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ORIGINAL ARTICLE

# Postprandial hyperglycemia and hyperinsulinemia associated with renal arterio-arteriolosclerosis in chronic kidney disease

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**Hypertension has an important function in the formation of renal arterio-arteriolosclerosis. However, renal arterio-arteriolosclerosis is sometimes found in biopsy specimens of normotensive patients, which indicates unknown factors may contribute to renal arterio-arteriolosclerosis. In this study, we aimed to evaluate the effects of glucose metabolism/insulin resistance on renal arterio-arteriolosclerosis. Forty-eight patients with biopsy-proven non-diabetic chronic glomerular disease were included. Renal arterio-arteriolosclerosis was evaluated as the percentage of vessels showing hyaline changes or wall thickening. We correlated renal arterio-arteriolosclerosis with clinical parameters including indices obtained by 75 g oral glucose tolerance test. Of the 48 patients, 30 had hypertension. The results of univariate analysis showed significant association of renal arterio-arteriolosclerosis with hypertension, increased serum creatinine (S-Cr), hypertriglyceridemia, increased 2-h plasma glucose (PG) and increased 2-h plasma insulin (PI). In stepwise multiple regression analysis, hypertension ($\beta$=0.344, $P$=0.009), S-Cr ($\beta$=0.287, $P$=0.03) and 2-h PG ($\beta$=0.274, $P$=0.03) were independently associated with renal arterio-arteriolosclerosis. Eleven of the 30 hypertensive patients did not have renal arterio-arteriolosclerosis. The hypertensive patients with renal arterio-arteriolosclerosis showed significantly higher 2-h PG ($134 \pm 25$ *vs.* $106 \pm 26$ mg per 100 ml, $P$=0.008) and higher 2-h PI ($67.7 \pm 34.9$ *vs.* $48.3 \pm 30.0\ \mu U\ ml^{-1}$, $P$=0.04) compared with those without renal arterio-arteriolosclerosis, but the difference in S-Cr was not significant. Postprandial hyperglycemia and hyperinsulinemia may contribute to the formation of renal arterio-arteriolosclerosis independently of hypertension.**
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**Keywords:** chronic kidney disease; impaired glucose tolerance; insulin resistance; renal arterio-arteriolosclerosis; tubulointerstitial injury

## INTRODUCTION

Insulin resistance is related to atherosclerotic lesions not only in diabetic but also in non-diabetic patients.[1,2] An association between insulin resistance and uremia has long been established,[3] and recent studies have consistently reported that insulin resistance is present early in the course of chronic kidney disease (CKD).[4,5] In addition, glucose metabolism/insulin resistance seems to have a role in the progression of CKD. For example, it has been reported that in a general non-diabetic population, higher fasting plasma insulin (FPI) accelerates age-related decline of renal function.[6] In patients with IgA nephropathy, Kaartinen *et al.*[7] showed that higher FPI and homeostasis model assessment of insulin resistance (HOMA-IR) were associated with the progression of renal insufficiency. However, the effects of glucose metabolism/insulin resistance on human renal pathology remain to be elucidated. Recently, we reported the association between renal pathological changes and indices of glucose metabolism/insulin resistance determined by 75 g oral glucose tolerance test in non-diabetic CKD patients.[8] This study included 23 patients, and showed significant correlation between fasting plasma glucose (FPG) and interstitial fibrosis; 2-h plasma glucose (2-h PG) and renal arterio-arteriolosclerosis; and HOMA-IR and interstitial fibrosis. To our knowledge, this was the first study showing the association between renal pathology and glucose metabolism/insulin resistance.

Renal arterio-arteriolosclerosis is an important pathological finding, because it is related to renal function and prognosis.[9–12] Hypertension is known to have an important function in the pathogenesis of renal arterio-arteriolosclerosis.[12–14] In clinical practice, however, the evidence of renal arterio-arteriolosclerosis is sometimes found even in renal biopsy specimens of patients without hypertension. For example, Wu *et al.*[11] reported that 42 of 191 normotensive patients with IgA nephropathy had moderate to severe renal arterio-arteriolosclerosis.

