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Risk factors for renal glomerular and vascular changes in an autopsy-based population survey: The Hisayama Study

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Risk factors for renal glomerular and vascular changes in an autopsy-based population survey: The Hisayama Study.

Background. Information of the effect of cardiovascular risk factors on renal glomerular and vascular changes is scarce in the general population.

Method. Between 1962 and 1994, 1394 autopsies were performed in Hisayama, for a total autopsy rate of 80%. Of these, 839 individuals who preserved adequate renal tissues and had recent health examinations data before death were eligible for the present study. We examined the degree of glomerular sclerosis, renal arteriolar hyalinosis, and arteriosclerosis, and evaluated their risk factors by means of a logistic regression model.

Results. The development of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis were 16%, 16%, and 18% in men, respectively, and 27%, 15%, and 24% in women, respectively. All these frequencies increased linearly with advancing age. In the multivariate analysis, both age and systolic blood pressure were significant independent risk factors for almost all these glomerular and vascular changes. In addition, glucose intolerance and proteinuria for men were found to be significant risk factors for glomerular sclerosis. Elevated total cholesterol levels significantly increased the risk of arteriolar hyalinosis in men. Electrocardiogram (ECG) abnormalities were an independent risk factor for arteriosclerosis in both men and women, and proteinuria was an additional risk factor in women. Alcohol intake tended to have a protective effect on glomerular sclerosis and arteriosclerosis in women.

Conclusion. Our data confirmed that age and systolic blood pressure are common risk factors for all glomerular and renal vascular changes in the general population. In addition, glucose intolerance, total cholesterol, ECG abnormalities, and proteinuria affect either glomerular or vascular changes.

Key words: glomerular sclerosis, arteriolosclerosis, arteriosclerosis, diabetic nephropathy, nephrosclerosis, risk factor, population-based study, autopsy.

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Despite recent advances in nephrology and dramatic decreases in the incidence of cardiovascular disease [1], the number of patients beginning renal replacement therapy is annually increasing in Japan as well as in Western countries [2, 3]. Major causes of end-stage renal disease (ESRD) are diabetes and hypertension; however, the effects of other cardiovascular risk factors on the human kidney are not well understood. Further clarification of the pathogenesis and risk factors of renal histologic changes in the general population might provide useful information for preventing chronic renal diseases that tend to be asymptomatic and often go undiagnosed. However, most of the reported findings concerning this issue have come from animal models [4–7] or selected patients [8–10]; little information has been made available with respect to the general population, due to various methodologic obstacles in etiologic research on renal diseases [11].

A prospective population-based study of cardiovascular disease has been carried out since 1961 in Hisayama Town on Kyushu Island in southern Japan. The most characteristic feature of this study is that the cause of death has been verified by autopsy in 80% of the deceased subjects from the study population [12–15]. A previous report of 270 autopsies of Hisayama residents [12] showed that both age and hypertension were closely related to the reduction in kidney weight, as well as the progression of glomerular sclerosis and nephrosclerosis. However, it did not assess the effects of other cardiovascular risk factors. The Honolulu Heart Program [16, 17] is, to our knowledge, the only other population-based study that has examined this issue, although the autopsy rate in this study was low (20.6%). In the present study, we examined renal histologic changes in most of the deceased Hisayama residents and showed that various cardiovascular risk factors were associated with the development of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis.

METHODS

Study population

The population of Hisayama Town is approximately 7500 and has been shown to be representative of Japan as a whole based on data from the national census [12, 13]. The study design and characteristics of the subject population have been described in detail elsewhere [14, 15]. From January 1962 to December 1994, a total of 1742 Hisayama residents of all age groups died, and of these, 1394 (80.0%) underwent autopsy examinations. Autopsy rate was not different between men (78.7%) and women (81.6%). Among these consecutive autopsy subjects, 1168 participated in at least one of the six health examinations in 1961, 1967, 1974, 1978, 1983, and 1988. In every examination, the participation rate exceeded more than 80% of all the Hisayama residents 40 years old or older. We excluded 98 subjects who were missing the preserved renal tissues, 33 subjects with degenerated or small renal tissues, 80 subjects who underwent autopsy examination in other hospitals, and 118 subjects who had had no recent health examination data before death. Finally, 839 subjects with adequate renal tissues and health examination data just before death (mean period, 3.5 ± 1.8 years; range, 0 to 7 years) were enrolled in the present study.

