

## Cystatin C as a Promising Biomarker of Atherosclerotic Plaque

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Complex atherosclerotic lesions of the aorta, including those of the aortic arch and descending aorta are challenging. When performing surgery for aortic aneurysm, the preoperative assessment of atherosclerotic plaque in the aorta is important to minimize embolic complications affecting the brain and distal organs. However, biomarkers for aortic plaque have not yet been fully investigated.

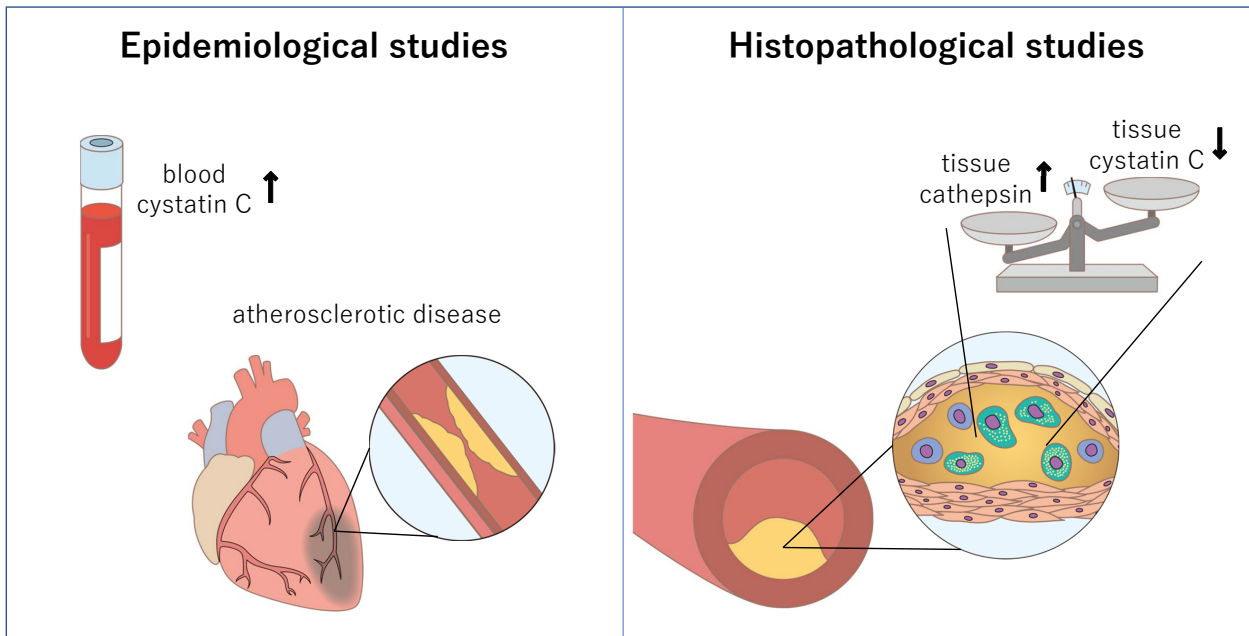
In this issue of the Journal of Atherosclerosis and Thrombosis, Nishimura Y *et al.*<sup>1)</sup> examined the association of serum cystatin C levels with aortic plaques of the descending aorta in patients scheduled to undergo surgery for aortic arch aneurysm. Nishimura Y *et al.* assessed the quantity and quality of descending aorta plaques using the Hounsfield unit (HU) method of computed tomography angiography (CTA). They revealed the following novel findings. First, soft plaque volume of the descending aorta in patients with chronic kidney disease (CKD) was higher than in those without CKD. Second, serum cystatin C levels correlated with the total and soft plaque volumes of the descending aorta in those without CKD. Notably, however, serum creatinine levels had no correlation with any types of plaque volume. Third, soft plaque volume was higher in patients with high cystatin C level ( $>0.95$  mg/L) than in those with low cystatin C level ( $\leq 0.95$  mg/L), despite normal renal function ( $eGFR \geq 60$  mL/min/1.73m<sup>2</sup>).

Cystatin C is a protein encoded by the CST3 gene and is a cysteine protease inhibitor produced by all nucleated cells at a constant rate; it is found in all tissues and body fluids<sup>1)</sup>. Cystatin C plays an important role in the atherosclerotic process, i.e., inhibiting the cathepsin-dependent proteolytic activity in the

vascular wall. The remodeling of the extracellular matrix (ECM) in the vascular wall is an important feature of the atherosclerosis pathogenesis. The imbalance between cathepsin and cystatin C in vascular local sites may result in increased degradation of ECM, leading to the development of an atherosclerotic plaque. Indeed, human pathological studies have shown increased cathepsin and decreased cystatin C expressions in atherosclerotic lesions<sup>3)</sup>.