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On the other hand, some patients with hypertension do not show renal arterio-arteriolosclerosis. Therefore, unknown factors seem to contribute to renal arterio-arteriolosclerosis independently of hypertension. In this study, we aimed to investigate clinical factors associated with renal arterio-arteriolosclerosis in CKD, with particular emphasis on glucose metabolism, insulin resistance and hypertension.

## METHODS

### Patients

Between January 2005 and December 2008, 173 patients underwent renal biopsy in our department. Of these patients, 98 patients agreed to undergo a 75 g oral glucose tolerance test. The inclusion criteria were patients whose biopsy specimen included more than three arteries/arterioles and those who gave informed consent for this study. The exclusion criteria were patients with diabetes mellitus, collagen disease, chronic liver disease, malignancy, renal artery stenosis, acute renal failure and proceeding treatment with steroids or immunosuppressants. Diabetes mellitus was defined as FPG $\geqslant$126 mg per 100 ml or 2-h PG $\geqslant$200 mg per 100 ml during a 75 g oral glucose tolerance test, based on the 2004 criteria of the American Diabetes Association.[15] Finally, 48 patients with chronic glomerular disease other than diabetic nephropathy were included in this study. Of the patients included this study, 23 patients were included also in our previous study.[8] The ethical committee of our hospital approved this study.

### Clinical evaluation

At biopsy, the following were recorded: patient's sex; age; blood urea nitrogen; serum creatinine (S-Cr); estimated glomerular filtration rate (eGFR); total cholesterol; triglyceride; high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; systolic and diastolic blood pressure; the presence of hypertension; duration of hypertension; smoking history; administration of angiotensin converting enzyme-inhibitor (ACE-I), angiotensin receptor blocker (ARB) and statin; and urinary protein excretion. Hypertension was defined as systolic blood pressure more than 140 mm Hg and/or diastolic blood pressure more than 90 mm Hg, or use of antihypertensive drugs at biopsy. Administration of ACE-I/ARB and statin was recorded, because these drugs have been reported to reduce insulin resistance.[16,17] Urinary protein excretion was evaluated by a 24-h urine collection. eGFR was calculated using the abbreviated Modification of Diet in Renal Disease Study equation modified by the Japanese coefficient:[18]

$$\mathrm{eGFR(ml/min/1.73\,m^2)} = 0.881\times186\times\mathrm{Age}^{-0.203}\times[\mathrm{s-Cr(mg\ per\ 100\,ml)}]^{-1.154}(\textit{if}\ \mathrm{female}\times0.742)$$

Regarding indices of glucose metabolism and insulin resistance, we recorded FPG, FPI, 2-h PG, 2-h plasma insulin (2-h PI) obtained during a 75 g oral glucose tolerance test; HOMA-IR; and body mass index (BMI). HOMA-IR was calculated as follows:

$$\mathrm{HOMA-IR} = [\mathrm{FPG(mg\ per\ 100\,ml)}\times\mathrm{FPI}(\mu\mathrm{U/ml})]/405$$

### Pathological evaluation

Two experienced kidney pathologists blinded to any information concerning each patient performed morphological evaluations (HM and SH). When there was discordance, the independent opinion of a third senior pathologist (TO) was adopted. As mentioned above, the patients whose biopsy specimens including more than three arteries/arterioles were included in this study. In all arteries/arterioles included in these specimens, the presence of arterio-arteriolosclerotic changes was examined. Arterio-arteriolosclerosis was shown as the percentage of vessels showing hyaline change or wall thickening.[19] Wall thickening was defined as the ratio of vascular luminal diameter to outer diameter, and was considered to be present when the ratio exceeded 0.5.

