Table 1. Characteristics of Included Cohort Studies

Regions	Cohort Name	No. of Population	Mean Age, y	Men, %	Mean sCr, μmol/L*	GFR <60, %†	Mean SBP/DBP, mm Hg	Mean Fasting Blood Glucose, mmol/L	Mean Total Cholesterol, mmol/L	Current Smoking, %	Follow-Up, y		No. of Events			
											Start-End	Mean	CVD	Stroke	MI	Death
Hokkaido	Tanno/Soubetsu	2066	60.1	43.9	89.6	19.4	133/78	5.1	5.0	25.9	1991–1999	5.5	120	93	27	136
Akita 2	Ikawa	2595	56.1	43.6	76.0	2.6	135/81	6.6	4.9	28.5	1985–1999	10.7	44	41	3	146
Ibaraki	Kyowa	4479	54.8	42.8	76.9	5.3	137/82	6.9	5.0	30.4	1985–1999	10.1	168	128	51	350
Niigata	Tokamachi	8480	58.0	33.1	79.6	7.7	127/73	NA	5.1	18.8	1993–2003	7.8	NA	NA	29	400
Osaka	Yao Minami-takayasu	3855	54.0	34.8	78.7	6.7	132/80	6.0	5.2	27.2	1985–1998	9.6	79	62	18	191
Shiga 1	Shigaraki	2934	56.6	41.1	81.3	10.5	132/78	6.0	5.0	29.4	1992–2001	7.3	82	69	13	260
Hiroshima	Hiroshima	2222	72.1	28.7	84.0	23.8	136/78	6.2	5.6	15.4	1992–2000	3.6	73	63	12	350
Ehime	Ohzu	5300	59.5	33.9	76.9	6.2	130/76	5.3	5.3	15.2	1996–2003	5.5	99	89	10	184
Fukuoka 1	Hisayama	757	60.8	39.5	83.1	9.5	133/78	5.4	5.4	21.1	1990–2000	9.9	57	45	14	86
Kumamoto	...	2465	47.0	70.0	65.4	0.2	127/80	5.7	5.4	46.4	1999–2003	4.2	5	2	3	1
Total	...	35 153	57.6	38.0	78.6	8.2	131/78	6.0	5.2	24.5	1985–2003	7.4	727	592	180	2104

sCr indicates serum creatinine; SBP/DBP, systolic or diastolic blood pressure; MI, myocardial infarction; and NA, not available.

*Serum creatinine was measured by Jaffe's method in 8 cohorts, by enzymatic method in the Ehime cohort, and by either method in the Niigata cohort. The values of serum creatinine measured by the enzymatic method were corrected by the addition of 18.3 μmol/L.

†GFR (unit: mL · min^{-1} · 1.73 m^{-2}) was estimated by the Modification of Diet in Renal Disease formula.

those with a GFR <90 mL · min^{-1} · 1.73 m^{-2} (all $P<0.01$). Subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} showed a significantly higher age- and sex-adjusted incidence of myocardial infarction and all-cause mortality than those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} ($P<0.001$). The age-adjusted incidences of CVD, stroke, and all-cause mortality were significantly higher in subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} than in those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} in both sexes (all $P<0.05$).

The risks of CVD, stroke, myocardial infarction, and all-cause death increased progressively with declining GFR levels in the overall population after adjustment for age and sex (Table 4). Even after adjustment for potential confounding factors, specifically age, sex, cohort, systolic blood pressure, diabetes, serum total cholesterol, body mass index, and current smoking status, the risks of CVD, myocardial infarction, and all-cause death were significantly higher in subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} than in the overall population. There was no evidence of heterogeneity in these associations among study cohorts (all P for heterogeneity >0.6; $Q=2.46$, $I^2=0\%$ for CVD; $Q=4.06$, $I^2=0\%$ for stroke; $Q=3.75$, $I^2=0\%$ for myocardial infarction; and $Q=1.14$, $I^2=0\%$ for all-cause death). Subjects with a GFR <60 mL · min^{-1} · 1.73 m^{-2} had a significantly greater risk of myocardial infarction and death in men and of CVD, stroke, and death in women.

Table 2. Baseline Characteristics of the Study Population by Sex

Risk Factors	Men (n=9574)	Women (n=13 459)
Age, y	56.9 (11.1)	58.2 (11.4)
Serum creatinine, μmol/L	87.3 (16.7)	71.6 (13.6)
GFR, mL · min^{-1} · 1.73 m^{-2}	87.3 (20.2)	81.0 (19.1)
GFR levels (mL · min^{-1} · 1.73 m^{-2}), %		
≥90	39.0	27.1
60–89	55.9	62.8
<60	5.2	10.1
Systolic blood pressure, mm Hg	133.6 (19.1)	132.3 (19.8)
Diastolic blood pressure, mm Hg	81.1 (11.5)	77.9 (11.0)
Blood pressure levels, %		
Normal	19.6	24.3
Prehypertension	41.8	41.0
Stage 1 hypertension	26.0	24.3
Stage 2 hypertension	12.6	10.4
Diabetes, %	9.5	5.2
Serum total cholesterol, mmol/L	5.0 (0.9)	5.4 (1.0)
Body mass index, kg/m^2	23.2 (3.0)	23.2 (3.3)
Current smoking, %	56.2	7.1

Values are means (SD) or frequencies.

The Figure shows the log-linear relationship between blood pressure levels at baseline and the hazard of CVD, stroke, and all-cause death regardless of kidney function status after adjustment for potential confounding factors (all P for trend <0.01). There was no evidence of heterogeneity of the patterns in the association of blood pressure levels with the risk of outcomes between subgroups of kidney function status (all P for heterogeneity >0.7). The age- and sex-adjusted HR of myocardial infarction increased in a log-linear fashion with increasing blood pressure levels in the normal, prehypertension, stage 1 hypertension, and stage 2 hypertension groups in subjects with a GFR ≥60 mL · min^{-1} · 1.73 m^{-2} (HR 0.56 [95% CI 0.33 to 0.95], 1.00 [reference], 1.60 [1.08 to 2.37], and 1.75 [1.06 to 2.87]; P for trend 0.03) and in those with a GFR <60 mL · min^{-1} · 1.73 m^{-2} (0.19 [0.02 to 1.47], 1.00 [reference], 1.72 [0.80 to 3.70], and 2.36 [1.02 to 5.44]; P for trend 0.04). The number of myocardial infarctions in subjects with normal blood pressure levels was too small to assess reliably for multivariate-adjusted analysis.

We also performed sensitivity analyses to assess the risk of CVD according to GFR levels estimated by the MDRD formula corrected according to the Japanese coefficient of 0.881.[15] The correction shifted the GFR distribution to a

Table 3. Incidence Rate of CVD According to Kidney Function Status

GFR Levels, mL · min^{-1} · 1.73 m^{-2}	Overall				Men				Women			
	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*	No. of Events	No. of Participants	PY at Risk	Incidence Rate per 1000 PY (95% CI)*
CVD												
GFR ≥90	105	7199	51 203	2.9 (2.1–3.6)	78	3672	23 964	4.4 (3.3–5.6)	27	3527	27 239	1.8 (0.9–2.8)
GFR 60–89	489	13 967	104 334	4.3 (3.9–4.7)†	245	5404	39 794	5.5 (4.8–6.2)	244	8563	64 540	3.5 (3.1–3.9)†
GFR <60	133	1867	12 013	6.5 (5.0–8.0)‡	49	498	3018	9.1 (5.7–12.5)‡	84	1369	8995	4.7 (3.6–5.8)‡
Stroke												
GFR ≥90	84	7206	51 315	2.2 (1.6–2.8)	61	3676	24 033	3.5 (2.5–4.5)	23	3530	27 281	1.4 (0.6–2.1)
GFR 60–89	404	14 003	104 808	3.5 (3.2–3.9)†	192	5433	40 160	4.2 (3.6–4.8)	212	8570	64 648	3.0 (2.6–3.4)†
GFR <60	104	1875	12 092	5.0 (3.7–6.4)‡	33	501	3048	6.6 (3.5–9.7)§	71	1374	9044	4.0 (3.0–5.0)‡
Myocardial infarction												
GFR ≥90	25	8350	60 807	0.6 (0.2–0.9)	21	4179	28 164	0.9 (0.4–1.4)	4	4171	32 643	0.4 (−0.2–0.9)
GFR 60–89	116	19 786	151 527	0.7 (0.6–0.8)	72	7345	54 855	1.1 (0.9–1.4)	44	12 441	96 672	0.4 (0.3–0.5)
GFR <60	39	2521	16 926	1.4 (0.9–1.9)‡	21	643	4039	2.4 (1.3–3.6)‡	18	1878	12 887	0.7 (0.4–1.1)
All-cause death												
GFR ≥90	289	8445	62 754	7.6 (6.4–8.7)	217	4225	29 119	11.4 (9.7–13.1)	72	4220	33 635	5.1 (3.5–6.6)
GFR 60–89	1388	20 280	161 168	7.0 (6.7–7.4)	809	7529	58 344	10.4 (9.7–11.1)	579	12 751	102 824	4.8 (4.4–5.2)
GFR <60	427	2649	18 935	12.9 (10.2–15.5)‡	184	681	4540	21.3 (14.9–27.7)‡	243	1968	14 395	7.3 (5.9–8.6)‡

PY indicates person-years.

*Incidence rates were adjusted for age by the direct standardized method. Overall results were additionally adjusted for sex.

†$P<0.01$, ‡$P<0.001$, §$P<0.05$ vs GFR ≥90 mL · min^{-1} · 1.73 m^{-2}.

lower level. Consequently, more participants (21%) were assigned to the group whose GFR was <60 mL · min^{-1} · 1.73 m^{-2}, and the age- and sex-adjusted risk of CVD among these subjects relative to those with a GFR ≥90 mL · min^{-1} · 1.73 m^{-2} was attenuated by 85% (95% CI 32% to 160%), although it was still significant. Similarly, a log-linear relationship between blood pressure levels and the risk of CVD was still observed in the subgroup whose GFR was <60 mL · min^{-1} · 1.73 m^{-2}, even after correction with the Japanese coefficient (Data Supplement Figure).

Discussion

In the present study, we demonstrated a clear association between reduced GFR and high risk of CVD. To the best of our knowledge, this is the first overview of this issue in a Japanese community-based longitudinal study. Furthermore, the relationship between blood pressure levels at baseline and CVD risk was found to be strong and continuous, regardless of kidney function status.