In clinical practice, serum cystatin C level is a well-established biomarker of the kidney function (filtration). Because cystatin C is a low-molecular-weight protein (13 kDa) consisting 120 amino acids, it is freely filtrated at the glomerulus, fully reabsorbed and catabolized, but not secreted, by the nephron tubule. Moreover, cystatin C is less influenced by age, gender, or muscle mass. Thus, serum cystatin C level is believed to be a more accurate biomarker than serum creatinine level for the estimation of kidney function<sup>4)</sup>.

Beyond its clinical use as a biomarker of kidney function, serum cystatin C level has been shown to be a superior predictor of cardiovascular disease compared to serum creatinine level. Several epidemiological studies consistently reported that the increased serum cystatin C levels were associated with the development of cardiovascular event or mortality<sup>5-8)</sup>. Shlipak MG *et al.*<sup>5)</sup> reported a cohort study of 4,637 elderly people living in the community. On comparison with the two lowest quintiles combined (serum cystatin C level,  $\leq 0.99$  mg/l), the highest quintile of cystatin C ( $\geq 1.29$  mg/l) was associated with a significantly elevated risk of death from cardiovascular causes (hazard ratio, 2.27; 95% confidence interval=1.73–2.97), myocardial infarction (hazard ratio, 1.48; 95% confidence interval=1.08–2.02), and stroke (hazard ratio, 1.47 95%; confidence inter-



**Fig. 1.**

The discrepancy between the increased blood cystatin C levels in cardiovascular disease in numerous epidemiological studies and decreased tissue cystatin C levels in atherosclerotic plaques in histopathological studies

val= 1.09–1.96) after multivariate adjustment. In contrast, the fifth quantile of serum creatinine level was not independently associated with any of these outcomes as compared with the first quintile. Furthermore, Gu FF *et al.*<sup>9)</sup> reported that serum cathepsin S and cystatin C levels were significantly higher in the unstable angina group than in the stable angina group, and serum cystatin C levels positively correlated with the coronary plaque area and plaque burden evaluated using intravascular ultrasound (IVUS) in the unstable angina group with normal renal function (eGFR  $\geq$  90 ml/min/1.73m<sup>2</sup>). Král, A *et al.*<sup>10)</sup> evaluated the association between serum cystatin C levels and coronary plaque phenotype in patients with preserved renal function (eGFR  $>$  60 ml/min/1.73m<sup>2</sup>). The coronary plaque phenotype was assessed according to the Liverpool Active Plaque Score (LAPS), which is designed to distinguish stable and unstable plaques using IVUS. Higher plasma cystatin C levels were associated with higher LAPS, indicating unstable plaque. Moreover, the positive association between serum cystatin C levels and atherosclerotic plaques has been reported in arteries other than the coronary artery. As for the carotid artery, Wen Y *et al.*<sup>11)</sup> reported that higher serum cystatin C levels were associated with higher plaque area and plaque score of carotid arteries using ultrasonography in patients with preserved renal function (eGFR  $\geq$  60 ml/min/1.73m<sup>2</sup>). As for the aorta, Nishimura Y *et al.*<sup>1)</sup> reported that serum cystatin C

level was associated with total and soft plaque volumes using CTA in patients without CKD (eGFR  $\geq$  60 mL/min/1.73m<sup>2</sup>). Altogether, several epidemiological studies have consistently documented the positive association between serum cystatin C level and atherosclerotic disease.

The discrepancy between the increased serum cystatin C levels in cardiovascular disease in numerous epidemiological studies and decreased tissue cystatin C levels in atherosclerotic plaques in pathological studies remain unsolved (Fig. 1). Atherosclerosis is an inflammatory disease characterized by remodeling of ECM of the arterial walls. Tissue cystatin C levels are reduced against proteolytic activity of cathepsin within atherosclerotic plaque. Inflammatory cytokine stimulates cells to produce cystatin C for systemic circulation, thus presumably compensating for the decreased cystatin C levels in atherosclerotic plaques. The above description is only a hypothesis, and further studies are needed to examine whether this hypothesis is correct.

### Conflict of Interest

None.

### References

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