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Age-related Changes in Renal Arterio-Arteriolosclerosis in Kidney Disease: Renal Biopsy-based Study

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Preglomerular afferent arterioles play a pivotal role in the regulation of glomerular hemodynamics.[S1] Morphologic analyses suggest that functional and morphologic changes in afferent arterioles might be linked to glomerular hypertension and renal ischemia,[1] which are common mechanisms underlying progressive kidney disease.[S2,S3] Traditional risk factors such as hypertension and diabetes mellitus are associated with renal arteriolosclerosis.[2–4] Previous studies have demonstrated that the prevalence rates of arteriolar hyalinosis and renal arterial narrowing increase with increasing age in healthy kidney donors.[S4,5] Aging may be an independent factor for renal arterio-arteriolosclerosis in individuals without chronic kidney disease (CKD), given that kidney donors rarely harbor traditional risk factors. CKD *per se* is an established risk factor for atherosclerotic diseases.[S5] Nontraditional risk factors for CKD, such as oxidative stress and inflammation, might induce systemic atherosclerosis, including the kidneys via vascular endothelial dysfunction.[6,S6] Thus, aging is suggested to worsen arterio-arteriolosclerosis, a major structural change observed in nephrosclerosis, in patients with CKD.[7] An autopsy study suggested that atherosclerotic lesions in aorta and coronary arteries might develop between adolescence and the age of <35 years.[S7] However, it remains unclear whether aging is associated with renal arterio-arteriolosclerosis in patients with CKD independently of the accumulation of traditional and nontraditional risk factors, especially during the years between adolescence and middle age.

We therefore conducted a cross-sectional study to examine the relationship between age and the severity of renal arterio-arteriolosclerosis in patients with kidney disease (including those with estimated glomerular filtration rate [eGFR] >60 ml/min per 1.73 m^2 and proteinuria and/or hematuria) who underwent renal biopsy (Supplementary Figure S1, Supplementary Tables S1 and S2). In this cross-sectional observational study of 139 patients with CKD (mean age, 44 years), semiquantitative assessment of renal arteriolar hyalinosis and arterial intimal thickening, and quantitative assessment of wall-to-lumen ratio were performed (Supplementary Methods, Supplementary Figure S2). We examined the prevalence and severity of these parameters across age groups (10–19 years, 20–29 years, 30–39 years, and ≥40 years).

The indices of arteriolar hyalinosis, arterial intimal thickening, and the wall-to-lumen ratio exhibited a linear increase with increasing age, independent of sex (Figure 1), although there were relatively small differences in the wall-to-lumen ratio across the age groups. The indices of arteriolar hyalinosis and arterial intimal thickening were significantly higher in the 30 to 39 years and the ≥40 years age groups compared with the 10 to 19 years age group (Figure 1a and 1c). The proportions of patients with grade ≥1 arteriolar hyalinosis, wall-to-lumen ratio, and arterial intimal thickening significantly increased with increasing age (Figure 1d–f). The multivariate logistic regression analysis revealed that age ≥30 years was significantly associated with the presence of arteriolar hyalinosis and arterial intimal thickening, independent of the traditional and nontraditional risk factors as well as eGFR (Table 1).