There have been few studies showing the association of reduced GFR with an increased risk of CVD or mortality in the general Japanese population.[6,8] The findings of the Hisayama study revealed that a GFR <60 mL · min^{-1} · 1.73 m^{-2} was a significant risk factor for the development of coronary heart disease in men and of CVD and stroke in women.[6] In a large cohort study conducted by Irie et al,[7] reduced GFR was strongly associated with mortality due to CVD or stroke. A report from NIPPON DATA 90 also showed an association between a GFR <30 mL · min^{-1} · 1.73 m^{-2} and a high risk of cardiovascular death.[8] In the present study, we demonstrated a clear association between reduced GFR and the risks of CVD, stroke, myocardial infarction, and death in an overview of 10 Japanese cohort studies. These results, therefore, highlight the importance of taking kidney function status into consideration in trying to reduce the burden of CVD in the general Japanese population.

There are several possible explanations for the association of reduced GFR with CVD.[3] First, reduced GFR is associated with a high prevalence of traditional CVD risk factors, such as aging, hypertension, diabetes, smoking habits, and dyslipidemia.[19] In the present study, reduced GFR was found to be a significant risk factor for the development of stroke after adjustment for demographic factors, but not after adjustment for potential traditional CVD risk factors, which suggests that an accumulation of traditional CVD risk factors in individuals with reduced GFR increases the risk of stroke. In contrast, the risks of CVD, myocardial infarction, and all-cause death in individuals with reduced GFR were also attenuated, although still significant, after adjustment for traditional CVD risk factors. Reduced GFR has been shown to be associated with increased levels of novel CVD risk factors, such as inflammation, asymmetric dimethylarginine, oxidative stress, and thrombogenic factors.[19,20] Second, reduced GFR may be a marker of vascular disease; it is well recognized that renal arteriosclerosis and glomerular sclerosis are closely related to systemic atherosclerosis.[21]

In the present study, reduced GFR was associated with a high risk of stroke in men after adjustment for demographic factors but not after adjustment for potential confounding factors; however, this relationship was still observed in women even after adjustment for confounding factors. This sex difference may be a consequence of the effects of residual confounding factors, specifically, hypercoagulable states[22] or gonadal steroids,[23] in women. Furthermore, the lack of a significant association between reduced GFR and a high risk of myocardial infarction is probably due to the relatively small number of events.

Table 4. Effects of Kidney Function on Development of CVD

	Age- and Sex-Adjusted*		Multivariate-Adjusted†	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.41 (1.13–1.75)	0.002	1.24 (0.98–1.58)	0.07
GFR <60	2.26 (1.71–2.99)	<0.001	1.57 (1.14–2.15)	0.005
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.40 (1.10–1.79)	0.007	1.24 (0.95–1.61)	0.11
GFR <60	2.06 (1.51–2.81)	<0.001	1.41 (0.99–2.00)	0.06
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.32 (0.84–2.08)	0.22	1.26 (0.77–2.05)	0.35
GFR <60	3.35 (1.94–5.79)	<0.001	2.37 (1.29–4.34)	0.005
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.01 (0.88–1.15)	0.94	1.10 (0.96–1.27)	0.17
GFR <60	1.70 (1.44–2.00)	<0.001	1.65 (1.38–1.97)	<0.001
Men				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.21 (0.93–1.58)	0.16	1.01 (0.75–1.35)	0.95
GFR <60	2.13 (1.45–3.11)	<0.001	1.47 (0.94–2.29)	0.09
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.17 (0.86–1.57)	0.32	0.99 (0.71–1.38)	0.95
GFR <60	1.69 (1.08–2.65)	0.02	1.10 (0.64–1.89)	0.72
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.25 (0.75–2.07)	0.39	1.05 (0.61–1.81)	0.85
GFR <60	3.95 (2.07–7.55)	<0.001	2.56 (1.24–5.27)	0.01
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	0.97 (0.83–1.14)	0.72	1.06 (0.90–1.25)	0.48
GFR <60	1.75 (1.42–2.16)	<0.001	1.73 (1.37–2.17)	<0.001
Women				
CVD				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.93 (1.28–2.92)	0.002	1.81 (1.17–2.79)	0.008
GFR <60	2.84 (1.79–4.52)	<0.001	1.97 (1.19–3.29)	0.009
Stroke				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	2.01 (1.28–3.14)	0.002	1.81 (1.14–2.89)	0.01
GFR <60	2.89 (1.75–4.79)	<0.001	1.98 (1.15–3.42)	0.01
Myocardial infarction				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.60 (0.55–4.60)	0.39	2.14 (0.63–7.24)	0.22
GFR <60	2.93 (0.93–9.23)	0.07	2.79 (0.74–10.56)	0.13
All-cause death				
GFR ≥90	1.00 (Reference)		1.00 (Reference)	
GFR 60–89	1.13 (0.87–1.47)	0.35	1.23 (0.94–1.62)	0.13
GFR <60	1.79 (1.34–2.38)	<0.001	1.68 (1.24–2.30)	<0.001

GFR was measured in mL · min^{-1} · 1.73 m^{-2}.

*Sex was removed from model for the analysis stratified by sex.

†Estimates were adjusted for age, sex, cohort, systolic blood pressure, diabetes, serum total cholesterol, body mass index, and current smoking status. Sex was removed from model for the analyses stratified by sex.

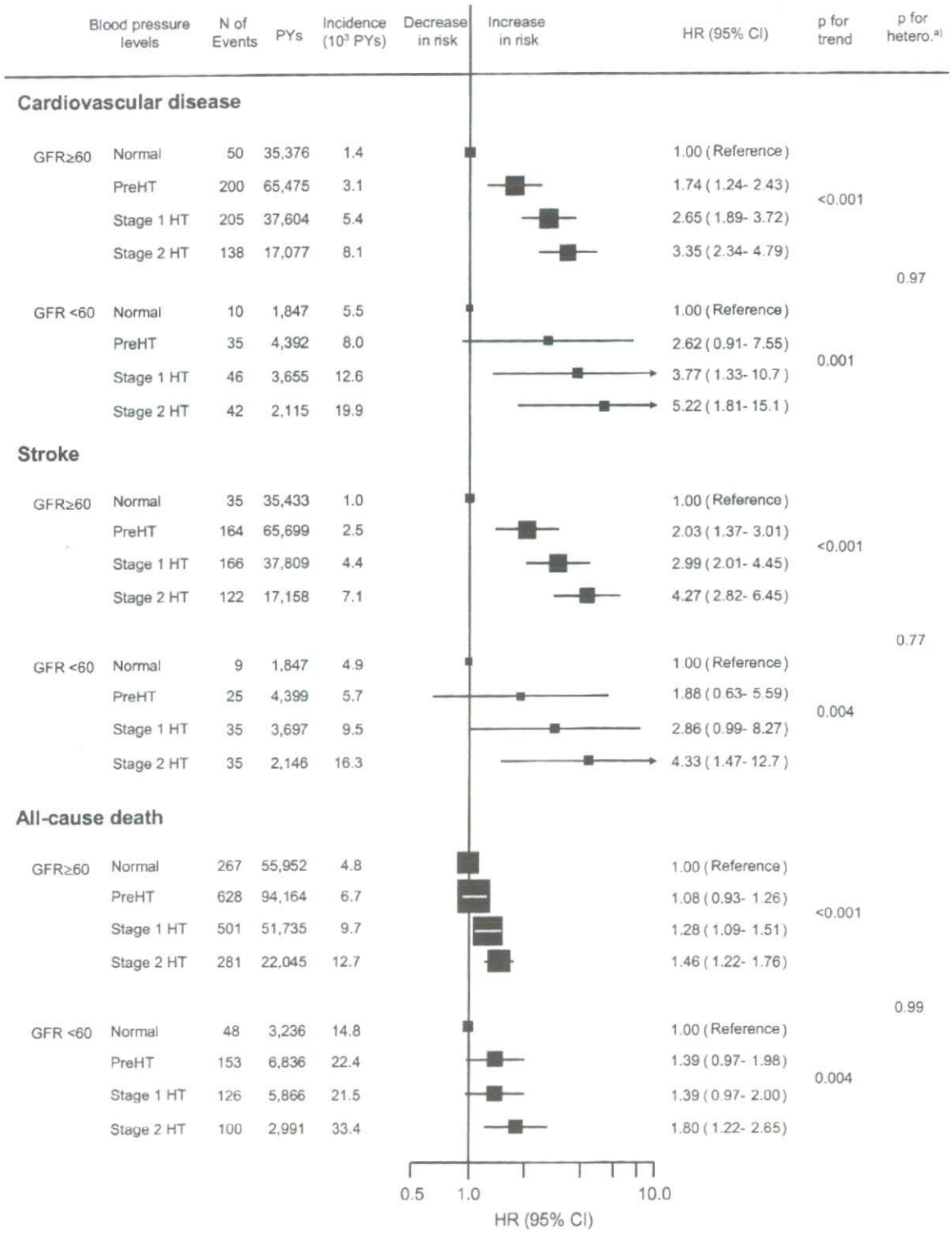

Figure. Effects of blood pressure levels on the development of CVD according to kidney function status. Estimates were adjusted for age, sex, cohort, diabetes, serum total cholesterol, body mass index, and current smoking status. Solid boxes represent estimates on the risk of outcomes for each blood pressure level. Areas of the boxes are proportional to the number of events. "*P* for trend" tested the log-linear relationship between blood pressure levels at baseline and the risk of outcomes by kidney function status. "*P* for hetero." tested the heterogeneity of the association of blood pressure levels with the risk of outcomes between kidney function status subgroups. HT indicates hypertension; PYs, person-years.

In the present study, we demonstrated a clear log-linear association between blood pressure levels and the risks of CVD, stroke, and all-cause death, regardless of kidney function status. These findings are consistent with the results of other studies conducted in the general population.[9,10] Recent publications of prospective cohort data suggest, however, that individuals with a reduced GFR and a systolic blood pressure below 120 mm Hg may be at increased risk of stroke or death.[12,13] Other post hoc analyses of trials conducted on individuals with coronary heart disease[24] and with diabetic nephropathy[25] suggest an increased risk of coronary events at the lower achieved blood pressures. In the present study, however, no evidence of an increased risk of myocardial infarction was observed at the lower blood pressure level. One possible explanation for the J-curve association observed in the previous studies may be the phenomenon of reverse causality,[26] in which extensive vascular disease or subclinical cardiac dysfunction is associated with lower blood pressure levels and reduced GFR and is associated independently with a relatively high risk of CVD, rather than with any adverse effects of low blood pressure itself.