### Statistical analysis

Data are shown as mean ± s.d. Comparisons between two groups were performed by Mann–Whitney's *U*-test or $\chi^2$-test, as appropriate. Correlations were tested by Spearman's correlation rank test. Stepwise multiple regression analysis was used to select factors independently associated with renal arterio-arteriolosclerosis among the factors significant in univariate analyses. Systolic blood pressure and the presence of hypertension were related to renal arterio-arteriolosclerosis in the univariate analysis, and we included the presence of hypertension as an independent variable in the multivariate analysis. Among the parameters of renal function (blood urea nitrogen, S-Cr and eGFR), we included S-Cr as an independent variable. In univariate analysis, ACE-I/ARB administration was associated with more severe arterio-arteriolosclerosis. However, this was a cross-sectional study not determining the effects of ACE-I/ARB, and all patients treated with these drugs had hypertension, which could explain more severe arterio-arteriolosclerosis. Therefore, administration of ACE-I/ARB was not included as an independent variable in stepwise multiple regression analysis. A *P*-value $<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 11.0 software (SPSS, Chicago, IL, USA).

## RESULTS

Clinical characteristics of the 48 patients are shown in Table 1. The patients included 29 males and 19 females with the mean age of

**Table 1 Clinical and pathological characteristics of 48 patients**

| | |
|---|---|
| Sex (M:F) | 29:19 |
| Age (year) | 53 ± 17 (17–77) |
| Systolic blood pressure (mm Hg) | 132 ± 14 (110–170) |
| Diastolic blood pressure (mm Hg) | 76 ± 10 (53–110) |
| BUN (mg per 100 ml) | 20.1 ± 10.1 (6.2–55.8) |
| S-Cr (mg per 100 ml) | 1.19 ± 0.62 (0.50–3.63) |
| eGFR (ml min$^{-1}$ per 1.73 m$^2$) | 68.8 ± 31.1 (15.9–130.5) |
| Total cholesterol (mg per 100 ml) | 219 ± 61 (104–479) |
| Triglyceride (mg per 100 ml) | 190 ± 120 (31–576) |
| HDL-C (mg per 100 ml) | 55.0 ± 13.1 (35.8–99.6) |
| LDL-C (mg per 100 ml) | 119 ± 43 (41–275) |
| Urinary protein (g per day) | 1.43 ± 2.23 (0.01–8.12) |
| Hypertension | 30 (62.5%) |
| Smoking history | 19 (39.6%) |
| ACE-I/ARB | 16 (33.3%) |
| Statin | 10 (20.8%) |
| Fasting plasma glucose (mg per 100 ml) | 95 ± 10 (78–125) |
| 2-h plasma glucose (mg per 100 ml) | 124 ± 31 (64–192) |
| Fasting plasma insulin (μU ml$^{-1}$) | 7.2 ± 4.0 (0.9–16.0) |
| 2-h plasma insulin (μU ml$^{-1}$) | 62.1 ± 44.8 (6.3–241.0) |
| >64.0 | 22 (45.8%) |
| HOMA-IR | 1.73 ± 1.02 (0.18–4.34) |
| >1.73 | 20 (41.7%) |
| Body mass index (kg m$^{-2}$) | 25.1 ± 4.2 (17.4–37.7) |
| *Pathological findings* | |
| Diagnosis | |
| Mesangial proliferative glomerulonephritis | 31 (64.6%) |
| Focal segmental glomerulosclerosis | 6 (12.5%) |
| Membranous nephropathy | 4 (8.3%) |
| Minor glomerular abnormalities | 3 (6.3%) |
| Chronic tubulointerstitial nephritis | 3 (6.3%) |
| Benign nephrosclerosis | 1 (2.0%) |
| Arterio-arteriolosclerosis (%) | 20.0 ± 25.6 (0–100) |

Abbreviations: ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; S-Cr, serum creatinine.
The values in parenthesis indicate the range of each parameter.