Morphologic examination of renal tissue

For light microscopic study, paraffin-embedded renal tissues obtained by standard autopsy methods were cut at 2 μm thickness and stained with periodic acid-Schiff (PAS). The semiquantitative score according to the method of Raij, Azar and Keane [18] was used to evaluate the degree of glomerular sclerosis. For each tissue specimen, 100 glomeruli from the superficial to deep cortex were examined uniformly, and the severity of the lesion in each glomerulus was graded from 0 to 4+ according to the percentage of glomerular sclerosis. Specifically, a score of 0 represented a complete absence of sclerotic lesion of the glomerulus, 1+ represented 1% to 25% involvement of sclerotic lesion of the glomerulus, and 2+, 3+, and 4+ represented 26% to 50%, 51% to 75%, and 76% to 100% involvement of the glomerulus, respectively. An injury score was then obtained by multiplying the degree of damage (0 to 4+) by the number of glomeruli with the same degree of injury. That is, the glomerular sclerosis index was calculated by the following formula:

$$\text{Glomerular sclerosis index} = \frac{n_0 \times 0 + n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4}{4}$$

The variables n_0, n_1, n_2, n_3, and n_4 indicate the number of glomeruli showing sclerotic lesion scores of 0 to 4+, respectively.

The degree of arteriolar hyalinosis was assessed semiquantitatively by the method of Bader and Meyer [19]. For each tissue specimen, 50 arterioles were examined and the severity of the lesion in each arteriole was graded from 1+ to 4+ according to the extent of arteriolar hyalinosis as follows: 1+ represented the absence of any conspicuous alteration of the arteriolar wall, 2+ represented arteriolar wall hyalinosis comprising less than 50% of the arteriolar circumference, 3+ represented arteriolar wall hyalinosis of more than 50% but less than 100% of the arteriolar circumference, and 4+ represented hyalinization of the entire arteriolar wall. The arteriolar hyalinosis index was calculated by the following formula:

$$\text{Arteriolar hyalinosis index} = \frac{n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4}{50}$$

Here, n_1, n_2, n_3, and n_4 indicate the number of arterioles showing hyalinosis scores of 1+ to 4+, respectively.

The wall-lumen ratio was evaluated as the severity of arteriosclerosis by the method of Kernohan, Anderson, and Keith [20]. For each tissue specimen, all arteries with an outer diameter exceeding 60 μm were examined using an eyepiece micrometer. The outer diameter and the lumen diameter of least axis of the elliptic profile were directly measured. The wall-lumen ratio was calculated in each artery as lumen diameter/(outer diameter − lumen diameter)/2, and the mean value among all arteries in each subject was used as the index of arteriosclerosis. Because the wall-lumen ratio differs by arterial size, we further examined the degree of arteriosclerosis by classifying arteries into four categories according to their size. However, because the frequencies and risk profiles for all these categories were highly similar, we showed only the results of all arteries together in the present study. Renal tubulointerstitial changes were not examined in this study, since many subjects underwent autopsy examination more than 24 hours after death. All histologic evaluations were carried out by one of the authors (M.K.) with no information other than the serial autopsy number.

To differentiate the effect of cardiovascular risk factors from age-related changes, we selected 103 subjects who had none of the following characteristics: proteinuria, hematuria, renal failure (creatinine clearance ≤0.5 mL/second as estimated by the Cockcroft-Gault formula), hypertension, glucose intolerance, or primary renal disease at autopsy. Using this subgroup, the cut-off limits were drawn from the upper 95th percentile or the lower 5th percentile of these histologic parameter distributions; that is, the development of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis were defined as a glomerular sclerosis index >20, an arteriolar hyalinosis index >1.56, and a wall-lumen ratio <1.30, respectively.

Risk factors

Blood pressures were measured three times using a standard mercury sphygmomanometer at every examination, and the mean values were used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961 and 1967, by fasting and postprandial glucose concentrations in 1974, 1978, and 1983, and by a 75 g oral glucose tolerance test in 1988, in addition to medical history of diabetes. Electrocardiogram (ECG) was recorded at every examination, and ECG abnormalities were defined as Minnesota code 3-1 and/or 4-1,2,3. Serum cholesterol levels were measured by the Zak-Henly method with a modification by Yoshikawa in 1961 and 1967, by the Zurkowski method in 1974, and by the enzymatic method after 1978. Serum creatinine concentration was measured by Jaffe's method after 1974, and glomerular filtration rate was calculated by the Modification of Diet in Renal Disease (MDRD) Study Group formula [21]. Freshly voided urine samples were tested by the sulfosalicylic acid method in 1961 and 1967, by the dipstick method after 1974, and proteinuria and hematuria were defined as 1+ or more. Body height and weight were measured in light clothing without shoes and the body mass index (kg/m^2) was calculated. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained by means of a standard questionnaire, and classified as current habitual use or a lack thereof.