Several limitations of the present study should be noted. First, the generalizability of our findings to some populations at high risk for CVD may be limited. The participants excluded from the analysis due to missing baseline examination data or event data were likely to have a higher cardiovascular risk, because they were older (mean 63 years), had higher blood pressure levels (mean 138/80 mm Hg), and had a greater prevalence of diabetes (8.7%) than the study population. This bias has the potential to alter our findings, which may therefore be conservative. Second, the present GFR estimates, which were made with a simplified prediction equation, may not be sufficiently correct, which possibly could lead to a certain number of misclassifications of estimated kidney function status. Such misclassifications would weaken the association found in the present study, biasing the results toward the null hypothesis. Third, we were unable to obtain information regarding the use of antihypertensive drugs, medication compliance, or blood pressure control during the follow-up period. The lack of this information may reduce the accuracy of our findings to some extent. Fourth, the applicability of the present results to populations with severe kidney dysfunction is limited, because very few of our subjects (0.1%) had a GFR <30 mL $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}. Moreover, the absence of data on proteinuria in the present study makes it impossible to assess the effects of the earliest stages of kidney disease on the risk of CVD. Finally, creatinine measurement was conducted locally rather than at a central laboratory, which introduces a certain amount of variability that may reduce the reliability of the results.

In conclusion, the present findings suggest that a reduced GFR is associated significantly with a high risk of CVD in the general Japanese population. Furthermore, we observed a continuous relationship between blood pressure levels at baseline and the risk of CVD, regardless of kidney function status. The optimization of blood pressure control in individuals with kidney dysfunction is therefore likely to substantially reduce the burden of CVD in the general population.

Acknowledgments

The authors gratefully acknowledge the efforts of the JALS investigators, research coordinators, and committee members. A list of these individuals has been published previously[14] and is provided in the Appendix (Data Supplement).

Sources of Funding

This study was supported by a research grant from Japan Arteriosclerosis Prevention Fund.

Disclosures

None.

References

1. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J Am Soc Nephrol*. 2003;14(suppl 2):S131–S138.
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003;41:1–12.
3. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108:2154–2169.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
5. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41:47–55.
6. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. *Kidney Int*. 2005;68:228–236.
7. Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, Kanashiki M, Saito Y, Ota H, Nose T. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. *Kidney Int*. 2006;69:1264–1271.
8. Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, Saitoh S, Sakata K, Okayama A, Ueshima H; the NIPPON DATA90 Research Group. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circ J*. 2006;70:954–959.
9. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990;335:765–774.
10. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S; Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707–716.
11. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003;362:1527–1535.
12. Weiner DE, Tighiouart H, Levey AS, Elsayed E, Griffith JL, Salem DN, Sarnak MJ. Lowest systolic blood pressure is associated with stroke in stages 3 to 4 chronic kidney disease. *J Am Soc Nephrol*. 2007;18:960–966.
13. Kovesdy CP, Trivedi BK, Kalantar-Zadeh K, Anderson JE. Association of low blood pressure with increased mortality in patients with moderate to severe chronic kidney disease. *Nephrol Dial Transplant*. 2006;21:1257–1262.

14. Japan Arteriosclerosis Longitudinal Study Group. Japan Arteriosclerosis Longitudinal Study-ECC: rationale, design, and population characteristics. *Circ J.* 2008;72:1563–1568.
15. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol.* 2007;11:41–50.
16. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(suppl 1):S1–S266.
17. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee: seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206–1252.
18. Woodward M. *Epidemiology: Study Design and Data Analysis.* 2nd ed. Boca Raton, Fla: Chapman & Hall/CRC Press; 2005.
19. Uhlig K, Levey AS, Sarnak MJ. Traditional cardiac risk factors in individuals with chronic kidney disease. *Semin Dial.* 2003;16:118–127.
20. Madore F. Uremia-related metabolic cardiac risk factors in chronic kidney disease. *Semin Dial.* 2003;16:148–156.
21. Keane WF, Kasiske BL, O'Donnell MP. Lipids and progressive glomerulosclerosis: a model analogous to atherosclerosis. *Am J Nephrol.* 1988; 8:261–271.
22. Tracy RP, Arnold AM, Ettinger W, Fried L, Meilahn E, Savage P. The relationship of fibrinogen and factors VII and VIII to incident cardiovascular disease and death in the elderly: results from the cardiovascular health study. *Arterioscler Thromb Vasc Biol.* 1999;19:1776–1783.
23. Gabriel SR, Carmona L, Roque M, Sánchez GL, Bonfill X. Hormone replacement therapy for preventing cardiovascular disease in postmenopausal women. *Cochrane Database Syst Rev.* 2005;2:CD002229.
24. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med.* 2006;144:884–893.
25. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esmatjes E, Hricik D, Pohl M, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis EJ; the Collaborative Study Group. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol.* 2005;16:2170–2179.
26. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int.* 2003;63:793–808.

CLINICAL PERSPECTIVE

There have been several studies reporting a strong association between reduced kidney function and cardiovascular risk. The findings, however, have been inconsistent in Asian populations, and there has been no attempt to date to review the evidence. Hence, we conducted an overview of individual participant data from Japanese community-based cohort studies to reliably assess the impact of reduced kidney function on cardiovascular risk in the general Japanese population. Our findings suggest a clear association between reduced kidney function and a 57% greater risk of cardiovascular disease in the Japanese population, as well as a log-linear relationship between blood pressure levels and cardiovascular risk in individuals with reduced kidney function. The optimization of blood pressure control in individuals with reduced kidney function is therefore likely to substantially reduce the burden of cardiovascular disease in the general population. Given that the prevalence of reduced kidney function is ≈10% in the general population, we believe that these novel findings are significant in the areas of clinical and public health.

Go to http://cme.ahajournals.org to take the CME quiz for this article.

Original Article

Incidence of Hypertension in Individuals with Abdominal Obesity in a Rural Japanese Population: The Tanno and Sobetsu Study

Hirofumi OHNISHI[1),2)], Shigeyuki SAITOH[1)], Hiroshi AKASAKA[1)], Kaneto MITSUMATA[1)], Mizue CHIBA[1)], Makoto FURUGEN[1)], Tetsuaki FURUKAWA[1)], Mitsuru MORI[2)], and Kazuaki SHIMAMOTO[1)]

Although abdominal obesity (AO) assessed by waist circumference (WC) is an important component of the metabolic syndrome (MetS), the usefulness of AO as a predictor of hypertension (HT) is not known. In this study, we investigated the incidence of HT in residents of two rural communities in Japan. The subjects were 187 men and 209 women selected from 712 residents who had undergone medical examinations in the towns of Tanno and Sobetsu, Hokkaido, in 1994 and 2002. Participants with HT in 1994 were excluded. Participants with AO were determined according to the WC criteria in the Japanese definition of MetS (≥85 cm for men, ≥90 cm for women). The participants were divided into two groups: a non-AO group and an AO group. We compared the incidence of HT between the two groups and found a significantly higher incidence in the AO group. The results of logistic regression analysis showed that the relative risk of developing HT in individuals with AO was 2.33 (p=0.017; 95% confidence interval [CI], 1.17–4.63) and that the risk per 1-cm increase in WC from 1994 to 2002 was 1.06 (p=0.003; 95% CI, 1.02–1.10), both adjusted for several confounding factors. The results of this study suggest that, to prevent HT in Japanese, it is important to manage abdominal obesity and to monitor WC in individuals with or without abdominal obesity. (*Hypertens Res* 2008; 31: 1385–1390)

***Key Words*: abdominal obesity, hypertension, waist circumference, metabolic syndrome, community-based survey**

Introduction

In 2005, the Japanese Society of Internal Medicine and eight related scientific societies jointly announced new Japanese diagnostic criteria for the metabolic syndrome (MetS) (*1*). The new criteria include abdominal obesity as defined by waist circumference (WC).

The Ministry of Health, Labour and Welfare started a new program of health examinations in Japan in April 2008 (Health Service Bureau, Ministry of Health, Labour and Welfare: Standard program of medical examination and health guidance (fixed version). http://www.mhlw.go.jp/bunya/kenkou/seikatsu/index.html [accessed February 7, 2008; in Japanese]). This program adopts the Japanese diagnostic criteria for MetS in order to identify individuals at high risk for lifestyle-related and atherosclerotic diseases. Although the WC criterion will also be used to identify high-risk individuals in the new system, the usefulness of the criterion's definition of abdominal obesity as a predictor of hypertension (HT) is not known.

In this study, we investigated the incidence of HT in resi-

From the [1)]Second Department of Internal Medicine and [2)]Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Japan.

Address for Reprints: Hirofumi Ohnishi, M.D., Ph.D., Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060–8543, Japan. E-mail: hohnishi@sapmed.ac.jp

Received February 8, 2008; Accepted in revised form April 8, 2008.

dents of two rural communities in Japan to determine the relationship between HT and abdominal obesity.

Methods

Of the 1,525 residents who were aged 30 years or older when they received medical examinations in the towns of Tanno and Sobetsu, Hokkaido, in 1994, 712 also underwent medical examinations in 2002. We excluded the following individuals from those 712 residents: 14 individuals without data on blood pressure (BP) or WC, 140 individuals who were defined as having HT (systolic BP [SBP]≥140 mmHg and/or diastolic BP [DBP]≥90 mmHg) without medication, 146 individuals who were on medication for HT, and 16 individuals who had received medical treatment for coronary heart disease or cerebral vascular disease. The remaining 396 individuals were participants in this analysis. We received written informed consent from all participants.

WC, body mass index (BMI), SBP, DBP, fasting plasma glucose (FPG), total cholesterol (T.chol), triglyceride (TG), and HDL cholesterol (HDL-C) were measured in each subject. Blood samples were collected early every morning when the subjects felt hungry, at least 10 h after they had last eaten.

Participants with abdominal obesity were determined according to the new Japanese diagnostic criteria for MetS (*1*). Abdominal obesity is defined as WC≥85 cm for men and ≥90 cm for women.

The participants were divided into two groups: an abdominal obesity (AO) group and a non-AO group. The measured items were compared between the groups. We also compared the incidence of HT between the groups for subjects who were newly determined as having HT (subjects with SBP≥140 mmHg and/or DBP≥90 mmHg or subjects who were on medication for HT) on the basis of the 2002 medical examination data. Moreover, we estimated and compared the relative risk of developing HT between the groups.

SPSS Ver.12.0J (SPSS, Chicago, USA) was used for statistical analysis. All numerical values are expressed as means±SD. The unpaired *t*-test and the χ^2 test were used for the examination of intergroup differences and for frequency comparison, respectively. Multiple logistic regression analysis was used to estimate the relative risk of HT. The relative risk was adjusted for age, sex, and high-normal BP (SBP≥130 mmHg and/or DBP≥85 mmHg) in 1994, smoking (yes/no), FPG, and T.chol. In the same model, we assessed the effect of an increase in WC on the development of HT by using ΔWC (=WC [cm] in 2002 − WC [cm] in 1994). The significance level in all analyses was set at $p<0.05$.