**Table 2 Comparisons of renal arterio-arteriolosclerosis based on categorical parameters**

| | N | *Arterio-arteriolosclerosis (%)* | P |
|---|---|---|---|
| *Sex* | | | |
| Male | 29 | 18.2 ± 26.5 | 0.49 |
| Female | 19 | 22.6 ± 24.8 | |
| *Hypertension* | | | |
| Yes | 30 | 28.7 ± 27.6 | 0.001 |
| No | 18 | 5.4 ± 12.7 | |
| *Smoking history* | | | |
| Yes | 19 | 24.8 ± 29.7 | 0.33 |
| No | 29 | 16.8 ± 22.6 | |
| *ACE-I/ARB* | | | |
| Yes | 16 | 33.0 ± 30.8 | 0.01 |
| No | 32 | 13.5 ± 20.1 | |
| *Statin* | | | |
| Yes | 10 | 31.1 ± 26.5 | 0.12 |
| No | 38 | 17.1 ± 25.0 | |

Abbreviations: ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker.

**Table 3 Correlation coefficients between renal arterio-arteriolosclerosis and continuous parameters**

| | r | P |
|---|---|---|
| Age | 0.145 | 0.32 |
| Systolic blood pressure | 0.340 | 0.01 |
| Diastolic blood pressure | 0.259 | 0.07 |
| S-Cr | 0.441 | 0.002 |
| Total cholesterol | 0.063 | 0.67 |
| Triglyceride | 0.321 | 0.02 |
| HDL-C | 0.060 | 0.69 |
| LDL-C | −0.144 | 0.32 |
| Urinary protein | 0.151 | 0.30 |
| Fasting plasma glucose | 0.240 | 0.10 |
| 2-h plasma glucose | 0.388 | 0.006 |
| Fasting plasma insulin | 0.168 | 0.25 |
| 2-h plasma insulin | 0.335 | 0.02 |
| HOMA-IR | 0.183 | 0.21 |
| Body mass index | 0.022 | 0.88 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; S-Cr, serum creatinine.

**Table 4 Stepwise multiple regression analysis for independent determinants of renal arterio-arteriolosclerosis**

| | β | P |
|---|---|---|
| Hypertension | 0.344 | 0.009 |
| S-Cr | 0.287 | 0.03 |
| 2-h plasma glucose | 0.274 | 0.03 |
| Triglyceride | 0.131 | 0.32 |
| 2-h plasma insulin | −0.029 | 0.85 |
| $r^2$=0.388 | | |

Abbreviation: S-Cr, serum creatinine.

**Table 5 Correlation coefficients between age and glucose metabolism/insulin resistance**

| | r | P |
|---|---|---|
| Fasting plasma glucose | 0.108 | 0.46 |
| 2-h plasma glucose | 0.098 | 0.50 |
| Fasting plasma insulin | −0.104 | 0.48 |
| 2-h plasma insulin | −0.074 | 0.61 |
| HOMA-IR | −0.070 | 0.63 |
| Body mass index | −0.307 | 0.03 |

Abbreviation: HOMA-IR, homeostasis model assessment of insulin resistance.

53 ± 17 years. S-Cr was 1.19 ± 0.62 mg per 100 ml, and eGFR was 68.8 ± 31.1 ml min$^{-1}$ per 1.73 m$^2$. The mean value of triglyceride was elevated at 190 mg per 100 ml. The mean values of systolic and diastolic blood pressure were 132 and 76 mm Hg, respectively. Thirty patients had hypertension with mean duration of 9.6 ± 10.6 years (range 0.5–40). ACE-I/ARB and statin were administered in 16 and 10 patients, respectively. All indices of glucose metabolism/insulin resistance were not significantly different between those treated with and those not treated with these drugs (data not shown). Two hours PI more than 64.0 μU ml$^{-1}$ and HOMA-IR more than 1.73, which have been used as the criteria of insulin resistance,[20,21] were found in 22 (45.8%) and 20 patients (41.7%), respectively. Pathological diagnosis showed the predominance of mesangial proliferative glomerulonephritis in 31 patients (64.6%, IgA nephropathy in 17, non-IgA nephropathy in 14). The percentage of vessels showing hyaline change or wall thickening was 20.0 ± 25.6%, and ranged from 0 to 100%. Of the 30 patients with hypertension, 11 did not have renal arterio-arteriolosclerosis. On the other hand, 3 of the 18 normotensive patients had renal arterio-arteriolosclerosis.