Statistical analysis

Mean values and frequencies of variables were compared using Student *t* test and chi-square test as appropriate. A logistic regression model was applied to identify the effect of cardiovascular risk factors on the development of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. In multivariate analysis, only significant variables obtained in the age-adjusted analysis were used. Men and women were separately examined in all analyses. Levels of $P < 0.05$ were considered to indicate statistical significance.

RESULTS

Table 1 summarizes the characteristics of the 839 autopsy subjects at the health examinations by gender. Women were approximately 5 years older on average at death than men. Men had higher serum creatinine level than women, while mean glomerular filtration rate was higher in women. Women had higher mean systolic blood pressure and pulse pressure than men, but there was no gender difference in mean diastolic blood pressure and mean arterial pressure. The frequencies of glucose intolerance, alcohol intake, and smoking habits were higher in men, while the mean total cholesterol level was higher in women. Mean body mass index level and the frequencies of proteinuria, hematuria, antihypertensive treatment, and ECG abnormalities were not different between men and women.

Table 1. Characteristics of the 839 autopsy subjects at health examinations before death by sex, The Hisayama Study

Variables	Men ($N = 458$)	Women ($N = 381$)
Age at death *years*	73 ± 12	78 ± 11[a]
Serum creatinine *mmol/L*	97 ± 29	87 ± 50[a]
Glomerular filtration rate *mL/min/1.73 m²*	75.6 ± 19.7	87.1 ± 23.8[a]
Proteinuria %	13.9	16.7
Hematuria %	5.3	6.0
Systolic blood pressure *mm Hg*	147 ± 29	154 ± 28[a]
Diastolic blood pressure *mm Hg*	81 ± 14	80 ± 14
Mean arterial pressure *mm Hg*	103 ± 17	104 ± 17
Pulse pressure *mm Hg*	66 ± 23	74 ± 23[a]
Antihypertensive agents %	20.5	23.0
Glucose intolerance %	27.1	16.5[a]
ECG abnormalities %	25.0	29.8
Total cholesterol *mmol/L*	4.5 ± 1.1	4.9 ± 1.2[a]
Body mass index *kg/m²*	20.7 ± 2.8	21.0 ± 3.6
Alcohol intake %	50.1	6.6[a]
Smoking habits %	59.0	14.2[a]

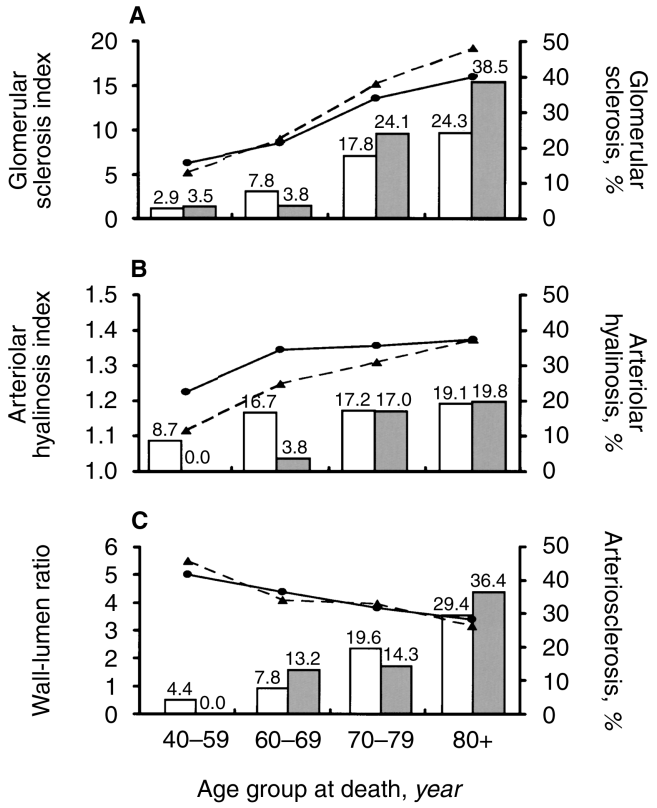
Glomerular filtration rate determined by Modification of Diet in Renal Disease (MDRD) Study Group formula [21]. Serum creatinine, glomerular filtration rate, and hematuria were measured in 329 men and 270 women who died after 1974. Values are expressed as mean ± SD or percentage.