This study was approved by the Ethics Committee of Sapporo Medical University.

Results

Table 1 shows the characteristics of the subjects in the non-AO and AO groups in 1994. Age, percentage of men, BMI, SBP, DBP, TC, TG, and FPG were higher in the AO group than in the non-AO group. HDL-C was significantly lower in the AO group than in the non-AO group.

Table 1. Basal Characteristics in the Non-AO Group and the AO Group in 1994

	Non-AO group (n=312)	AO group (n=84)
Age	57.2±9.3	59.5±8.8*
Men/women	112/200	75/9#
BMI (kg/m^2)	22.4±2.3	25.5±3.0*
SBP (mmHg)	121.3±10.5	126.3±9.5*
DBP (mmHg)	73.5±6.9	77.4±6.6*
T.chol (mg/dL)	188.4±30.1	193.8±29.0*
TG (mg/dL)	110.1±68.5	159.8±82.1*
HDL-C (mg/dL)	58.1±13.8	48.6±12.2*
FPG (mg/dL)	92.1±11.7	105.1±27.8*

Age, percentage of men, BMI, SBP, DBP, TC, TG, and FPG were higher in the AO group than in the non-AO group. HDL-C was significantly lower in the AO group than in the non-AO group. *$p<0.05$, unpaired *t*-test, #$p<0.05$ χ^2 test. AO, abdominal obesity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T.chol, total cholesterol; TG, triglyceride; HDL-C, HDL cholesterol; FPG, fasting plasma glucose.

In the 1994 data, there are significant positive correlations between WC and SBP and between WC and DBP in both men and women. There are also significant positive correlations between WC in 1994 and SBP in 2002 and between WC in 1994 and DBP in 2002 in both men and women (Fig. 1).

Figure 2 shows the percentage of HT in 2002 in each 1994 WC category. The higher the WC category, the higher the incidence of HT in both men and women. *p* for the trend was significant in both men and women.

The results of 10–11 years of follow-up are shown in Fig. 3. There were 312 individuals in the non-AO group and 84 in the AO group. Of the 312 individuals in the non-AO group, 177 remained in the non-AO category in 2002, but the remaining 79 individuals were changed to the AO category in 2002. Sixty-nine of the 84 individuals in the AO group remained in the AO category in 2002, but the remaining 15 individuals changed to the non-AO category. We divided the participants into these four groups (non-AO to non-AO, non-AO to AO, AO to non-AO and AO to AO) and compared the incidence of HT among them.

Figure 4 shows the incidences of HT in the four groups. The incidence was higher in the non-AO to AO group than in the non-AO to non-AO group (45.6% *vs.* 31.8%, $p=0.019$). It was also higher in the AO to AO group than in the AO to non-AO group (58.0% *vs.* 26.7%, $p=0.027$). There was no significant difference in the incidence of HT between the non-AO to non-AO group and the AO to non-AO group ($p=0.782$), or between the non-AO to AO group and the AO

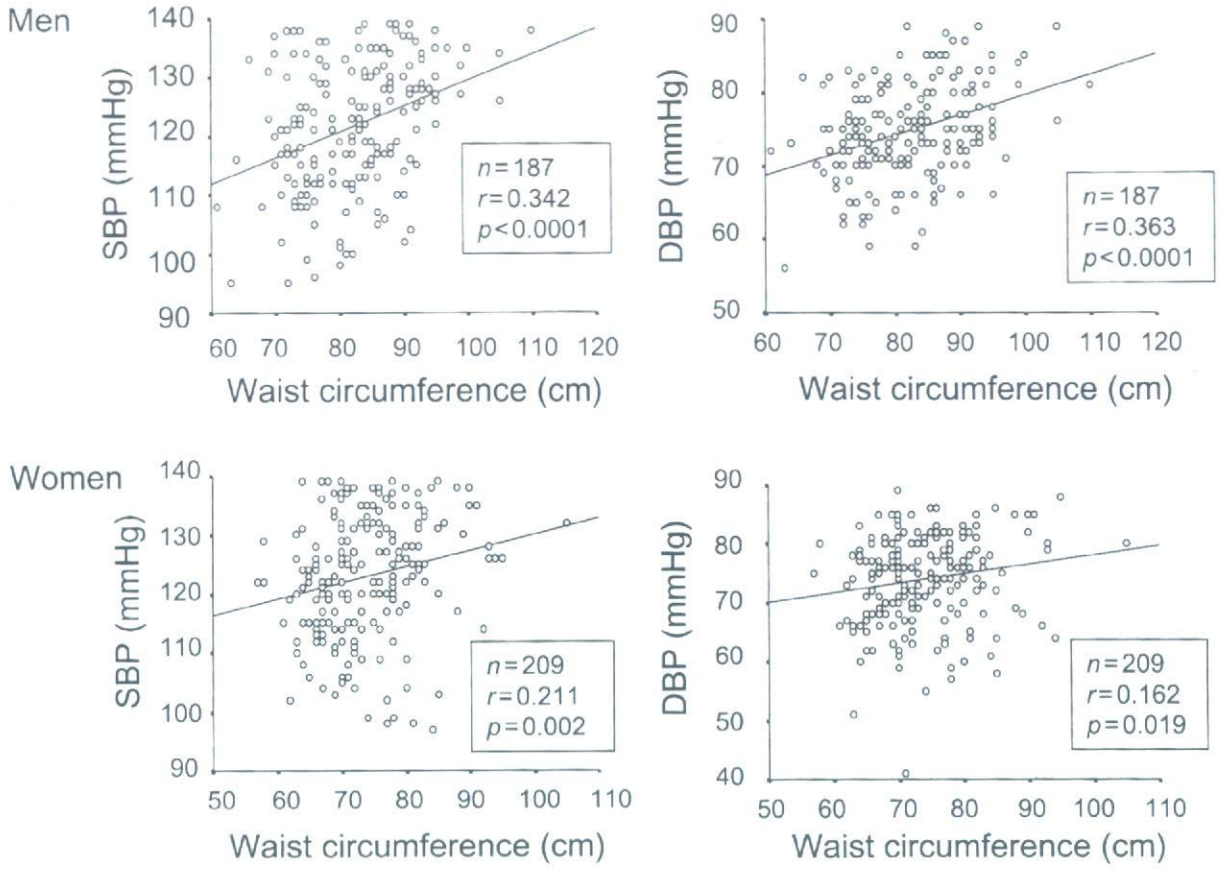

Fig. 1. *Correlations of waist circumference in 1994 with SBP and DBP in 2002. Upper: for men; lower: for women. Graphs on the left are relationships between waist circumference and SBP, and graphs on the right are relationships between waist circumference and DBP. Waist circumference shows significant positive correlations with SBP and DBP in both men and women.*

to AO group (p=0.142).

Table 2 shows the results of multiple logistic regression analysis. The relative risk of developing HT in individuals with AO was 2.33 (p=0.016; 95% confidence interval [CI], 1.17–4.63), and the risk per 1-cm increase in WC from 1994 to 2002 was 1.06 (p=0.003; 95% CI, 1.02–1.10), both adjusted for age, sex, high-normal BP in 1994, smoking (yes/no), FPG, and T.chol. When we additionally adjusted for BMI≥25 (yes/no) in the logistic regression model, the significance of AO disappeared (data not shown).

Discussion

The main findings of this study are 1) the incidence of HT was higher in the AO group than in the non-AO group, 2) increased WC, which may indicate the accumulation of visceral fat, increased the incidence of HT, 3) AO assessed by WC was significantly related to the development of HT (relative risk of HT: 2.33), 4) increasing WC was significantly related to the development of HT after adjustment for 1994 AO.

The Japanese Society of Internal Medicine and eight related scientific societies in Japan jointly announced new Japanese diagnostic criteria for MetS in April 2005 (*1*). According to the new criteria, the definition of MetS must include abdominal obesity, because the accumulation of visceral fat in individuals with MetS is considered to be important for the mechanism underlying the accumulation of risk factors for cardiovascular disease. Accumulation of visceral fat leads to insulin resistance and disorder of adipocytokines, and these factors in turn lead to high BP *via* mechanisms such as an increase in reabsorption of sodium in the renal tubule, hyperactivity of the sympathetic nervous system, proliferation of vascular smooth muscle cells and development of atherosclerosis. The results of this study show that abdominal obesity is significantly related to the development of HT and that an increase in WC, which may indicate the accumulation of visceral fat, is a risk factor for the development of HT.

It is well known that obesity is significantly related to HT, and many reports show relationships between BP levels and

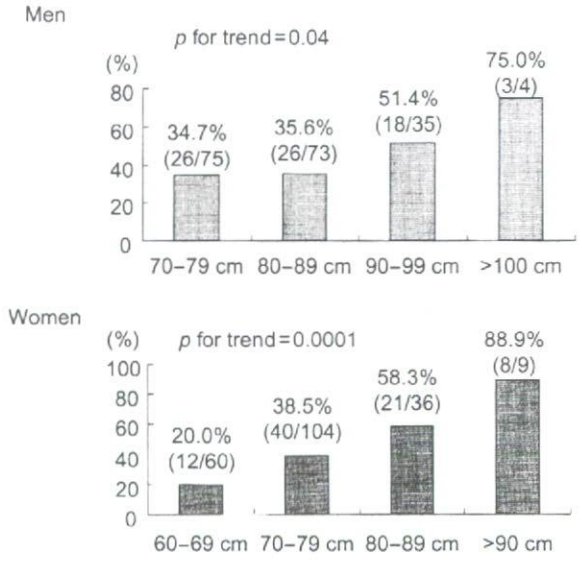

Fig. 2. *Percentage of hypertension (HT) in 2002 in each 1994 waist circumference (WC) category. The higher the WC category, the higher the incidence of HT in both men and women. p for the trend is significant in both men and women.*

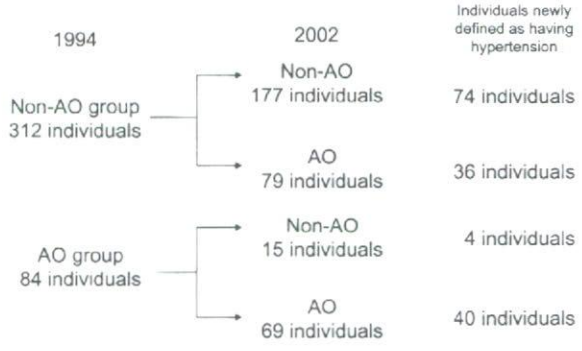

Fig. 3. *Follow-up results. There were 312 individuals in the non-AO group and 84 in the AO group. Of the 312 individuals in the non-AO group, 177 remained in the non-AO category in 2002, but the remaining 79 individuals changed to the AO category in 2002. Sixty-nine of the 84 individuals in the AO group remained in the AO category in 2002, but the remaining 15 individuals changed to the non-AO category in 2002. AO, abdominal obesity. Hypertension (HT): SBP ≥140 mmHg and/or DBP ≥90 mmHg and/or receiving medication for HT.*

various anthropometric parameters (*2–12*). We also have reported a strong correlation between obesity assessed by BMI and the development of HT according to our cohort data (*13*), as well as a correlation between ultrasound-assessed visceral fat accumulation and BP levels (*14*).