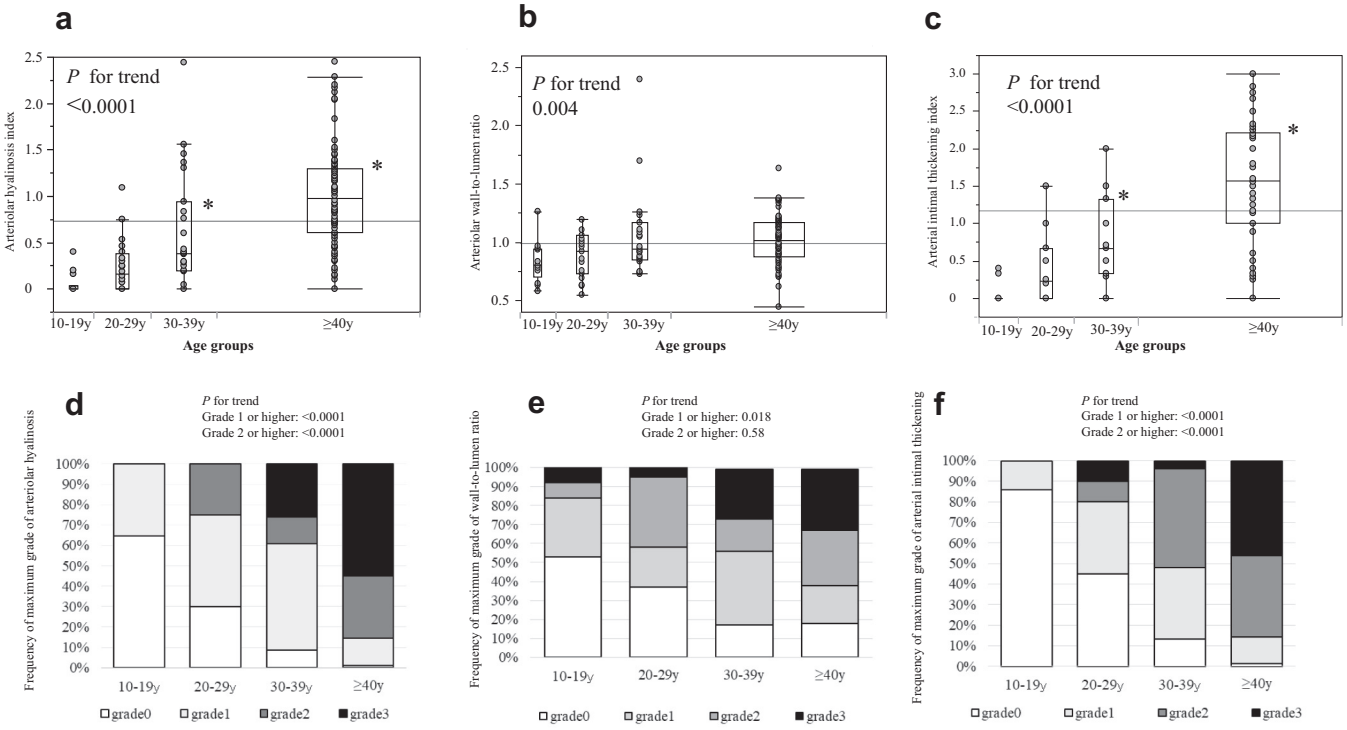

Figure 1. (a–c) Box-and-whisker plots of arteriolar hyalinosis index (a), wall-to-lumen ratio (b), and arterial intimal thickening index (c) across the age groups. Boxes indicate medians with IQRs. Error bars indicate maximum and minimum values defined as third quartile +1.5 times the IQR and first quartile −1.5 times the IQR, respectively. Outliers (small circles) are defined as data points >1.5 times the IQR beyond the first or third quartiles. Sex-adjusted trend in each index across the age groups was evaluated using linear regression analysis. Differences in arterio-arteriosclerosis indices across the age groups were evaluated using Dunnett's test, with adolescents used as reference. (d–f) Mosaic plots showing maximum grades of arteriolar hyalinosis (d), arteriolar wall thickening (e), and arterial intimal thickening (f) across the age groups. Trends in the frequency of grade ≥1 and grade ≥2 changes in arterio-arteriosclerosis indices were evaluated using the Cochran–Armitage test. *$P < 0.05$ compared with adolescents. IQR, interquartile range.

Our findings are consistent with those observed in healthy kidney donors, in whom the prevalence rates of arteriolar hyalinosis and arterial luminal narrowing were reported to increase with increasing age.[5,S4] Aging has been suggested to have an additive effect on the morphologic changes observed in renal structures including vessels. The prevalence of arterial intimal thickening in the 20 to 29 years age group patients with kidney disease who did not have diabetes, hypertension, or renal dysfunction in the present study was higher in comparison with the rate of arterial narrowing in those aged 18 to 29 years among healthy kidney donors[5] (47% vs. 14%). In patients with CKD, the accumulation of traditional risk factors for atherosclerosis, such as hypertension, diabetes mellitus, lipid abnormalities, and cigarette smoking, is related to morphologic changes in renal vessels.[6] Nevertheless, the present study demonstrates that age group was significantly associated with arteriolar hyalinosis and small arterial intimal thickening, but not with arteriolar remodeling, independent of the traditional risk factors. The independent association of aging with the development of renal arterio-arteriolosclerosis was also supported by the trending increase observed in the prevalence of the arterio-arteriolosclerosis indices from adolescents to patients aged in their 40s, in whom the prevalence rates of hypertension and diabetes mellitus were low (Supplementary Results, Supplementary Table S1). Similar trends were observed among the patients without hypertension and those with preserved eGFR (Supplementary Figure S3). Although prehypertension was shown to increase the risk of renal arteriosclerosis,[S8] the adjustment with traditional risk factors including systolic blood pressure did not affect the results. Overall, these findings suggest that age-related trends were not attributable to the accumulation of traditional risk factors. The markers of nontraditional risk factors, such as oxidative stress, increased with increasing age, whereas eGFR decreased with increasing age (Supplementary Table S1). The adjustment for the nontraditional risk factors and eGFR did not affect the significant age-related trends in arteriolar hyalinosis and arterial intimal thickening. Furthermore, the present study suggests that endothelial function was decreased in those aged ≥40

