6. Arteaga-Solis E, Gayraud B, Ramirez F. Elastic and collagenous networks in vascular diseases. *Cell Struct Funct* 2000; 25:69–72.
7. Roberts AB, McCune BK, Sporn MB. TGF-beta: regulation of extracellular matrix. *Kidney Int* 1992; 41:557–559.
8. Border WA, Noble NA. Interactions of transforming growth factor-beta and angiotensin II in renal fibrosis. *Hypertension* 1998; 31:181–188.
9. Zacchigna L, Vecchione C, Notte A, Cordenonsi M, Dupont S, Maretto S, Cifelli G, Ferrari A, Maffei A, Fabbro C, Braghetta P, Marino G, Selvetella G, Aretini A, Colonnese C, Bettarini U, Russo G, Soligo S, Adorno M, Bonaldo P, Volpin D, Piccolo S, Lembo G, Bressan GM. Emilin1 links TGF-beta maturation to blood pressure homeostasis. *Cell* 2006; 124:929–942.
10. Lijnen PJ, Petrov VV, Fagard RH. Association between transforming growth factor-beta and hypertension. *Am J Hypertens* 2003; 16:604–611.
11. Li B, Khanna A, Sharma V, Singh T, Suthanthiran M, August P. TGF-beta1 DNA polymorphisms, protein levels, and blood pressure. *Hypertension* 1999; 33: 271–275.
12. Doliana R, Canton A, Bucciotti F, Mongiat M, Bonaldo P, Colombatti A. Structure, chromosomal localization, and promoter analysis of the human elastin microfibril interfase located protein (EMILIN) gene. *J Biol Chem* 2000; 275:785–792.
13. Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; 17:151–183.
14. Haketa A, Soma M, Nakayama T, Sato M, Kosuge K, Aoi N, Matsumoto K. Two medium-chain acyl-coenzyme A synthetase genes, SAH and MACS1, are associated with plasma high-density lipoprotein cholesterol levels, but they are not associated with essential hypertension. *J Hypertens* 2004; 22: 1903–1907.
15. Nakayama T, Soma M, Rahmutula D, Ozawa Y, Kanmatsuse K. Isolation of the 5'-flanking region of genes by thermal asymmetric interlaced polymerase chain reaction. *Med Sci Monit* 2001; 7:345–349.
16. Sano M, Kuroi N, Nakayama T, Sato N, Izumi Y, Soma M, Kokubun S. Association study of calcitonin-receptor-like receptor gene in essential hypertension. *Am J Hypertens* 2005; 18:403–408.
17. Livak KJ, Marmaro J, Todd JA. Towards fully automated genome-wide polymorphism screening. *Nat Genet* 1995; 9:341–342.
18. Olson JM, Wijsman EM. Design and sample-size considerations in the detection of linkage disequilibrium with a disease locus. *Am J Hum Genet* 1994; 55: 574–580.
19. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from in complete data via the EM algorithm. *J R Stat Soc* 1977; 39:1–22.
20. Massagué J, Blain SW, Lo RS. TGFbeta signaling in growth control, cancer, and heritable disorders. *Cell* 2000; 103:295–309.
21. Suthanthiran M, Li B, Song JO, Ding R, Sharma VK, Schwartz JE, August P. Transforming growth factor-beta 1 hyperexpression in African-American hypertensives: A novel mediator of hypertension and/or target organ damage. *Proc Natl Acad Sci USA* 2000; 97:3479–3484.
22. Chun TY, Chander PN, Kim JW, Pratt JH, Stier CT Jr. Aldosterone, but not angiotensin II, increases profibrotic factors in kidney of adrenalectomized stroke-prone spontaneously hypertensive rats. *Am J Physiol Endocrinol Metab* 2008; 295:E305–E312.
23. Zanetti M, Braghetta P, Sabatelli P, Mura I, Doliana R, Colombatti A, Volpin D, Bonaldo P, Bressan GM. EMILIN-1 deficiency induces elastogenesis and vascular cell defects. *Mol Cell Biol* 2004; 24:638–650.
24. Yokota M, Ichihara S, Lin TL, Nakashima N, Yamada Y. Association of a T29–>C polymorphism of the transforming growth factor-beta1 gene with genetic susceptibility to myocardial infarction in Japanese. *Circulation* 2000; 101: 2783–2787.
25. O'Donnell CJ, Lindpaintner K, Larson MG, Rao VS, Ordovas JM, Schaefer EJ, Myers RH, Levy D. Evidence for association and genetic linkage of the angiotensin-converting enzyme locus with hypertension and blood pressure in men but not women in the Framingham Heart Study. *Circulation* 1998; 97:1766–1772.
26. Ono K, Mannami T, Iwai N. Association of a promoter variant of the haeme oxygenase-1 gene with hypertension in women. *J Hypertens* 2003; 21: 1497–1503.
27. Yamada Y, Fujisawa M, Ando F, Niino N, Tanaka M, Shimokata H. Association of a polymorphism of the transforming growth factor-beta1 gene with blood pressure in Japanese individuals. *J Hum Genet* 2002; 47:243–248.
28. Ivanov VP, Solodilova MA, Polonnikov AV, Belugin DA, Shestakov AM, Ushachev DV, Khoroshaya IV, Katargina LN, Kozhukhov MA, Kolesnikova OE. Arg25Pro polymorphism of transforming growth factor-beta1 and its role in the pathogenesis of essential hypertension in Russian population of the Central Chernozem Region. *Bull Exp Biol Med* 2007; 144:66–68.
29. Shen C, Lu X, Li Y, Zhao Q, Liu X, Hou L, Wang L, Chen S, Huang J, Gu D. Emilin1 gene and essential hypertension: a two-stage association study in northern Han Chinese population. *BMC Med Genet* 2009; 10:118.
30. Sadeghi M, Daniel V, Naujokat C, Weimer R, Opelz G. Strikingly higher interleukin (IL)-1alpha, IL-1beta and soluble interleukin-1 receptor antagonist (sIL-1RA) but similar IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta and interferon IFN-gamma urine levels in healthy females compared to healthy males: protection against urinary tract injury? *Clin Exp Immunol* 2005; 142:312–317.