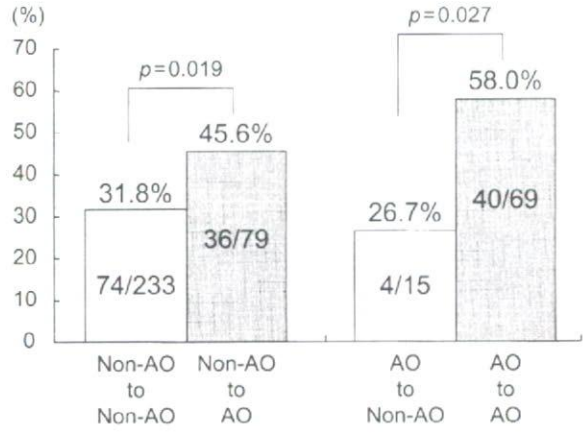

Fig. 4. *Incidences of hypertension (HT) in participants in the four groups. The incidence of HT is higher in the non-AO to AO group than in the non-AO to non-AO group (45.6% vs. 31.8%, p=0.019). The incidence of HT is also higher in the AO to AO group than in the AO to non-AO group (58.0% vs. 26.7%, p=0.027). There is no significant difference in the incidence of HT between the non-AO to non-AO group and the AO to non-AO group (p=0.782), or between the non-AO to AO group and the AO to AO group (p=0.142). AO, abdominal obesity.*

It is also known that a reduction in body weight leads to a decrease in BP levels (*15–20*). In the present study, no significant difference was found between the incidences of HT in the non-AO to non-AO group and the AO to non-AO group. Although this study was not interventional, the results suggest that weight reduction is effective for the prevention of HT. These results suggest that, to prevent hypertension, lifestyle modification is important for individuals with AO as well as for individuals with high-normal BP.

There are grounds for controversy about the current Japanese cutoff points for abdominal obesity (85 cm for men and 90 cm for women). The International Diabetes Federation (IDF) recommends that Asian cutoff points (90 cm for men and 80 cm for women) should be used for diagnosing MetS in Japanese people (The IDF consensus worldwide definition of the metabolic syndrome. http://www.idf.org/webdata/docs/MetS_def_update2006.pdf [accessed February 7, 2008]). In the present study, the prevalence of abdominal obesity was significantly lower in women than in men. According to Fig. 1, the incidence of HT in women increased continuously with the increase of WC. We tried to plot the receiver operator characteristic (ROC) curves for WC to predict the development of HT in men and women separately. The areas under the curves were 0.560 for men and 0.684 for women. According to the ROC curves, the cutoff levels yielding the maximal sensitivity plus specificity for predicting the development of

Table 2. Relative Risks for Hypertension (HT) in Individuals with Abdominal Obesity (AO)

	Wald	*p*	Relative risk	95% CI
Age	11.28	0.001	1.05	1.02–1.08
Sex	1.07	0.301	1.47	0.71–3.02
High normal category in 1994 (yes/no)*	54.42	<0.0001	6.33	3.84–10.43
Smoking	0.78	0.379	1.34	0.70–2.56
FPG	0.22	0.64	0.99	0.98–1.01
T.chol	0.68	0.41	0.99	0.98–1.01
Abdominal obesity in 1994 (yes/no)†	5.78	0.016	2.33	1.17–4.63
ΔWaist circumference (cm)§	8.59	0.003	1.06	1.02–1.10

The relative risk for development of HT in individuals with AO was 2.33 (p=0.016; 95% CI, 1.17–4.63) and the risk for HT in individuals with increase in waist circumference of 1 cm from 1994 to 2002 was 1.06 (p=0.003; 95% CI, 1.02–1.10), both adjusted for age, sex, high normal category of blood pressure in 1994 (yes/no), smoking, FPG and T.chol. *High normal category of blood pressure, SBP≥130 mmHg and/or DBP≥85 mmHg. †Abdominal obesity, waist circumference ≥85cm for men and ≥90cm for women. §ΔWaist circumference=(waist circumference in 2002) − (waist circumference in 1994). CI, confidence interval; FPG, fasting plasma glucose; T.chol, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

HT were 84 cm for men and 74 cm for women. These results suggest that the current cutoff point in men is acceptable but that a lower cutoff point is appropriate to identify women at high risk for HT. Further studies are needed to establish appropriate cutoff points of WC in the Japanese population.

Despite this controversy, in the present study we used the current Japanese WC cutoff points because the Ministry of Health, Labour and Welfare started a new program of health examinations in Japan in April 2008 (Health Service Bureau, Ministry of Health, Labour and Welfare: Standard program of medical examination and health guidance [fixed version]). The Japanese WC criterion is used to identify high-risk individuals in the new program. Therefore, an accumulation of evidence using the current WC cutoff points is important for medical staff who will be involved in the new health examination program, such as doctors in clinics, public health nurses, and senior nutritionists in local governments. The results of this study showed the usefulness of the current WC cutoff points for identifying individuals at high risk for HT. The results also indicated the possibility that many individuals, especially women, who are at high risk for HT will be missed if attention is given to only abdominal obesity defined by the current cutoff points.

In conclusion, our results suggest that, to prevent HT in Japanese, it is important to manage abdominal obesity and to monitor waist circumference in individuals with or without abdominal obesity.

References

1. The Committee on the Diagnosis of Metabolic Syndrome: The definition and diagnostic criteria of metabolic syndrome. *Nippon Naika Gakkai Zasshi* 2005; **94**: 795–809 (in Japanese).
2. Kannel WB, Brand N, Skinner JJ Jr, Dawber TR, McNamara PM: The relation of adiposity to blood pressure and development of hypertension: the Framingham study. *Ann Intern Med* 1967; **67**: 48–59.
3. Garrison RJ, Kannel WB, Stokes J, *et al*: Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med* 1987; **16**: 235–251.
4. Stamler J: Epidemiologic findings on body mass index and blood pressure in adults. *Ann Epidemiol* 1991; **1**: 347–362.
5. Miyao M, Furuta M, Sakakibara H, *et al*: Analysis of factors related to hypertension in Japanese middle-aged male workers. *J Hum Hypertens* 1992; **6**: 408–413.
6. Kannel WB, Garrison RJ, Dannenberg AL: Secular blood pressure trends in normotensive persons. *Am Heart J* 1993; **125**: 1154–1158.
7. Huang Z, Willett WC, Manson JE, *et al*: Body weight, weight change, and risk of hypertension in women. *Ann Intern Med* 1998; **128**: 81–88.
8. Brown CD, Higgins M, Donato KA, *et al*: Body mass index and prevalence of hypertension and dyslipidemia. *Obesity Res* 2000; **8**: 605–619.
9. Bell AC, Adair LS, Popkin BM: Ethnic differences in the association between body mass index and hypertension. *Am J Epidemiol* 2002; **155**: 346–353.
10. Mokdad AH, Ford ES, Bowman BA, *et al*: Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003; **289**: 76–79.
11. Sakurai M, Miura K, Takamura T, *et al*: Gender differences in the association between anthropometric indices of obesity and blood pressure in Japanese. *Hypertens Res* 2006; **29**: 75–80.
12. Nakamura K, Okamura T, Hayakawa T, *et al*, NIPPON DATA80, 90 Research Group: The proportion of individuals with obesity-induced hypertension among total hypertensives in general Japanese population: NIPPON DATA80, 90. *Eur J Epidemiol* 2007; **22**: 691–698.
13. Saitoh S, Takagi S, Takahashi H, *et al*: Epidemiology of obesity: an epidemiological study in rural communities of Hokkaido, Japan. *Intern Med* 1999; **38**: 195–197.
14. Chiba Y, Saitoh S, Takagi S, *et al*: Relationship between visceral fat and cardiovascular disease risk factors: the

Tanno and Sobetsu Study. *Hypertens Res* 2007; **30**: 229–236.
15. Stevens VJ, Obarzanek E, Cook NR, *et al*, Trials of Hypertension Prevention Research Group: Long-term weight loss and changes in blood pressure: results of the trials of hypertension prevention, phase II. *Ann Intern Med* 2001; **134**: 1–11.
16. Whelton PK, Appel LJ, Espeland MA, *et al*, TONE Collaborative Research Group: Sodium reduction and weight loss in the treatment of hypertension in older persons. A randomized controlled trial of nonpharmacologic interventions in the elderly. *JAMA* 1998; **279**: 839–846.
17. Culter JA: Randomized clinical trials of weight reduction in normotensive persons. *Ann Epidemiol* 1991; **1**: 363–370.
18. Kawamura M, Adachi T, Nakajima J, Fujiwara T, Hiramori K: Factors that affect calorie-sensitive and calorie-insensitive reduction in blood pressure during short-term calorie reduction in overweight women. *Hypertension* 1996; **27**: 408–413.
19. Davis BR, Blaufox MD, Oberman A, *et al*: Reduction in long-term antihypertensive medication requirements. Effects of weight reduction by dietary intervention in overweight persons with hypertension. *Arch Intern Med* 1993; **153**: 1773–1782.
20. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM: Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2003; **42**: 878–884.