Comparisons of renal arterio-arteriolosclerosis based on categorical parameters are shown in Table 2. The hypertensive patients showed more severe renal arterio-arteriolosclerosis compared with the normotensive patients. All of the patients treated with ACE-I/ARB had hypertension and showed more severe renal arterio-arteriolosclerosis. Table 3 shows the correlation coefficients between renal arterio-arteriolosclerosis and continuous parameters. Systolic blood pressure, S-Cr and triglyceride showed a significant correlation, but age and urinary protein excretion did not. Among the indices of glucose metabolism/insulin resistance, 2-h PG and 2-h PI showed significant correlation. Stepwise multiple regression analysis showed that hypertension, S-Cr and 2-h PG were independently associated with renal arterio-arteriolosclerosis (Table 4). Generally, aging is related to renal pathological changes[22] and glucose intolerance/insulin resistance,[23] but all indices but BMI were not in this study, as shown in Table 5.

We noted that 11 of the 30 hypertensive patients did not have renal arterio-arteriolosclerosis, and compared clinical parameters between the hypertensive patients with and without renal arterio-arteriolosclerosis (Table 6). The hypertensive patients with renal arterio-arteriolosclerosis showed significantly higher 2-h PG and 2-h PI compared with those without arterio-arteriolosclerosis. Notably, the difference of S-Cr was not significant.

## DISCUSSION

Insulin resistance is present early in the course of CKD,[4,5] and is one of potential factors inducing systemic atherosclerotic lesions in CKD

**Table 6 Comparisons of clinical parameters between hypertensive patients with and without renal arterio-arteriolosclerosis**

| | *Arterio-arteriolosclerosis* | | |
|---|---|---|---|
| | + | − | P |
| *N* | 19 | 11 | |
| Male patients (*n*, %) | 11 (57.9) | 6 (54.5) | 0.99 |
| Age (year) | 59 ± 11 | 53 ± 18 | 0.58 |
| Duration of hypertension (year) | 11.9 ± 11.9 | 5.0 ± 5.5 | 0.11 |
| S-Cr (mg per 100 ml) | 1.54 ± 0.79 | 1.03 ± 0.29 | 0.10 |
| Total cholesterol (mg per 100 ml) | 217 ± 49 | 238 ± 84 | 0.55 |
| Triglyceride (mg per 100 ml) | 244 ± 147 | 174 ± 72 | 0.26 |
| HDL-C (mg per 100 ml) | 55.1 ± 13.0 | 52.4 ± 17.1 | 0.31 |
| LDL-C (mg per 100 ml) | 112 ± 38 | 136 ± 46 | 0.09 |
| Urinary protein (g per day) | 1.69 ± 2.54 | 2.00 ± 2.63 | 0.96 |
| Smoking history (*n*, %) | 9 (47.4) | 4 (36.4) | 0.70 |
| ACE-I/ARB (*n*, %) | 11 (57.9) | 5 (45.5) | 0.51 |
| Statin (*n*, %) | 7 (36.8) | 2 (18.2) | 0.41 |
| Fasting plasma glucose (mg per 100 ml) | 99 ± 11 | 92 ± 8 | 0.18 |
| 2-h plasma glucose (mg per 100 ml) | 134 ± 25 | 106 ± 26 | 0.008 |
| Fasting plasma insulin ($\mu U\,ml^{-1}$) | 7.8 ± 3.9 | 7.7 ± 4.7 | 0.99 |
| 2-h plasma insulin ($\mu U\,ml^{-1}$) | 67.7 ± 34.9 | 48.3 ± 30.0 | 0.04 |
| HOMA-IR | 1.95 ± 1.05 | 1.81 ± 1.16 | 0.80 |
| Body mass index ($kg\,m^{-2}$) | 24.8 ± 4.0 | 25.9 ± 2.9 | 0.39 |

