R^2 = 0.0146, p = 0.0383) whereas the adjusted serum calcium level did not show a significant correlation (R^2 = 0.0040, p = 0.2615). A similar relationship between the serum phosphate level, adjusted serum calcium level, and AC-VI was confirmed when the total AC-VI was divided into the thoracic AC-VI and abdominal AC-VI. Multivariate analysis indicated that the serum phosphate level was an independent positive predictor of higher total AC-VI quartiles (β = 0.8013, p = 0.0160).

Conclusions: An increase in serum phosphate level was associated with an increased AC burden in non-HD patients undergoing cardiovascular surgery.

Introduction

Vascular calcification (VC) is closely associated with cardiovascular events and mortality [1–3]. It is mediated by complex pathways, including vascular aging, inflammation, and ectopic osteogenesis [4–9]. Although the cardiovascular system serves as the "host" of VC, it is unclear whether the etiology of and risk factors for VC are similar among different cardiovascular tissue types, such as the elastic artery, muscular artery, valvular attachments, leaflets, and sinuses. Therefore, it is unclear how these complex multifactorial interactions amplify VC [4,9].

High serum phosphate levels are a well-known risk factor for VC in hemodialysis (HD) patients [10–12]. Moreover, several recent observational studies involving non-HD patients demonstrated that

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higher serum phosphate levels—even those within the normal range—may be a risk factor for coronary artery calcification [13], aortic valve calcification [14], and aortic and mitral annular calcification in the general population [15]. However, whether serum phosphate levels have a similar impact on the total aortic calcification (AC) volume in non-HD patients remains unclear. In this study, we aimed to assess the contribution of the serum phosphate level to the prediction of AC volume in non-HD patients by quantifying the total AC volume using a volume-rendering (VR) method with multidetector-row computed tomography (MDCT) [16].

Materials and methods

Study population

Between January 2011 and December 2013, non-electrocardiogram-gated thoracoabdominal non-contrast-enhanced computed tomography (CT) was performed in 134 patients who were scheduled to undergo cardiovascular surgery. Nine patients with aortic aneurysms (maximum minor axis ≥45 mm for the thoracic aorta, ≥30 mm for the abdominal aorta), three patients undergoing HD, and five patients with a history of aortic surgery were excluded. All the patients underwent clinical history taking, coronary risk factor screening, physical examination, laboratory analyses, transthoracic echocardiography, carotid ultrasonography, and pulse wave velocity (PWV) assessment. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive agents. Dyslipidemia was defined as a low-density lipoprotein cholesterol level ≥ 140 mg/dL, high-density lipoprotein cholesterol level < 40 mg/dL, triglyceride level ≥ 150 mg/dL, or the use of oral lipid-lowering agents. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL, random non-fasting glucose level ≥ 200 mg/dL, hemoglobin A1c ≥ 6.5%, or the use of an oral hypoglycemic agent or insulin. MDCT was performed as a preoperative general evaluation to obtain detailed information regarding AC around the vascular access and clamping and anastomotic sites to prevent perioperative cardiovascular complications, as well as to evaluate the lung field to prevent perioperative pulmonary complications. Every MDCT scan was performed after informed consent was obtained, and the study received approval from the institutional review board of the Kobe University Hospital.

Laboratory analyses

A blood sample was collected in the morning with the patients in a fasting state. Serum inorganic phosphate and serum total calcium levels were determined with enzyme methods using commercially available test reagents (Kyowa Medex, Tokyo, Japan; Shino-Test, Tokyo, Japan, respectively) on the auto-analyzer (BioMajesty JCA-BM 8040, JEOL, Tokyo, Japan). The serum calcium level was adjusted using the following equation: adjusted serum calcium level (mg/dL) = serum calcium level (mg/dL) + 4.0 − albumin (g/dL) (apply 4.0 if albumin ≥ 4.0). Renal function was estimated based on the serum creatinine level [estimated glomerular filtration rate (eGFR)] from the following equation defined by the Japanese Society of Nephrology: eGFR = 194 × serum creatinine level (mg/dL)$^{-1.094}$ × age (years)$^{-0.287}$ (if female × 0.739) (mL/min/1.73 m^2).