原　著

メタボリックシンドローム、危険因子集積と尿中微量アルブミンとの関連　－端野・壮瞥町研究－

大西　浩文[*1,2]　斎藤　重幸[*1]　赤坂　憲[*1]
三俣　兼人[*1]　千葉　瑞恵[*1]　古堅　真[*1]
古川　哲章[*1]　森　満[*2]　島本　和明[*1]

要　約　【目的】端野・壮瞥町住民健診受診者を対象に、地域一般住民におけるメタボリックシンドローム（MetS）、危険因子集積と尿中微量アルブミン（U-Alb）との関連を検討した。
【方法】対象は2005年度端野・壮瞥町住民健診受診者1349名中、糖尿病（空腹時血糖値126mg/dl以上あるいは治療中の者）、降圧薬内服中の者および顕性蛋白尿（尿中アルブミン・クレアチニン比(ACR)≧300mg/g・Cr）を認める者を除いた863名である。わが国の診断基準に基づいたMetSおよびMetSを構成する危険因子（血圧高値、血糖高値、脂質代謝異常）の保有数とU-Alb陽性(ACR≧30mg/g・Cr)頻度との関連について検討した。また危険因子集積の背景と考えられるインスリン抵抗性の影響に関しても、HOMA-Rを用いて検討した。
【結果】MetS群は非MetS群と比較してU-Alb陽性者の頻度は有意に高率であった。またMetSを構成する危険因子数が増加するにつれてU-Alb陽性者の頻度は増加した。U-Alb陽性を従属変数としたロジスティック回帰分析より、危険因子を持たない者を1としたオッズ比は、危険因子1つでは2.73 (95%CI: 1.37-5.44)、危険因子2つでは3.98 (95%CI: 1.78-8.87)、危険因子3つでは9.16 (95%CI: 2.07-40.52）であった。インスリン抵抗性の指標としてHOMA-Rを用いると、U-Alb陽性を従属変数としたロジスティック回帰分析により、血圧高値や脂質異常症の有無とは独立してHOMA Rが有意な説明変数として採択された。
【結論】今回の検討より地域一般住民においてMetSおよび危険因子集積はU-Alb陽性と強い関連があること、また危険因子集積の背景であるインスリン抵抗性がU-Alb陽性に関与していることが示唆された。

キーワード：メタボリックシンドローム、インスリン抵抗性、尿中微量アルブミン、端野・壮瞥町研究、危険因子集積
（日循予防誌　43：132－138，2008）

Ⅰ．緒　　言

メタボリックシンドローム（MetS）が心血管疾患のリスクとなることが国内外の報告より明らかにされ[1),2)]、わが国では2005年4月に日本内科学会を中心に関連8学会合同の診断基準が発表された[3)]。平成20年4月からは特定健診・特定保健指導が開始されることになっており、その中でMetSは重要な骨子として採用され、MetSに該当する者やMetS予備群に対しては積極的に介入して生活習慣病や心血管疾患を予防する方針となっている[4)]。

1999年のWHOによるMetSの診断基準[5)]では、微量アルブミン尿の存在が診断項目の一つとして挙げられており、また近年種々の研究よりMetSが慢性腎臓病(CKD)の独立した危険因子であることが知られている[6),7)]。一方で尿中微量アルブミン(U-Alb)は糖尿病性腎症の早期マーカーであるばかりでなく、全身性の血管内皮細胞障害を反映

[*1] 札幌医科大学医学部内科学第二講座
[*2] 札幌医科大学医学部公衆衛生学講座
（〒060-8556　札幌市中央区南1条西17丁目）
受付・受理日　2008年9月2日

するマーカーとしても注目されており、U-Albが将来の心血管イベントの予測因子であること[8),9)]も明らかとなってきた。

しかし、わが国の診断基準によって判定されたMetSや危険因子の集積とU-Albとの関連についてはあまり知られていないため、端野・壮瞥町住民健診者を対象に地域一般住民におけるMetSや危険因子集積とU-Albとの関連を検討した。

Ⅱ．方　　法

対象は2005年度端野・壮瞥両町の住民健診受診者1,349名中、データ欠損者、糖尿病(空腹時血糖≧126 mg/dlまたは治療中)の者・降圧薬内服中の者・顕性蛋白尿(尿中アルブミン・クレアチニン比(ACR)≧300mg/g・Cr)陽性者を除外した863名(男性315名、平均年齢60.4±13.6歳、女性548名、平均年齢57.4±12.7歳)である。

早朝空腹時に、身長、体重、臍周囲腹囲径、安静坐位血圧値（収縮期血圧（SBP)、拡張期血圧(DBP))、空腹時血糖値(FPG)、空腹時インスリン値(FIRI)、中性脂肪値(TG)、総コレステロール値(T-chol)、HDLコレステロール値(HDL-C)、血清クレアチニン値(S-Cr)、尿中アルブミン値を測定した。

U-Alb陽性の基準は、ACR≧30mg/g・Crとし、インスリン抵抗性の指標としてHOMA-Rを用いた(HOMA-R＝FPG×FIRI/405)。

わが国の診断基準[3)]に基づき対象をMetS群と非MetS群の2群に分け、U-Alb陽性者の頻度を比較検討した。また、MetSの診断基準の血圧高値(SBP≧130mmHg and/or DBP≧85mmHg)、糖代謝異常（FPG≧110mg/dl)、脂質代謝異常（TG≧150mg/dl and/or HDL-C＜40mg/dl）の危険因子保有数をカウントし、危険因子保有数とU-Alb陽性者頻度との関連を検討した。

統計解析にはSPSSver.12.0Jを使用した。統計学的有意水準は$p < 0.05$とし、値は平均値±標準偏差で表している。連続変数の差の検定にはunpaired t-testを、頻度の差の検定にはカイ2乗検定を用いた。また、ロジスティック回帰分析により、年齢、性別、血清クレアチニン値、喫煙、T-cholで調整したMetSのU-Alb陽性に対するOdds Ratio（OR）を求めた。また、腹部肥満の有無と危険因子保有数のU-Alb陽性に対するORも同様の調整により検討し、さらに危険因子集積の背景と考えられるインスリン抵抗性とU-Alb陽性との関連を検討するために、当教室既報[10)]のHOMA-R≧1.73をインスリン抵抗性ありと判定し、年齢、性別、血清クレアチニン値、喫煙、T-cholおよび血圧高値、高TG血症、低HDL-C血症で調整したロジスティック回帰分析を用いてインスリン抵抗性とU-Alb陽性との関連も検討した。

本研究は札幌医科大学倫理委員会の承認を得ており、また健診受診者全員に研究内容説明の上、文書による同意が得られた者のみを対象としている。

Ⅲ．結　　果

表1にMetS群と非MetS群での対象背景を示す。MetS群において非MetS群と比較して、男性の比率、腹囲径、BMI、SBP、DBP、TG、FIRI、HOMA-R、高血圧者の頻度は有意に高値であり、HDL-Cは有意に低値であった。喫煙者の頻度は男性の比率が高いためMetS群で非MetS群と比較して有意に高かった。

非MetS群とMetS群の2群間でU-Alb陽性者

表1　メタボリックシンドローム群、非メタボリックシンドローム群での対象背景

MetS群において非MetS群と比較して、男性の比率、腹囲径、SBP、DBP、TG、FIRI、HOMA-R、高血圧者の頻度は有意に高値であり、HDL-Cは有意に低値であった。
MetS：メタボリックシンドローム、SBP：収縮期血圧値、DBP：拡張期血圧値、FPG：空腹時血糖値、T-chol：総コレステロール値、TG:トリグリセリド値、HDL-C:HDLコレステロール値、S-Cr：血清クレアチニン値、BUN：尿素窒素値、FIRI：空腹時インスリン値、ACR：尿中アルブミン・クレアチニン比

	MetS群 (n=67)	非MetS群 (n=796)
年齢(歳)	61.6±10.9*	58.3±13.2
男性(%)	73.1*	33.4
腹囲径(cm)	93.1±6.1*	81.6±9.6
SBP(mmHg)	149.1±18.6*	127.4±20.1
DBP(mmHg)	85.7±9.1*	73.2±11.1
FPG(mg/dl)	100.5±11.2*	92.0±9.0
T-chol(mg/dl)	206.1±29.3	200.2±31.6
TG(mg/dl)	179.5±88.1*	93.8±52.2
HDL-C(mg/dl)	51.0±9.7*	60.7±13.9
S-Cr(mg/dl)	0.71±0.13	0.63±0.13
BUN(mg/dl)	16.0±3.5	15.6±4.1
FIRI(μU/ml)	8.6±10.5*	4.2±2.8
ACR(mg/g・Cr)	21.9±34.1*	16.1±25.5
HOMA-R	2.16±2.76*	0.98±0.73
喫煙者の頻度(%)	55.2*	37.3
高血圧者の頻度(%)	71.6*	27.1

*p<0.05, inpaired t-test, #p<0.05, chi-square test

の頻度を比較したところ、非MetS群の7.2%に対してMetS群では17.9%と有意に高値を示した（図1）。またMetS基準の危険因子保有数とU-Alb陽性頻度との関連について検討したところ、危険因子保有数の増加とともにU-Alb陽性者の頻度も増加するという傾向が確認された（図2）。

U-Alb陽性を従属変数としたロジスティック回帰分析において、年齢、性別、S-Cr、T-chol、喫煙で調整したMetSのORは2.71 (p=0.006, 95%CI: 1.32-5.54) であった（表2）。

また、同様の交絡要因で調整したロジスティック回帰分析により、腹部肥満の有無は有意な説明変数として採択されなかったのに対し、危険因子を持たない者を1としたORは危険因子1つでは2.73 (95%CI: 1.37-5.44)、危険因子2つでは3.98 (95%CI: 1.78-8.87)、危険因子3つでは9.16 (95%CI: 2.07-40.52) であり、危険因子保有数が増加するほどリスクが高くなることが示された。（表3）。

さらに危険因子集積の背景であるインスリン抵

表2　メタボリックシンドロームと尿中微量アルブミン陽性との関連

年齢、性別、S-Cr、T-chol、喫煙で調整したロジスティック回帰分析を行うとMetSの尿中微量アルブミン陽性に対するORは2.71 (p=0.006, 95%CI: 1.32 - 5.54) であった。

	Wald	P-value	Odds Ratio	95% C.I.
Age	4.71	0.032	1.02	1.00-1.05
Sex	0.23	0.631	1.21	0.55-2.68
S-Cr	0.22	0.642	1.78	0.16-20.37
Smoking	0.02	0.877	1.05	0.56-1.97
T-chol	0.13	0.715	0.99	0.99-1.01
MetS	7.42	0.006	2.71	1.32-5.54

S-Cr:血清クレアチニン値、T-chol:総コレステロール、
MetS:日本基準によるメタボリックシンドロームの有無

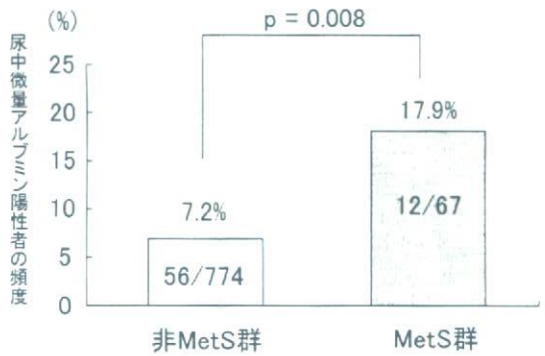

図1　メタボリックシンドローム群と非メタボリックシンドローム群における尿中微量アルブミン陽性者の頻度の比較

非MetS群とMetS群の2群間でU-Alb陽性者の頻度を比較したところ、非MetS群の7.2%に対してMetS群では17.9%と有意に高値を示した。
MetS：メタボリックシンドローム