[a] $P < 0.01$ vs. men

The age-specific mean values of renal histologic parameters are shown by gender in Figure 1. With elevating age, the mean values of the glomerular sclerosis index and arteriolar hyalinosis index linearly increased, and that of the wall-lumen ratio linearly decreased in both men and women.

The frequencies of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis were 15.5%, 16.4%, and 18.1% in men, respectively, and 26.8%, 15.2% and 23.9% in women, respectively. The frequency of glomerular sclerosis was 2.9% for men and 3.5% for women in the 40- to 59-year-old age group, and significantly increased to 24.3% and 38.5% in subjects 80 years old or older, respectively (Fig. 1). Likewise, the frequency of arteriolar hyalinosis significantly increased from 8.7% to 19.1% for men and from 0% to 19.8% for women. A similar pattern was observed for arteriosclerosis; the frequency increased from 4.4% to 29.4% for men and from 0% to 36.4% for women. These associations of glomerular and renal vascular changes with age were similar for both men and women.

We estimated the age-adjusted ORs and 95% CIs of each cardiovascular risk factor for the development of glomerular and vascular changes by gender (Tables 2 and 3). Serum creatinine, glomerular filtration rate, and



Number of subjects				
Men	69	90	163	136
Women	29	53	112	187

Fig. 1. Age-specific mean values and frequencies of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis among the 839 autopsy subjects by gender [men (□) (●) and women (■) (▲)], The Hisayama Study, 1962-1994. Solid and dashed lines indicate age-specific mean values of glomerular sclerosis index, arteriolar hyalinosis index, and wall-lumen ratio in men and women, respectively.

proteinuria significantly associated with the risk of glomerular sclerosis in both men and women. Systolic blood pressure and pulse pressure significantly increased the risk of glomerular sclerosis in both men and women, and mean arterial pressure increased the risk only in women. Pulse pressure remained a significant risk factor for glomerular sclerosis after being adjusted for age and mean arterial pressure in both men and women (OR, 1.17; 95% CI, 1.03 to 1.33 for men; and OR, 1.25; 95% CI, 1.09 to 1.43 for women). In addition, glucose intolerance was found to be a significant risk factor in men, as were ECG abnormalities in women. Alcohol intake had a significant protective effect on glomerular sclerosis in women.

For arteriolar hyalinosis, higher serum creatinine level for men and lower glomerular filtration rate for women were significant risk factors. Proteinuria significantly increased the risk of arterial hyalinosis in both men and women. Systolic, diastolic, mean, and pulse pressures were all significant risk factors in both men and women. After adjustment of age and mean arterial pressure, pulse pressure was a significant risk factor for arterial hyalinosis in men (OR, 1.17; 95% CI, 1.02 to 1.34), but was not in women (OR, 1.06; 95% CI, 0.91 to 1.23). Glucose intolerance, ECG abnormalities and total cholesterol levels were additional risk factors in men. For arteriosclerosis, glomerular filtration rate and proteinuria were significant risk factors in both men and women. Systolic blood pressure, mean arterial pressure, and pulse pressure were found to be significant risk factors in both men and women, as was diastolic blood pressure in women. After adjusted for age and mean arterial pressure, pulse pressure remained a significant risk factor for both men and women (OR, 1.28; 95% CI, 1.11 to 1.47 for men; and OR, 1.14; 95% CI, 1.00 to 1.31 for women). In addition, ECG abnormalities significantly increased the risk of arteriosclerosis in both men and women, and alcohol intake had a significant protective effect in women.

Results of the multivariate analysis of risk factors for the development of glomerular and renal vascular changes are summarized by gender in Table 4. We did not include serum creatinine and glomerular filtration rate in the multivariate analysis, since these parameters were not the cause but the result of renal glomerular and vascular changes. Both age and systolic blood pressure were significant independent risk factors for each of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis in both men and women. In addition, glucose intolerance and proteinuria for men were found to be significant risk factors for glomerular sclerosis. Elevated total cholesterol level significantly increased the risk of arteriolar hyalinosis in men. ECG abnormalities were an independent risk factor for arteriosclerosis in both men and women, and proteinuria was an additional risk factor in women. Alcohol intake tended to have a protective effect on glomerular sclerosis ($P = 0.07$) and arteriosclerosis ($P = 0.06$) in women. When using mean arterial pressure instead of systolic blood pressure in the multivariate model, mean arterial pressure similarly increased the risk for glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis for both men and women (data not shown). In the multivariate analysis, including mean arterial pressure and pulse pressure simultaneously, the latter was a significant risk factor for glomerular sclerosis (OR, 1.23; 95% CI, 1.00 to 1.33), arteriolar hyalinosis (OR, 1.19; 95% CI, 1.01 to 1.39), and arteriosclerosis (OR, 1.23; 95% CI, 1.05 to 1.45) for men. Likewise, for women, pulse pressure was also a significant risk factor for glomerular sclerosis (OR, 1.32; 95% CI, 1.13 to 1.54), but not for arteriolar hyalinosis (OR, 1.06; 95% CI, 0.90 to1.24), or arteriosclerosis (OR, 1.11; 95% CI, 0.96 to 1.29). Additional multivariate models were fit to explore the possi-

