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Editorial

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Chronic Kidney Disease and Atherosclerosis: An Important Implication of Carotid Intima-Media Thickness

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Recently, noninvasive simple methods including carotid intima-media thickness (IMT), pulse wave velocity (PWV), ankle-brachial index (ABI), flow-mediated vasodilatation (FMD), and coronary artery calcification score (CACS) are available to evaluate atherosclerotic vascular damage. These parameters could provide reproducible and reliable information and are used not only as risk assessment and predicting factors for future cardiovascular (CV) events but also as tools to evaluate the efficacy of interventional treatment[1].

A vicious association might exist between chronic kidney disease (CKD) and atherosclerosis. Carotid max-IMT is increased in patients with CKD even in its early stage[2], and has an impact as a predictor of future CV events and deaths in predialysis and dialysis CKD patients[3-5]. Decreased renal function was associated with accelerated increase of carotid IMT[6]. Many factors, including increased production of proinflammatory cytokines, oxidative stress, acidosis, altered lipid metabolism, accumulation of uremic toxins such as indoxyl sulfate, and gut microbiota dysbiosis, contribute to the setting of inflammatory status of CKD. Relationship between circulating inflammatory monocytes and carotid IMT has also been recently reported[7]. Thus, inflammatory status of CKD might promote the accelerated increase of carotid IMT. Inversely, whether carotid IMT is useful to predict the progression of kidney disease was not clarified[8]. Previous studies failed to demonstrate increased carotid IMT as a predictor for accelerated decline of glomerular filtration ratio (GFR)[3, 5]. In this issue of Journal of Atherosclerosis and Thrombosis, Manabe *et al.* provided for the first time the evidence that carotid IMT was a predictor of renal outcome in patients with CKD[9] **(Fig. 1)**. They revealed a higher carotid max-IMT independently predicted renal outcomes including estimated GFR decline and end-stage renal disease in patients with CKD aged <65 years in a long-term prospective observational study. On the contrary, in patients with aged $\geqq 65$ years, disease progression was not significantly associated with carotid max-IMT. It might be important to evaluate carotid max-IMT in all CKD patients including elderly. However, the meaning of carotid max-IMT may be different between younger and elderly patients with CKD.

Carotid IMT is comprised of three portions, i.e., common carotid artery (CCA)-IMT, carotid bulb-IMT, and internal carotid artery (ICA)-IMT. Carotid max-IMT usually means max CCA-IMT or most thickened IMT among CCA, bulb, and ICA. In general, max CCA-IMT is used for the evaluation of atherosclerosis and risk stratification for future CV events. Max CCA-IMT usually indicates diffuse arterial wall thickening, and max ICA-IMT reflects the existence of focal atherosclerotic plaques. Polak *et al.*[10] reported segment-specific associations of carotid IMT with CV risk factors (CCA-IMT with fasting blood glucose and diastolic blood pressure, bulb-IMT with hypertension, diabetes and smoking, and ICA-IMT with low-density lipoprotein cholesterol) in the general population. They also reported that the max-IMT more than 1.5 mm (and presence of plaque in) of ICA, not max CCA-IMT, significantly contributed to the increase of the predictive power of the risk factors for CV events used in Framingham risk score[11]. Therefore, when we evaluate carotid IMT, it is important to consider where (CCA, bulb, or ICA), how (max-IMT or mean-IMT), and which is the major

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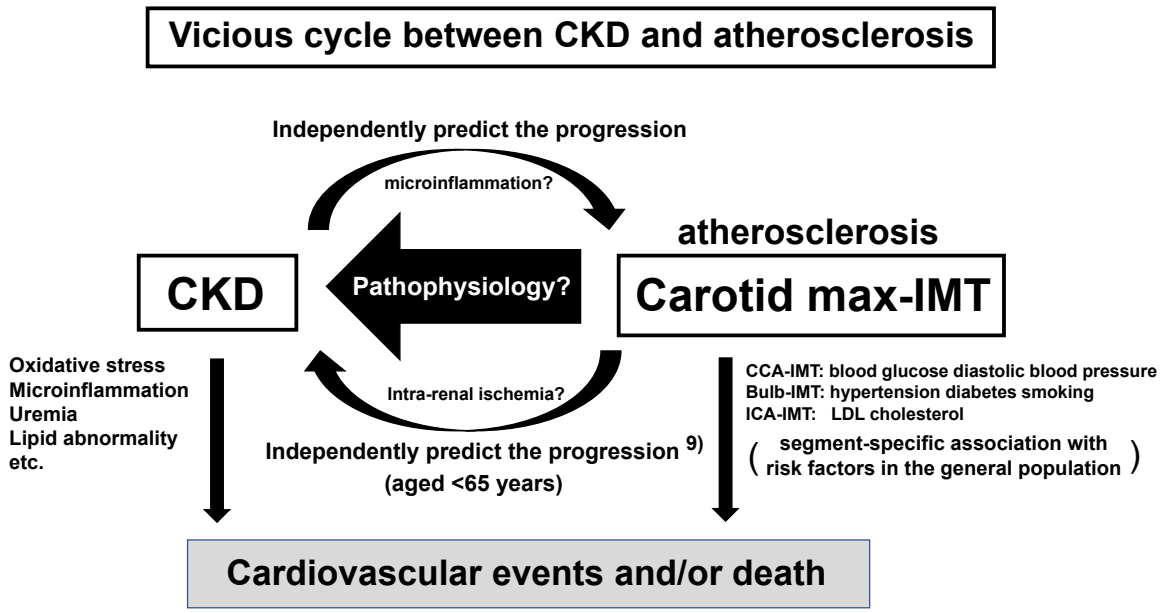

Fig. 1. Vicious cycle between CKD and atherosclerosis

CKD; chronic kidney disease, IMT; intima-media thickness, CCA; common carotid artery, ICA; internal carotid artery, LDL; low-density lipoprotein.

determinant of IMT. In the manuscript by Manabe *et al.*[9], distribution of max-IMT in 112 CKD patients was CCA/bulb/ICA=16.1%/33.9%/50.0%, and the major determinant of max-IMT was max-ICA-IMT. As shown in their study, carotid max-IMT, especially max ICA-IMT (and existence of plaque), might be an important predictive factor for the progression to end-stage renal disease, as well as its implication for the progression of CVD. The precise mechanisms why increased carotid max-IMT predict the progression of CKD to end-stage renal disease still remains to be elucidated. Because the increased carotid max ICA-IMT usually implies the existence of plaques in the arterial walls, micro plaque constituents in the blood stream delivered by plaque rupture might be associated with the progression of CKD. Progression of atherosclerotic vascular damage in renal vasculature might be another possible explanation. Evaluation of circulating plaque-related substances such as cholesterol crystals along with the changes of arterial walls, or association between renal histology and carotid IMT might be necessary to further elucidate the pathophysiology of close association between CKD and atherosclerosis. Furthermore, besides the changes of arterial walls due to atherosclerosis, blood rheology might be associated with microcirculatory renal impairment[12].

Undoubtedly, noninvasive measurement of carotid IMT could provide us reproducible and reliable information. To break off the vicious cycle between CKD and atherosclerosis which starts from their early stages, risk stratification of progression to end-stage renal disease should be, at least, correctly performed with additive noninvasive reliable tests including carotid IMT.

Conflict of Interest

Dr.Ohtake: no conflict of interest.

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