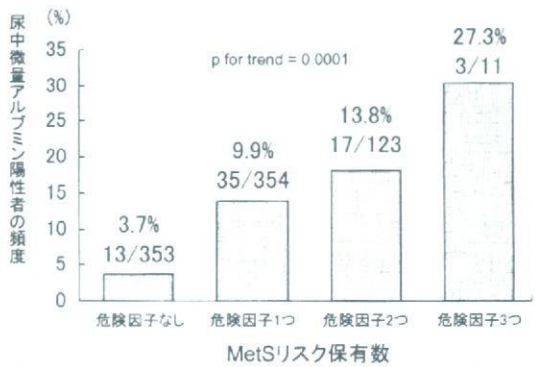

図2　メタボリックシンドローム構成危険因子保有数と尿中微量アルブミン陽性者の頻度との関連

非MetS群とMetS群の2群間でU-Alb陽性者の頻度を比較
MetS構成危険因子保有数の増加とともにU-Alb陽性者の頻度も増加するという傾向が確認された。MetS：メタボリックシンドローム、U-Alb：尿中微量アルブミン、
MetS構成危険因子：血圧高値（SBP ≧ 130mmHg and/or DBP ≧ 85mmHg）、血糖高値（FPG ≧ 110mg/dl）、脂質代謝異常（TG ≧ 150mg/dl and/or HDL-C < 40mg/dl）

表3　腹部肥満、MetS構成危険因子保有数と尿中微量アルブミンとの関連

年齢、性別、S-Cr、T-chol、喫煙で調整したロジスティックU-Alb陽性を従属変数として年齢、性別、S-Cr、T-chol、喫煙で調整したロジスティック回帰分析により、腹部肥満の有無は有意な説明変数として採択されなかったのに対し、危険因子保有数に関しては数の増加に伴いU-Albに対するリスクは増加した。

	Wald	P-value	Odds Ratio	95% C.I.
腹部肥満の有無	2.87	0.09	1.62	0.93-2.81
MetS構成危険因子1つ	8.16	0.004	2.73	1.37-5.44
MetS構成危険因子2つ	11.38	0.001	3.98	1.78-8.87
MetS構成危険因子3つ	8.53	0.003	9.16	2.07-40.52

腹部肥満：男性腹囲≧85cm、女性腹囲≧90cm
MetS構成危険因子数：血圧高値、血糖高値、脂質代謝異常のうちの保有数
S-Cr：血清クレアチニン値、T-chol：総コレステロール値

抗性とMetSの各構成要因およびインスリン抵抗性とU-Alb陽性との関連を検討するため、同様のロジスティック回帰分析を行うと、血圧高値のORは2.57 (95%CI: 1.38-4.76)、HOMA-R ≧ 1.73のORは2.43 (95%CI: 1.26-4.68) であった（表4）。

Ⅳ. 考　　察

今回の検討より、①地域一般住民においてMetSがU-Alb陽性に対する有意なリスクであること、②MetS構成危険因子の保有数が増加するにつれてU-Alb陽性頻度が増加し、U-Alb陽性に対するリスクも増加したこと、③危険因子集積の背景にあると考えられるインスリン抵抗性が他の交絡要因とは独立してU-Alb陽性に関与していることが示された。

以上のことは、海外の診断基準に基づくMetSとU-Alb陽性との関係[6,7]に矛盾しない結果であり、わが国の診断基準によって判定されたMetSもU-Alb陽性の有意なリスクであることが示唆された。

またChenらの報告[7]において、米国健康栄養調査（NHANES Ⅲ）のデータからMetSがU-Alb陽性の増加に関連していること、MetSの危険因子数増加とともにU-Alb陽性頻度も増加することが認められており、今回の我々の結果はこの結果を支持するものである。わが国のMetSの診断基準においては、内臓脂肪の蓄積がインスリン抵抗性を惹起させて危険因子が集積し、動脈硬化性疾患を引き起こすという病態機序を踏まえて、腹部肥満を必須項目とし加えて危険因子が集積している者をMetSと判定することとしている。よって今回の検討において腹部肥満は血圧高値、血糖高値、脂質代謝異常よりも上流にある背景因子と考えて危険因子保有数にはカウントしなかったが、米国National cholesterol Educational Program (NCEP)基準のように腹部肥満を危険因子の一つとしてカウントした場合にも同様に危険因子の増加数とともにU-Albのリスクも増加していた。

日本のMetSの診断基準では、糖尿病者においてもMetSを判定することとなっているが、糖尿病患者では細小血管障害としての腎障害を来しやすいこと、尿中微量アルブミンは糖尿病性腎症の早期マーカーとして知られていることから、糖尿病単独の影響かMetSの病態である危険因子の集積が影響するのかの判断が難しくなる可能性が考えられたため、今回の検討では糖尿病者は除外した。よって糖尿病を含む本来のMetSのU-Alb陽性に対するリスクは今回得られた結果よりも強いリスクとなることが予想される。降圧薬に関しては、今回の検討では投与薬剤の内容までは把握できていないため、ACE阻害薬やアンジオテンシンⅡ受容体拮抗薬のような腎保護作用・尿蛋白減少効果のある薬剤の有無・効果の判断が難しくなるため高血圧治療中の者は全て除外して解析を行った。薬剤の内容とU-Alb陽性との関連については今後の検討課題である。

MetSによる腎障害の機序はまだ明らかになっていないが[11]、これまでにいくつかの機序が考えられている。MetSは当然ながら構成要素として糖尿病や高血圧が含まれており、糖尿病や高血圧患者における早期腎障害の指標として尿中微量アルブミンが認められることも知られていることから、構成因子としての高血糖・高血圧による影響が考えられる。

それに加えて、以前よりインスリン抵抗性およびそれに伴う代償性の高インスリン血症が腎障害

表4　MetS構成要因と微量アルブミン尿との関連

危険因子集積の背景と考えられるインスリン抵抗性の影響に関して、HOMA-Rを説明変数、尿中微量アルブミン陽性を目的変数としたロジスティック回帰分析を行うと、HOMA-R ≧ 1.73のインスリン抵抗性と血圧高値が有意な説明変数として採択された。

	Wald	P-value	Odds Ratio	95% C.I.
血圧高値	8.92	0.003	2.57	1.38-4.76
HOMA-R≧1.73	7.08	0.008	2.43	1.26-4.68
高TG血症	0.44	0.508	1.27	0.63-2.58
低HDL-C血症	0.02	0.881	0.90	0.24-3.42
腹部肥満の有無	1.08	0.298	1.36	0.76-2.44

年齢、性別、S-Cr、T-chol、喫煙の有無で調整
血圧高値：収縮期血圧≧130 mmHgかつ／または拡張期血圧≧85mmHg、高TG血症：トリグリセリド≧150mg/dl、低HDL-C血症：HDL-C＜40mg/dl、腹部肥満：男性腹囲≧85cm、女性腹囲≧90cm
S-Cr: 血清クレアチニン値、T-chol：総コレステロール値

を引き起こすことも指摘されており、インスリン抵抗性の腎障害進展において高血圧が重大な影響を与えることも報告されている[12]。我々はこれまでにMetSとインスリン抵抗性との関連について報告してきた[13]。今回の検討においても危険因子集積数の増加に伴いU-Albに対するリスクが増加したことから、個々の危険因子の影響のみならず危険因子集積の背景としてのインスリン抵抗性の関与が示唆されたため、HOMA-Rを指標としてインスリン抵抗性の影響の検討を行った。その結果MetS群において非MetS群と比してインスリン抵抗性の指標であるHOMA-Rは有意に高値を示しており、さらにU-Alb陽性を従属変数としたロジスティック回帰分析ではHOMA-R≧1.73のインスリン抵抗性が有意な説明変数として採択された。また表4においてはHOMA-Rが計算式中に空腹時血糖値を含むことから独立変数として血糖高値を加えなかったが、表4のモデルにさらに血糖高値を説明変数として加えた場合もHOMA-Rは有意な説明変数として採択されたことより、MetSの重要な病態機序の一つであるインスリン抵抗性およびそれに伴う代償性の高インスリン血症がU-Alb陽性に関与している可能性が考えられた。

インスリン抵抗性および高インスリン血症における腎障害発生機序としては、RAA系の亢進、交感神経の活性化、血管平滑筋細胞の増殖などにより高血圧が引き起こされ、高血圧の臓器障害として腎障害が引き起こされることが知られているが、今回の検討においてHOMA-R≧1.73が血圧高値とは独立してU-Alb陽性の有意な説明変数として採択された。また表4において収縮期血圧値、中性脂肪値、HDL-C値を連続変数として用いた場合にも同様に収縮期血圧とHOMA-Rとが有意な独立変数として採択されたことから、インスリン抵抗性が高血圧を介した機序とは別の機序で糸球体内皮機能障害を起こしている可能性が考えられた。インスリン抵抗性状態では血圧上昇以外にも、脂肪細胞から分泌されるアディポサイトカインの産生・分泌異常が起こっていることが知られており、それによって惹起される慢性炎症反応が腎障害を引き起こす可能性も考えられる。Festaらは、U-Albを伴う2型糖尿病患者と正常者ではU-Albのない群と比べ血中のCRPやfibrinogenなどの炎症性物質が増加していること、fibrinogenがU-Alb出現の有意な説明変数であることを報告している[14]。また腹部肥満に伴うアディポサイトカインの産生亢進が全身性に慢性炎症の病態を引き起こしているとの報告もある[15]。Wolfらは、アディポサイトカインの一つであるレプチンによるラット糸球体内皮細胞の増殖、線維化、TGF-β1の産生亢進、またメサンギウム細胞の肥大などを確認し、さらにレプチンを注入したラットの腎で糸球体硬化、蛋白尿の悪化を確認している[16]。さらにMcCarthyらはTNF-αによる糸球体におけるアルブミン透過性の亢進において、スーパーオキシドを介する系が関係していると報告している[17]。