Table 2. Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of risk factors for the development of glomerular and vascular changes among 458 men autopsy subjects, The Hisayama Study, 1962 to 1994

	Glomerular sclerosis		Arteriolar hyalinosis		Arteriosclerosis	
Risk factor	OR	95% CI	OR	95% CI	OR	95% CI
Serum creatinine (10 mmol/L)	1.41[a]	1.22–1.63	1.12[b]	1.01–1.25	1.48[a]	1.27–1.72
Glomerular filtration rate (10 mL/min/1.73 m^2)	0.58[a]	0.47–0.73	0.87	0.73–1.03	0.54[a]	0.43–0.68
Proteinuria (Yes/no)	4.10[a]	2.21–7.63	2.52[a]	1.35–4.72	2.41[a]	1.28–4.54
Hematuria (Yes/no)	0.53	0.11–2.44	0.54	0.12–2.46	0.66	0.17–2.49
Systolic blood pressure (10 mm Hg)	1.11[b]	1.02–1.21	1.25[a]	1.15–1.37	1.38[a]	1.25–1.52
Diastolic blood pressure (10 mm Hg)	1.03	0.86–1.24	1.36[a]	1.12–1.64	1.49[a]	1.23–1.82
Mean arterial pressure (10 mm Hg)	1.12	0.93–1.30	1.41[a]	1.21–1.64	1.62[a]	1.38–1.91
Pulse pressure (10 mm Hg)	1.17[a]	1.05–1.30	1.28[a]	1.15–1.43	1.42[a]	1.27–1.60
Glucose intolerance (Yes/no)	2.43[a]	1.41–4.18	2.06[a]	1.23–3.46	1.30	0.75–2.25
Electrocardiogram abnormalities (Yes/no)	1.19	0.66–2.16	1.82[b]	1.07–3.12	4.62[a]	2.66–8.01
Total cholesterol (Yes/no)	1.01	0.79–1.29	1.50[a]	1.19–1.88	1.16	0.92–1.47
Body mass index (1 kg/m^2)	0.99	0.90–1.09	1.01	0.92–1.11	1.04	0.95–1.15
Alcohol intake (Yes/no)	0.72	0.42–1.24	0.66	0.39–1.11	0.85	0.51–1.41
Smoking habits (Yes/no)	0.75	0.44–1.28	1.09	0.65–1.82	1.08	0.64–1.81

Odds ratios were calculated for the increment in parentheses. Risk of serum creatinine, glomerular filtration rate, and hematuria were estimated in 329 men who died after 1974.
[a]$P < 0.01$; [b]$P < 0.05$

Table 3. Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of risk factors for the development of glomerular and vascular changes among 381 women autopsy subjects, The Hisayama Study, 1962 to 1994

	Glomerular sclerosis		Arteriolar hyalinosis		Arteriosclerosis	
Risk factor	OR	95% CI	OR	95% CI	OR	95% CI
Serum creatinine (10 mmol/L)	1.12[a]	1.01–1.23	1.03	0.97–1.08	1.07	0.98–1.16
Glomerular filtration rate (10 mL/min/1.73 m^2)	0.71[b]	0.61–0.82	0.85[a]	0.73–0.99	0.73[b]	0.63–0.84
Proteinuria (Yes/no)	2.53[b]	1.35–4.74	2.41[a]	1.20–4.83	3.55[b]	1.89–6.64
Hematuria (Yes/no)	0.43	0.11–1.65	NA		0.54	0.14–2.04
Systolic blood pressure (10 mm Hg)	1.20[b]	1.10–1.32	1.18[b]	1.06–1.30	1.16[b]	1.06–1.26
Diastolic blood pressure (10 mm Hg)	1.11	0.93–1.33	1.30[a]	1.06–1.60	1.14	0.95–1.37
Mean arterial pressure (10 mm Hg)	1.25[b]	1.08–1.45	1.32[b]	1.11–1.57	1.22[b]	1.05–1.42
Pulse pressure (10 mm Hg)	1.28[b]	1.14–1.43	1.17[a]	1.03–1.32	1.19[b]	1.07–1.33
Glucose intolerance (Yes/no)	1.60	0.87–2.94	1.63	0.81–3.26	1.05	0.54–2.02
Electrocardiogram abnormalities (Yes/no)	1.85[a]	1.11–3.09	1.52	0.84–2.75	3.03[b]	1.79–5.14
Total cholesterol (Yes/no)	1.16	0.95–1.42	1.08	0.85–1.36	1.08	0.87–1.33
Body mass index (1 kg/m^2)	1.01	0.94–1.08	1.04	0.96–1.13	0.93	0.86–1.00
Alcohol intake (Yes/no)	0.21[a]	0.05–0.92	1.94	0.73–5.18	0.11[a]	0.01–0.87
Smoking habits (Yes/no)	0.61	0.29–1.31	1.64	0.78–3.44	0.45	0.19–1.05