Table 1. Unadjusted and multivariable-adjusted odds ratios of arteriolar hyalinosis, arteriolar wall thickening, and arterial intimal thickening according to age groups

	Age groups				
Indices of arterio-arteriolosclerosis	10–19 yrs $n = 14$	20–29 yrs $n = 20$	30–39 yrs $n = 23$	≥40 yrs $n = 82$	*P*-value for trend
Arteriolar hyalinosis					
Number of lesions (%)	5 (36)	14 (70)	21 (91)	81 (99)	
Odds ratio (95% CI)					
Unadjusted	1.00 (reference)	4.20 (0.98–17.95)	18.90 (3.0–119.00)	145.80 (15.20–1390.00)	<0.0001
Model 1	1.00 (reference)	3.10 (8.65–14.91)	12.03 (1.64–88.40)	61.15 (4.95–755.99)	0.0013
Model 2	1.00 (reference)	4.09 (0.69–24.17)	34.04 (2.07–559.46)	46.44 (2.29–941.41)	0.0124
Arteriolar wall thickening					
Number of lesions (%)	1 (7)	7 (35)	10 (43)	39 (47)	
Odds ratio (95% CI)					
Unadjusted	1.00 (reference)	7.00 (0.74–65.95)	9.23 (1.02–83.34)	12.00 (1.48–96.81)	0.0197
Model 1[a]	1.00 (reference)	7.86 (0.78–78.54)	10.78 (1.12–103.24)	14.75 (1.62–134.20)	0.0169
Model 2[b]	1.00 (reference)	7.25 (0.68–76.61)	5.56 (0.54–57.48)	4.83 (0.45–51.50)	0.1916
Arterial intimal thickening					
Number of lesions (%)	2 (14)	11 (55)	20 (87)	81 (99)	
Odds ratio (95% CI)					
Unadjusted	1.00 (reference)	7.33 (1.29–41.66)	40.0 (5.82–274.21)	486.00 (40.8–5780.70)	<0.0001
Model 1	1.00 (reference)	6.39 (1.03–39.53)	46.82 (5.49–399.74)	740.9 (34.75–15800.70)	<0.0001
Model 2	1.00 (reference)	5.55 (0.83–37.20)	28.83 (2.85–291.91)	501.55 (15.50–16233.34)	0.0005

[a]Model 1 + outer diameter.
[b]Model 1 [a] + estimated glomerular filtration rate.
Model 1: sex, systolic blood pressure, hemoglobin A1c, total cholesterol, Brinkman index, and uric acid. Model 2: model 1 + oxidative index, % flow-mediated dilation and estimated glomerular filtration rate. Arteriolar wall thickening was defined as an arteriolar wall-to-lumen ratio of ≥1.0 (median value).

years (Supplementary Table S1), similar to that reported in the general population.[S9] Nevertheless, age-related trends in increased arteriolar hyalinosis and arterial intimal thickening were independent of percent flow-mediated dilation, a marker of arterial function. Unmeasured factors might be responsible for these age-related trends observed in the present study.

The current study's findings have significant clinical relevance considering that hyalinosis may be a marker of disrupted autoregulation of glomerular hemodynamics[8] and may potentiate susceptibility to blood pressure-dependent glomerular damage,[9] which is considered a mechanism of CKD progression. In a previous study on patients with IgA nephropathy, including many young patients aged <30 years, we reported that blood pressure-dependent reduction in eGFR was higher among those with renal arteriolar hyalinosis than in those without hyalinosis.[9] Therefore, our findings suggest that renal arterio-arteriolosclerosis should be considered a potential risk factor for renal dysfunction even in younger patients with CKD who may not have hypertension and diabetes mellitus.

In conclusion, our data suggest that changes associated with renal arterio-arteriolosclerosis might start in adolescence, independent of traditional and nontraditional cardiovascular risk factors. Future studies are needed to identify factors underlying the development of renal arterio-arteriolosclerosis especially in young patients with CKD.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Supplementary Results.

Supplementary References.

Figure S1. Study flow chart.

Figure S2. Representative microphotographs of arteriolar hyalinosis and arterial intimal thickening.

Figure S3. Box-and-whisker plots of indices of arterio-arteriolosclerosis across the age groups among the subgroups.

Table S1. Clinical characteristics according to age groups.

Table S2. Histological characteristics according to age groups.

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