平成20年4月からは特定健診・特定保健指導が開始され、現在のMetS診断基準によってハイリスク者を抽出して積極的に介入することとなっている[4]。今回の検討より地域一般住民においてわが国の診断基準によって判定されたMetSはU-Alb陽性に対する有意なリスクであることが示されたが、結果の解釈において注意すべき点がいくつか考えられる。腹囲径のカットオフ値に関しては現在も議論がなされているところであり、現在の腹囲基準を用いる場合、特に女性においてハイリスク者が見逃されている可能性を念頭に置いておく必要がある。今回は結果には示さなかったが、男女別に検討した場合には女性のMetSは非MetSと比較してもU-Alb陽性者の頻度に有意な差は認められなかった。この影響としてやはり腹囲基準によって女性のMetS該当者が少ないことが一部影響していると考えられた。しかし危険因子集積数とU-Albの関連については、男女別に検討を行っても男女とも同様の結果であり集積数の増加とともにU-Alb陽性者の頻度は有意に増加していたことから、男女とも危険因子の集積やその背景となるインスリン抵抗性がU-Albに影響することがうかがわれた。U-Alb陽性や心血管疾患イベント発生を予測しうる適切な腹囲径のカットオフ値に関しては今後さらなる検討が必要である。また今回腹部肥満は危険因子に含まずに検討したところ、危険因子集積数の増加が腹部肥満の有無とは独立してU-Alb陽性に対する有意なリスクとなっていた。特定健診・特定保健指導において、腹部肥満の有無やBMI≧25の有無に該当しない危険因子集積者の場合は、個々の危険因子が受診勧奨レベルに達していなければ保健指導の対象にならないが、今回の結果からは危険因子集積者に関してはたとえ肥満の基準に該当しなくとも積極的な介入

を行うことが必要となる可能性が考えられた。

MetSは心血管疾患に対するハイリスク状態であることやU-Albが将来の心血管イベントの予測因子であることから考えても、MetS該当者において個々の危険因子のコントロール状況を把握したり、将来のイベント発生を予測したりする上で日常臨床においてU-Albを評価することも重要である可能性が示唆された。また血圧値とは独立してインスリン抵抗性がU-Alb陽性に関与していたことから、MetSにおいて微量アルブミン尿の予防を考える上では血圧や血糖などの個々の危険因子を管理するだけではなく、危険因子集積の背景であるインスリン抵抗性への介入も必要であると考えられる。ライフスタイルの改善はもちろんのこと、個々の危険因子に対して薬物治療が必要な症例に関しては、薬剤選択に際してインスリン抵抗性改善作用の有無も重要なポイントとなる可能性がある。また危険因子の集積が強く影響することが示されたことから、インスリン抵抗性を念頭において、血圧、血糖、脂質代謝異常の個々の危険因子を早期から管理していくことも重要である可能性が示唆された。

（本論文の要旨は、第43回日本循環器病予防学会・日本循環器管理研究協議会総会：一般演題において発表された。）

文　献

1) Takeuchi H, Saitoh S, Takagi S, et al. Metabolic syndrome and cardiac disease in Japanese men : applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men--the Tanno and Sobetsu Study. Hypertens Res 2005 ; 28 : 203-208.
2) Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome : a summary of the evidence. Diabetes Care 2005 ; 28 : 1769-1778.
3) メタボリックシンドローム診断基準検討委員会. メタボリックシンドロームの定義と診断基準. 日本内科学会雑誌, 2005 ; 94 : 794-809.
4) 厚生労働省　生活習慣病関連資料. 標準的な健診・保健指導プログラム（確定版）. http://www.mhlw.go.jp/bunya/kenkou/seikatsu/index.html
5) World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and Its complications. Part I ; Diagnosis and Classification of Diabetes Mellitus. World Health Organization, Geneva. 1999.
6) Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome : NHANES III. Am J Hypertens. 2003 ; 16 : 952-958.
7) Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U. S. adults. Ann Intern Med. 2004 ; 140 : 167-174.
8) Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 ; 342 : 145-153.
9) Nathan DM, Cleary PA, Backlund JY, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005 ; 353 : 2643-2653.
10) 老松　寛, 斎藤重幸, 浦　信行, 他. インスリン抵抗性の簡便な臨床評価法に関する検討 - 本態性高血圧症例での検討 -. 糖尿病, 2000 ; 43 : 205-213.
11) Locatelli F, Pozzoni P, Del Vecchio L. Renal manifestations in the metabolic syndrome. J Am Soc Nephrol 2006 ; 17 : S81-S85.
12) El-Atat FA, Stas SN, McFarlane SI, et al. The relationship between hyperinsulinemia, hypertension and progressive renal disease. J Am Soc Nephrol 2004 ; 15 : 2816-2827.
13) 竹内　宏, 斎藤重幸, 高木　覚, 他. 日本人男性におけるMetabolic Syndromeとインスリン抵抗性の検討 - 端野・壮瞥研究 -. 糖尿病, 2003 ; 46 : 739-744.
14) Festa A, D'Agostino R, Howard G, et al. Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects : The Insulin Resistance Atherosclerosis Study. Kidney Int 2000 ; 58 : 1703-1710.
15) Wisse BE. The inflammatory syndrome : the

role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004 ; 15 : 2792-2800.
16) Wolf G, Ziyadeh FN. Leptin and renal fibrosis. Contrib Nephrol 2006 ; 151 : 175-183.
17) McCarthy ET, Sharma R, Sharma M, et al. TNF-alpha increases albumin permeabilityneration of superoxide. J Am Soc Nephrol 1998 ; 9 : 433-438.

ABSTRACT

Relationship of metabolic syndrome and accumulation of risk factors with microalbuminuria in rural communities in Japan -The Tanno and Sobetsu Study-

Hirofumi Ohnishi*[1,2], Shigeyuki Saitoh*[1], Hiroshi Akasaka*[1], Kaneto Mitsumata*[1], Mizue Chiba*[1], Makoto Furugen*[1], Tetsuaki Furukawa*[1], Mitsuru Mori*[2] and Kazuaki Shimamoto*[1]

*[1] Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

*[2]Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Japan

Aim: We investigated the relationship of metabolic syndrome (MetS) and accumulation of risk factors with microalbuminuria in rural communities in Japan.

Method: The participants were 863 citizens who underwent medical examinations in the towns of Tanno and Sobetsu, Hokkaido in 2005. The following participants were excluded: those with missing data, those with type 2 diabetes (fasting plasma glucose (FPG) ≥ 126 mg/dl and/or those who were on medication for diabetes), those who were on medication for hypertension and those with macroalbuminuria (urinary albumin creatinine ratio (ACR) ≥ 300 mg/g□Cr). The subjects were divided into two groups according to the Japanese criteria of MetS: a MetS group and a non-MetS group. The percentages of subjects with microalbuminuria (ACR ≥ 30 mg/g□Cr) in the two groups were compared. The relationship between number of risk factors (high blood pressure, high FPG, and dyslipidemia including high triglyceride and low HDL cholesterol) and microalbuminuria was also investigated.

Result: The percentage of subjects with microalbuminuria was significantly higher in the MetS group than in the non-MetS group. Multiple logistic regression analysis showed that there was a significant relationship between MetS and microalbuminuria (Odds Ratio: 2.71, 95%CI: 1.32-5.54). The higher the number of risk factors was, the higher was the Odds Ratio for microalbuminuria for which the reference was a no risk group (1 risk factor group: 2.73, 95%CI: 1.14-3.20; 2 risk factors group: 3.98, 95%CI: 1.78-8.87; 3 risk factors group: 9.16, 95%CI: 2.07-40.52).

Conclusion: It may be important for prevention of microalbuminuria in individuals with MetS not only to manage blood pressure and blood glucose but also to manage insulin resistance, which is part of the background of accumulation of these risk factors.

Key Words : *Metabolic syndrome, Insulin resistance, Microalbuminuria, Tanno and Sobetsu Study, accumulation of risk factors*

Received • Accepted Sep. 2, 2008. (JJCDP 43:132-138, 2008)

Original Article

Leptin Gene and Leptin Receptor Gene Polymorphisms Are Associated with Sweet Preference and Obesity

Einosuke MIZUTA[1], Yoshihiro KOKUBO[2], Itaru YAMANAKA[1], Yoshihiro MIYAMOTO[3], Akira OKAYAMA[2], Yasunao YOSHIMASA[3], Hitonobu TOMOIKE[4], Hiroko MORISAKI[1], and Takayuki MORISAKI[1,5]

Leptin is an adipocyte-secreted hormone that regulates food intake and body weight, and that was recently reported to suppress sweet sensitivity in an animal model. We investigated the associations among sweet preference, obesity, and polymorphisms of the leptin gene (*LEP*) or leptin receptor gene (*LEPR*). A total of 3,653 residents randomly selected from among the citizens of Suita City, Osaka, Japan were enlisted as subjects, in whom we investigated sweet preference, clinical characteristics, including obesity and serum leptin level, and the polymorphisms of *LEP* and *LEPR* (G−2548A and A19G for *LEP*; R109K, R223Q, and rs3790439 for *LEPR*). We determined the associations among the parameters using logistic regression analysis, in order to consider potential confounding factors for sweet preference and/or obesity. The *LEP* A19G and *LEPR* R109K polymorphisms were associated with sweet preference, whereas the serum leptin level was not. Further, the *LEPR* 109KK genotype was found to be associated with obesity along with sweet preference. In conclusion, our results are the first to show associations of *LEP* and *LEPR* polymorphisms with sweet preference, and may provide useful information for diagnosis and treatment of lifestyle-related diseases. (*Hypertens Res* 2008; 31: 1069–1077)

Key Words: leptin, genetic polymorphism, obesity, taste

Introduction

Obesity is a risk factor for lifestyle-related and cardiovascular diseases (*1*), while leptin is an adipocyte-secreted hormone that regulates food intake, energy expenditure, and body weight (*2, 3*), and is well known to be related to obesity based on its ability to activate the leptin receptor (*4*). There have been numerous studies examining the association between human leptin gene (*LEP*) or leptin receptor gene (*LEPR*) polymorphisms and obesity (*5–10*), with some of these studies reporting a positive correlation and some a negative correlation between the two.

Leptin has been shown to suppress sweet preference in animal models (*11*), and it suppressed neural and behavioral responses to sweet substances through its action on the leptin

From the [1]Department of Bioscience, National Cardiovascular Center Research Institute, Suita, Japan; [2]Division of Cardiovascular Preventive Medicine, National Cardiovascular Center, Suita, Japan; [3]Division of Arteriosclerosis, Metabolism, and Clinical Nutrition, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan; [4]National Cardiovascular Center Hospital, Suita, Japan; and [5]Department of Molecular Pathophysiology, Osaka University Graduate School of Pharmaceutical Sciences, Suita, Japan.

This work was supported in part by a Grant for the Promotion of Fundamental Studies in Health Science of the Organization for Pharmaceutical Safety and Research (OPSR) of Japan, by the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO) and by Research Grants for Cardiovascular Diseases from the Ministry of Health, Labour and Welfare, Japan.

Address for Reprints: Takayuki Morisaki, M.D., Ph.D., Department of Bioscience, National Cardiovascular Center Research Institute, 5–7–1 Fujishirodai, Suita 565–8565, Japan. E-mail: morisaki@ri.ncvc.go.jp

Received October 30, 2007; Accepted in revised form December 28, 2007.