NA, Not available. Odds ratios were calculated for the increment in parentheses. Risk of serum creatinine, glomerular filtration rate, and hematuria were estimated in 270 women who died after 1974.
[a]$P < 0.05$; [b]$P < 0.01$

bility of interactions between the variables in the model, but no such interaction was identified. There was no evidence of a lack of fit in the multivariate model composed of significant risk factors.

To examine the combined effect of blood pressure and glucose intolerance, we stratified the subjects into four groups according to hypertension and glucose intolerance status (Table 5). The age-adjusted analysis showed that hypertension alone significantly increased the risk of glomerular sclerosis, arteriolar hyalinosis, and arteriosclerosis in both men and women, while glucose intolerance alone did not. When glucose intolerance was combined with hypertension, the age-adjusted ORs for glomerular and vascular changes further increased in both men and women, but this additive effect was modest for arteriosclerosis.

In 187 subjects with glucose intolerance, the age- and gender-adjusted analysis showed similar results as those of the whole subjects. In the multivariate analysis, age and proteinuria were significant independent risk factors for glomerular sclerosis, and alcohol intake had a protective effect. Likewise, systolic blood pressure and total cholesterol level were found to be independent risk factors for arteriolar hyalinosis. Age, ECG abnormalities, and proteinuria significantly increased the risk of arteriosclerosis.

DISCUSSION

In this autopsy-based population survey, we histopathologically examined glomerular sclerosis, renal arteriolar hyalinosis, and arteriosclerosis, and analyzed the effects

Table 4. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) of risk factors for the development of glomerular and renal vascular changes among the 839 autopsy subjects by gender, The Hisayama Study, 1962 to 1994

	Glomerular sclerosis		Arteriolar hyalinosis		Arteriosclerosis	
Risk factor	OR	95% CI	OR	95% CI	OR	95% CI
Men ($N = 458$)						
Age at death (10 years)	1.76[a]	1.32–2.34	1.14	0.88–1.46	2.19[a]	1.59–3.02
Systolic blood pressure (10 mm Hg)	1.07	0.97–1.17	1.23[a]	1.11–1.37	1.31[a]	1.18–1.46
Glucose intolerance (Yes/no)	2.29[a]	1.28–4.09	1.72	0.95–3.10		
Electrocardiogram abnormalities (Yes/no)			1.25	0.66–2.37	2.78[a]	1.51–5.13
Total cholesterol (1 mmol/L)			1.57[a]	1.21–2.03		
Proteinuria (Yes/no)	3.45[a]	1.80–6.59	1.65	0.81–3.34	1.69	0.84–3.43
Women ($N = 381$)						
Age at death (10 years)	2.11[a]	1.55–2.88	1.45[b]	1.05–2.00	2.12[a]	1.54–2.91
Systolic blood pressure (10 mm Hg)	1.16[a]	1.04–1.30	1.15[b]	1.02–1.30	1.04	0.93–1.17
Electrocardiogram abnormalities (Yes/no)	1.36	0.78–2.39			2.41[a]	1.36–4.25
Alcohol intake (Yes/no)	0.24	0.05–1.15			0.14	0.02–1.13
Proteinuria (Yes/no)	1.63	0.80–3.30	1.63	0.75–3.55	2.81[a]	1.39–5.69

Age and all significant risk factors available in the age-adjusted analysis were included in the multivariate model. Odds ratios were calculated for the increment in parentheses.