Abbreviations: ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; S-Cr, serum creatinine.

patients.[4] We showed earlier the association between glucose metabolism/insulin resistance and renal pathology; FPG and interstitial fibrosis; 2-h PG and renal arterio-arteriosclerosis; and HOMA-IR and interstitial fibrosis.[8] Among these pathological changes, renal arterio-arteriolosclerosis is important, because it is known to be related to renal function and prognosis.[9–12] However, whether clinical factors other than hypertension have an impact on renal arterio-arteriolosclerosis remains to be elucidated. Therefore, we noted glucose metabolism/insulin resistance as a cause of renal arterio-arteriolosclerosis in this study. However, to estimate whether glucose metabolism/insulin resistance affects renal arterio-arteriolosclerosis independently of hypertension seems difficult, because insulin resistance is commonly related to hypertension.[24] Indeed, in our previous study including 23 patients, there were only 2 normotensive patients with renal arterio-arteriolosclerosis. Moreover, in this study, 30 of the 48 patients had hypertension. Of the remaining 18 normotensive patients, only 3 had renal arterio-arteriolosclerosis. Therefore, we noted hypertensive patients without renal arterio-arteriolosclerosis in this study.

We showed that in the comparison between hypertensive patients with and without renal arterio-arteriolosclerosis, the patients with renal arterio-arteriolosclerosis had significantly higher 2-h PG and 2-h PI. In other words, even if patients have hypertension, renal arterio-arteriolosclerosis may not occur under normal postprandial PG and insulin. It is well known that post-challenge hyperglycemia is associated with increased all-cause and cardiovascular mortality.[25,26] Therefore, the pathogenic effects of postprandial hyperglycemia rather than fasting hyperglycemia have been stressed in some reviews.[27,28] On the other hand, hyperinsulinemia has a variety of harmful effects potentially leading to vascular changes, such as anti-natriuretic effect, oxidant stress and decreased production of nitric oxide.[29] Considering these results, it seems likely that postprandial hyperglycemia and hyperinsulinemia may contribute to renal arterio-arteriolosclerosis.

Renal arterio-arteriolosclerosis leads to chronic hypoxia in the tubulointerstitium, which is a central mechanism of tubulointerstitial injury and progression of CKD.[30,31] Hypoxia of tubular and interstitial cells leads to apoptosis or epithelial–mesenchymal transdifferentiation resulting in interstitial fibrosis. As a result of fibrosis, oxygen diffusion from peritubular capillaries to tubular and interstitial cells decreases, and finally, a vicious cycle is formed. Our previous study showed the association of glucose metabolism/insulin resistance with interstitial and intra-renal vascular changes, but not with glomerular changes.[8] Previous studies showed 'atypical' renal pathology in a substantial proportion of patients with type 2 diabetes mellitus: absent or mild glomerular changes with disproportionately severe tubulointerstitial injury and renal arterio-arteriolosclerosis.[32] Renal insufficiency with almost normal urinalysis can be a clinical manifestation of absent or mild glomerular changes with severe tubulointerstitial injury and renal arterio-arteriolosclerosis.[30] Recently, it has been noted that a substantial proportion of type 2 diabetes mellitus patients have renal insufficiency without albuminuria.[33,34] MacIsaac *et al*.[34] showed that in type 2 diabetes mellitus patients with renal insufficiency, intra-renal resistive index obtained by Doppler ultrasound, which reflects intra-renal vascular injury,[35] was high regardless of the amount of albuminuria. Considering the results obtained in our studies, abnormal glucose metabolism/insulin resistance may induce tubulointerstitial injury and renal arterio-arteriolosclerosis even before the development of diabetes. In this regard, we have recently reported that long-standing and low-grade ischemic nephropathy, evidenced by increased renal artery resistance, might be involved in the pathophysiology of renal insufficiency without evident proteinuria.[36]

