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EDITORIAL COMMENT

Arterial Stiffness as a Predisposing Factor for Chronic Kidney Disease*

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Chronic kidney disease (CKD) is a progressive condition resulting in cardiovascular diseases (CVDs) or death, and the global burden of CKD is substantial and growing. Because CKD is an irreversible process, it is essential to reduce the global burden by early interventions to slow the progression of CKD in people at risk. It is well known that CKD is most commonly attributed to diabetes and/or hypertension.[1,2] Apart from hypertension and diabetes, many ongoing researches are into finding potential contributory factors, among which is arterial stiffness (AS).

AS is recognized as an independent risk factor for CVD, distinct from other risk factors. The traditional method for measuring AS is through carotid-femoral pulsed wave velocity (cfPWV). Association of AS measured by cfPWV with hypertensive complications and cardiovascular risk, including kidney disease, is globally well recognized. Brachial-ankle pulsed wave velocity (baPWV), an alternative measurement tool, offers the convenience of measurement and various advantages over baPWV, and encompasses not only the central or elastic arteries, which are age-sensitive, but also the peripheral or muscular arteries. The Japanese Society of Hypertension guidelines already recognized the usefulness of baPWV for hypertension management,[3] and the 2023 European Society of Hypertension guidelines also recommend it as a screening tool.[4] Even though some studies suggest that baPWV may predict CVD similar to cfPWV, considering it as an independent risk factor,[5] there is a need for further research due to the lack of standardization in measurement methods, the lack of clinical application, and a shortage of large prospective studies. It is still somewhat overlooked in Western countries for several reasons. Therefore, caution is still warranted in its interpretation and application of the test, and it is currently the subject of active research in East Asian countries.

There are several previous studies on showing the association of AS and CKD or suggesting the pathomechanism of the association. AS can lead to CKD through mechanisms such as high systolic blood pressure, high pulse pressure, and high pulsatility in microcirculation, resulting in glomerular injury, hypoxia, and fibrosis, ultimately contributing to CKD progression. Conversely, the increase in AS due to CKD is elucidated by hyperphosphatemia, hyperuricemia, increased body sodium, activation of the renin-angiotensin-aldosterone system, and high sympathetic activity, which result in endothelial cell dysfunction via reduced nitric oxide production and increased oxidative stress, along with the accumulation of atheroma plaque, inflammatory cytokines, collagen deposition, and calcification in the tunica intima and media, ultimately increasing the AS.[6]

In this issue of *JACC: Asia*, Tian et al[7] utilized the existing Kailuan cohort in China to investigate the association between baPWV and the incidence of CKD using longitudinal data. A total of 10,535 participants who were free of history of CVD or CKD and had first baPWV and estimated glomerular filtration rate (eGFR) data prior to 2014 were enrolled in longitudinal analysis, and among those, 7,753 patients were able to have a follow-up baPWV study. When compared with a normal AS group, borderline AS and elevated AS groups had 54% and 120% higher risks of developing CKD, respectively. Furthermore, the authors used cross-lagged panel analyses to estimate directional relationships from one to another and vice versa. As a result, baseline baPWV was associated

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with the subsequent incidence of CKD, indicating AS as a causative factor of CKD.

First, while there have been some studies with similar results, this paper stands out from other reports for its large population study design, with 7,753 patients enrolled in the study, while other studies were only able to enroll hundreds of patients with baPWV values. Second, this study employed a crossed-lagged panel study, rather than a cross-sectional approach, succeeding in analyzing the temporal relationship between the 2 factors. While some previous studies presented the 2-way pathomechanism between AS and CKD,[6] this research distinguishes itself by showing insignificant association from decline eGFR to subsequent AS, indicating that kidney function decline was the consequence of increased AS. Furthermore, by conducting several additional sensitivity analyses by using Chronic Kidney Disease-Epidemiology Collaboration China equation, excluding incident CKD events within <1-year follow-up, using a competing risk model, adjusting HR with age and blood pressure category, and imputing missing data, the authors were able to obtain more robust results.

In conclusion, this paper ultimately asserts that AS can potentially serve as a primary cause of CKD, and recommends that measures to control AS should be undertaken to prevent the onset and progression of CKD. This study specifically highlights that renin-angiotensin-aldosterone system blockers can alter the properties of arterial walls and reduce vascular resistance and cardiac output, thereby lowering AS. Because both angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are already noted for their capability in reducing the development of CKD, their use can concurrently impede the occurrence of both AS and CKD.

However, because the aim of this study is to examine the changes in eGFR values over time in relation to an individual's increase of AS, the focus should be on capturing within-person effects rather than between-person effects, and utilizing a random intercept cross-lagged panel model would have been more appropriate, as mentioned in the Study Limitations. Moreover, conducting investigations with multiple waves data, rather than 2 waves of measurement, would have yielded more reliable results. Using baPWV as an indicator of AS can be imprecise, as baPWV reflects muscular arteries, which are less sensitive to aging and cardiovascular risks. Furthermore, baPWV can vary depending on many factors such as patient's vascular condition, height, age, and race. An insignificant relationship between eGFR decline and subsequent baPWV should also not be interpreted as no effect of CKD on AS, considering that the threshold effect and patients with CKD at the baseline were excluded in this study.

For the clinical implication of this research, further prospective research should be done to determine whether early interventions of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with increased AS but without kidney dysfunction could reduce the incidence of CKD.

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