CT image acquisition

Image acquisitions were performed using commercially available MDCT scanners (Aquilion One, Toshiba Medical Systems, Tochigi, Japan; SOMATOM Definition Flash, Siemens Healthcare, Erlangen, Germany) with a routine protocol. All images were acquired during an inspiratory breath hold, with the following parameters: tube voltage, 120 kV; tube current, modulated with automated exposure control; and gantry rotation time, 500 ms. To reconstruct the raw image data, we used a section thickness of 5 mm, field of view of approximately 30 cm, and a matrix of 512 × 512.

VC evaluation and AC quantification

The prevalence of coronary arterial calcification, aortic and mitral valvular calcification, and AC was assessed using MDCT. Further, total AC volume was quantified using a validated VR quantification method that we previously reported [16]. Three-dimensional images of AC reconstructed using the VR method are shown in Fig. 1. Briefly, from the reconstructed volume-rendered image of the entire body trunk, the volume with a density of ≥130 HU, from just above the left main trunk to the aortic bifurcation, was extracted using semi-automatic software. Crude clipping of the volume, including the total aorta, was then performed. After being viewed from multiple directions, the total AC volume was extracted and quantified by deleting any

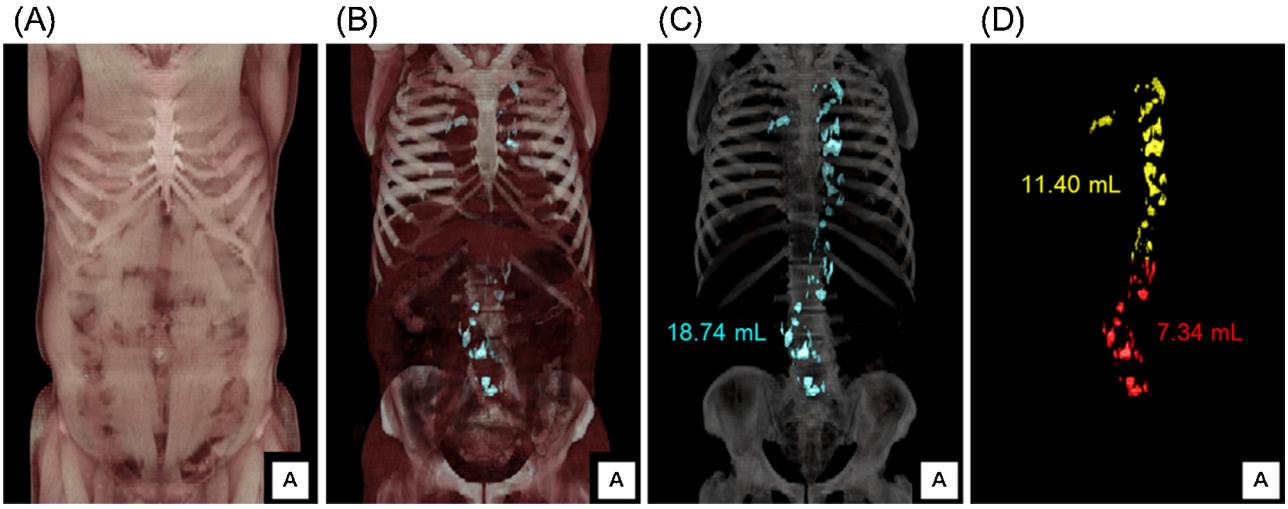

Fig. 1. Volume-rendered total aortic calcification image that was fused with a body trunk image. Aortic calcification volume (sky-blue) was extracted using a volume-rendering method and fused with a volume-rendered whole body trunk image. The transparency of the body trunk was increased (A–C) to emphasize the location of the total aortic calcification. The total aortic calcification volume (≥130 HU) was quantified as 18.74 mL (C). The total aortic calcification was divided into thoracic (yellow) and abdominal (red) aortic calcifications (D). The thoracic and abdominal aortic calcification volumes were quantified as 11.40 and 7.34 mL, respectively.