In addition to harmful effects by postprandial hyperglycemia and hyperinsulinemia, other factors related to insulin resistance potentially induce renal arterio-arteriolosclerosis. For example, Iwasa *et al*.[37] showed that decreased serum adiponectin was independently associated with intra-renal vascular changes in patients with IgA nephropathy. Adiponectin directly acts on blood vessel walls, and prevents monocyte adhesion, smooth muscle cell proliferation and foam cell adhesion, which lead to vascular protection.[38] In addition to adiponectin, asymmetric dimethylarginine also may influence intra-renal vascular lesions. Asymmetric dimethylarginine, an endogenous nitric oxide synthase inhibitor, negatively correlates with GFR[39] and is related to endothelial dysfunction, atherosclerosis and coronary artery calcification.[39] Therefore, whether adiponectin and asymmetric dimethylarginine are related to renal arterio-arteriolosclerosis seems an issue of interest.

General risk factors for arteriosclerosis include aging, hypertension, dyslipidemia or smoking, but the impacts of these factors on renal arterio-arteriolosclerosis remain unclear, except hypertension. In our study, age did not correlate with renal arterio-arteriolosclerosis and all parameters of glucose metabolism/insulin resistance but BMI. Therefore, the impacts of aging on our results do not appear to be significant. Lipid abnormality is an important component of metabolic syndrome, and is known to be associated with CKD.[40] Experimental studies have provided *in vivo* and *in vitro* data indicating contributions of dyslipidemia to renal pathological injury. However, the impact of lipid abnormality on human renal pathology remains unclear. In IgA nephropathy, some studies found significant association between hypertriglyceridemia and intra-renal vascular lesions.[37,41] It remains unknown whether hypertriglyceridemia itself may induce intra-vascular changes, or may reflect other metabolic disorders

leading to intra-vascular changes. In addition, a few studies have reported that smoking was associated with intra-renal vascular lesions,[42] which seems not conclusive. In our study, hypertriglyceridemia was associated with renal arterio-arteriolosclerosis, but smoking history and gender were not. More studies are required to elucidate the association between these risk factors and human renal pathology.

There are some difficulties in trying to examine the relationship between renal pathology and glucose metabolism/insulin resistance in biopsy studies. First, pathogenic effects of primary glomerular disease and glucose metabolism/insulin resistance on intra-renal vessels cannot be distinguished. Second, the amount of renal tissue obtained by renal biopsy is limited. Regarding the pathological assessment of intra-renal vessels, it remains to be determined how many arteries/arterioles should be included in a biopsy specimen. In this study, we included the patients whose biopsy specimen including more than three arteries/arterioles, and arterio-arteriolosclerosis was evaluated as the percentage of vessels showing hyaline change or wall thickening. It may be desirable to evaluate intra-renal vascular lesions based on the size of the vessels, and intimal and medial changes should be separately evaluated. However, such detailed evaluation can be performed only in autopsy studies. Third, the predominance of mesangial proliferative glomerulonephritis, in particular IgA nephropathy, in our patients might affect the results. As mentioned above, HOMA-IR was associated with the progression of IgA nephropathy.[7] In addition, increased levels of serum uric acid and triglyceride were associated with intra-renal vascular changes in IgA nephroptahy.[37,41] There is a possibility that the association between hyperglycemia/hyperinsulinemia and renal arterio-arteriolosclerosis may depend on the type of glomerular disease. Finally, we could not show a causal relationship because of cross-sectional design of this study.

In conclusion, it has been shown that 2-h PG and 2-h PI are positively associated with renal arterio-arteriolosclerosis in CKD patients. Although the precise mechanisms remain unknown, postprandial hyperglycemia and hyperinsulinemia seem to have pathogenic roles in the formation and progression of renal arterio-arteriolosclerosis independently of hypertension. Intervention for postprandial hyperglycemia and hyperinsulinemia may be very important not only to retard the development of diabetic nephropathy but also to suppress the progression of renal insufficiency in any other types of renal disease.

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