[a] $P < 0.01$; [b] $P < 0.05$

Table 5. Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the development of glomerular and renal vascular changes according to hypertension (HT) and glucose intolerance (GI) status by gender, The Hisayama Study, 1962 to 1994

	Number of	Glomerular sclerosis		Arteriolar hyalinosis		Arteriosclerosis	
Category	patients	OR	95% CI	OR	95% CI	OR	95% CI
Men ($N = 458$)							
No HT and No GI	132	1.00		1.00		1.00	
GI alone	38	2.50	0.81–7.69	2.85	0.92–8.80	1.49	0.36–6.25
HT alone	202	2.12	0.96–4.66	3.29[a]	1.47–7.36	4.94[a]	2.12–11.51
HT with GI	86	4.89[a]	2.11–11.32	5.78[a]	2.45–13.65	5.83[a]	2.30–14.75
Women ($N = 381$)							
No HT and No GI	98	1.00		1.00		1.00	
GI alone	15	0.99	0.19–5.17	1.65	0.17–15.96	1.21	0.23–6.37
HT alone	220	2.31[b]	1.17–4.54	4.66[a]	1.61–13.51	2.66[a]	1.30–5.42
HT with GI	48	3.83[a]	1.63–9.01	7.08[a]	2.13–23.54	2.55[b]	1.02–6.40

[a] $P < 0.01$; [b] $P < 0.05$

of cardiovascular risk factors on these renal pathologic changes using a logistic regression model. We confirmed that age and systolic blood pressure were common risk factors for all these histopathologic changes. In addition, metabolic abnormalities, that is, glucose intolerance and elevated serum cholesterol, and ECG abnormalities affected glomerular and vascular changes, while alcohol intake had a protective effect.

Age

Our study showed that the frequencies of each of glomerular sclerosis, hyaline arteriosclerosis, and arteriosclerosis linearly increased with advancing age in both men and women, and these associations were independent of other risk factors. It is well known that both glomerular filtration rate and renal blood flow progressively decline with age [5]. These findings, together with those of the present study, suggest that aging itself might induce the progression of glomerular sclerosis and arteriosclerosis, ultimately resulting in an age-related deterioration of renal function in the general population.

Hypertension

Hypertension is one of the major risk factors for development of ESRD [22, 23]. We showed that elevated blood pressure was a significant independent risk factor, not only for the development of arteriolar hyalinosis and arteriosclerosis, but also for glomerular sclerosis, even after adjustment for age and other risk factors. The impact of mean arterial pressure and pulse pressure on glomerular and vascular changes was similar to that of systolic blood pressure, and the impact of pulse pressure remained significant even after controlling for mean arterial pressure. Moreover, the effect of blood pressure was stronger for arteriolar hyalinosis and arteriosclerosis than glomerular sclerosis. Essential hypertension, the main type of hypertension seen in this study, is considered to cause arteriolar hyalinosis and arteriosclerosis, resulting in the progression of glomerular sclerosis [24].

Glucose intolerance

Diabetes is well known to cause diabetic nephropathy and accelerated atherosclerosis. In this study, glucose

intolerance was a significant risk factor for the development of glomerular sclerosis in men. When the combined effect of hypertension and glucose intolerance was examined, the risk of glomerular and vascular changes was mainly determined by hypertension, and glucose intolerance only had an additive effect, especially in women. Diabetic nephropathy is known to be more prevalent and to progress more rapidly in men than in women [6]. Moreover, in our cohort, the frequency of glucose intolerance was higher in men. These factors may have been responsible for the present finding that glucose intolerance was much more highly associated in men. In contrast, arteriosclerotic vascular change is generally a slow pathoanatomic process that may require a long period of time for progression. Our study subjects underwent autopsy within 7 years after their last health examination, and thus the findings of the present study might reflect only short-term effects. This, in turn, may have resulted in the finding that glucose intolerance was not a risk factor for renal vascular changes.

ECG abnormalities

Our data showed that ECG abnormalities were a significant independent risk factor for renal arteriosclerosis in both men and women. In our subjects, the frequency of ECG abnormalities increased with elevating age and blood pressure (data not shown), suggesting that these factors reflect a longer duration of hypertension. Another explanation is that renal arteriosclerosis might be closely related to systemic atherosclerosis, including that of coronary atherosclerosis. An autopsy study by the Honolulu Heart Program also found that the frequency of cardiovascular death and the degree of aortic atherosclerosis linearly increased with the progression of renal arteriosclerosis [16].

Total cholesterol

Experimental studies suggest that circulating lipoproteins play a significant role in the pathogenesis of glomerular sclerosis [25]. However, there have been no available data concerning the effect of hyperlipidemia on renal histologic changes in the general population. Our data showed that total cholesterol level was significantly related to the development of arteriolar hyalinosis in men. This finding is consistent with those of Tracy et al [8], who studied autopsies from a hospital and coroner's office. On the other hand, the total cholesterol level in our subjects was lower than that of Western populations, and this might be a reason for the lack of association between serum cholesterol level and arteriosclerosis in this study.

Alcohol intake

There has been little information concerning the effect of alcohol intake on renal histologic changes. The Honolulu Heart Program reported a protective association between alcohol intake and arteriolar hyalinosis [17], but did not examine the effect of alcohol intake on glomerular sclerosis and arteriosclerosis. Our data first showed that alcohol intake has a protective effect on the development of glomerular sclerosis and arteriosclerosis in women. The majority of our women drinkers consumed a small amount of alcohol [14], suggesting that light alcohol consumption might protect against the progression of glomerular sclerosis and arteriosclerosis. This finding is consistent with the fact that light-to-moderate alcohol consumption significantly reduces the risk of cardiovascular disease [14]. The protective effect of alcohol is thought to be mediated by the beneficial effect of alcohol on high-density lipoprotein cholesterol level [26].

Validation study

A previous report of Tracy et al [27] claimed that mean arterial pressure and age could be used to calculate interlobular artery wall thickness with great precision. Wall thickness (%) could be calculated from $0.171 \times$ mean arterial pressure $+ 0.047 \times$ age $+ 1.1$ and $0.140 \times$ mean arterial pressure $+ 0.092 \times$ age $+ 4.0$, for arteries of sizes of 80 to 150 μm and 150 to 300 μm, respectively. To evaluate the efficacy of this formula by Tracy et al, we performed a validation study using our study subjects. Mean wall thickness calculated as wall thickness/outer diameter, being $22.1\% \pm 5.2\%$ in our study, was not different from that of $22.3\% \pm 3.0\%$ by the Tracy et al formula for arteries of sizes of 150 to 300 μm, but it was significantly lower in our study ($18.3\% \pm 4.5\%$) than by the formula of Tracy et al ($25.4\% \pm 2.7\%$) for arteries of sizes of 80 to 150 μm. Since many cardiovascular risk factors affect renal arteriosclerosis, the formula of Tracy et al might have a poor predictable value for estimating renal arteriosclerosis of small artery.

Limitations of the study

We used the wall-lumen ratio as an index of arteriosclerosis. Arteries in autopsy tissues are collapsed, leading to a low wall-lumen ratio. This might result in overestimation of the degree of arteriosclerosis, when tissues are obtained without perfusion-fixation. Tracy, Heigle, and Velez-Duran [9] examined this problem using autopsy subjects in whom one kidney was perfusion-fixed and the other immersion-fixed. They showed that the outer diameter of immersion-fixed vessels was reduced and the wall thickness extended in the same proportion as in perfusion-fixed vessels, regardless of the vessel size. The wall-lumen ratio in each artery might be overestimated to the same degree. In the present study, since the development of arteriosclerosis was determined by the lower 5th percentile of the wall-lumen ratio, postmortem collapse of arteries was not likely to have distorted the findings.

Renal tubulointerstitial change is one of the causes of renal functional decline in animal models or patients with various renal diseases [4, 7]. However, we did not examine this pathologic change, since many subjects in our study underwent autopsy examination more than 24 hours after death, and their postmortem interstitial changes were severe. A previous autopsy study found no significant association between interstitial fibrosis and risk factors such as age and blood pressure, probably due to postmortem edema [10]. Thus, information on interstitial changes might not have substantially improved the value of our findings.

A consideration of great importance in any epidemiologic use of autopsies is the special subset of cases that entered the autopsy series by dying of conditions unrelated to cardiovascular diseases [28, 29]. These include cancers, infections, violence, and many other conditions. However, all of the glomerular and vascular changes in these subjects also similarly increased with age as those of the whole study subjects (data not shown). The Hisayama Study encourages performance of autopsy examinations in all of the deceased Hisayama residents, regardless of the cause of death, and maintains high autopsy rate throughout the study period. Therefore, the results of our findings might have generalizability. Because this study is based on autopsies, the subjects in this study may have shown a higher prevalence of risk factors and more severe renal histologic changes than the overall population. This selection bias might affect their associations with risk factors. Despite these limitations, we believe that the findings of this study provide useful information toward a better understanding of the pathogenesis of kidney damage in the general population.

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