Clinical and Experimental Hypertension, 32, 234–238, 2010

ISSN: 1064-1963 print / 1525-6006 online
DOI: 10.3109/10641963.2010.491888

informa
healthcare

Long-Term Compliance of Salt Restriction and Blood Pressure Control Status in Hypertensive Outpatients

Yuko Ohta, Takuya Tsuchihashi, Uran Onaka, Eri Miyata

Division of Hypertension, Clinical Research Institute, National Kyushu Medical Center, Fukuoka, Japan

ABSTRACT

The purpose of the present study was to investigate the long-term compliance with salt restriction and blood pressure (BP) control status in Japanese hypertensive outpatients. Subjects included 103 patients, 59 women and 44 men, mean age 67 ± 9 years, who underwent successful 24-h home urine collection more than 10 times over an interval of 5 years. Urinary salt, potassium, and creatinine were measured. During the follow-up period (average 8.6 years), participants underwent urine collection 11.4 times in average. Urinary salt excretion at the last visit was significantly lower than that of the first visit (8.2 ± 3.1 vs. 9.6 ± 3.7 g/day; $p < 0.01$). The achievement of urinary salt excretion <6 g/day increased from 18.5% at the first visit to 26.2% at the last visit. Similarly, BP at the last visit was significantly lower than that of the first visit (130 ± 14/69 ± 11 vs. 145 ± 17/86 ± 12 mmHg; $p < 0.01$). The achievement rate of BP <140/90 mmHg and <130/85 mmHg also increased significantly during this period (39.2% to 70.8% and 13.7% to 39.6%, respectively, $p < 0.01$). Results suggest that urinary salt excretion decreased by repeated measurements using 24-h home urine collection. Lifestyle modification including weight loss as well as the intensive antihypertensive treatment contributed to the improved BP control during this period.

KEYWORDS: salt restriction; 24-h home urine collection; urinary salt excretion; hypertensive patients; long-term compliance

INTRODUCTION

Excessive salt intake is known to be involved in the pathophysiology of hypertension, and thus salt restriction is strongly recommended for the management of hypertension (1–5). Treatment guidelines for hypertension such as the Seventh Report of the Joint National Committee (JNC 7) and the Japanese Society of Hypertension (JSH 2009) recommend sodium reduction to a level of no more than 100 mmol/day in hypertensive patients (6,7). Salt intake has been reported to be high in the Japanese population and we have previously reported that achieving the target level of salt restriction recommended by the guidelines seems to be difficult in Japanese patients (8). In the present study, we investigated the long-term compliance with salt restriction and its relation to blood pressure (BP) control status in the hypertensive outpatients.

PATIENTS AND METHODS

Participants were recruited from hypertensive outpatients who visited the National Kyushu Medical Center. Since 1998, we have assessed urinary salt excretion by using 24-h home urine collection, which is a recommended method to evaluate salt intake by the working group for the dietary salt reduction of the JSH (9). Twenty-four h urine samples were collected using a partition cup (proportional sampling method (10)), which collects a 1/50 portion of the 24-h urine. If the 24-h creatinine excretion was within ± 30% of the estimated values, the urine collection was considered successful. Patients with malignant hypertension, secondary hypertension, or diabetic nephropathy were excluded. Subjects included 103 patients, 59 women and 44 men, mean age 67 ± 9 years, who underwent successful 24-h home urine collection more than 10 times over an interval of 5 years. Urinary salt, potassium, and creatinine were measured. Blood pressure was measured with a sphygmomanometer by the doctors while the patients were seated. Hypertension was considered to be present in patients with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or those patients on antihypertensive medication. "Good control" was defined as SBP of <140 mmHg and DBP of <90 mmHg. "Satisfactory control" was defined as SBP of <130 mmHg and DBP of <85 mmHg. After each examination the patients were notified, of the measured value of urinary salt excretion and advices to reduce salt intake to the level of <6 g/day and to reduce body weight in overweight patients were given by the doctors. Advice

Received 31 August 2009; accepted 27 October 2009.

Correspondence: Yuko Ohta, MD, Division of Hypertension, Clinical Research Institute, National Kyushu Medical Center, Jigyohama 1-8-1, Chuo-Ku, Fukuoka 810-8563, Japan. E-mail: yukoo@qmed.hosp.go.jp

by trained dieticians was also provided when necessary. The protocol was explained in detail and informed consent was obtained from each patient.

Statistical Analysis

Values are presented as the mean ± standard deviation (SD). The differences in the variables were compared by one-way ANOVA. A chi-square test was also utilized when appropriate. P values less than 0.05 were considered significant.

RESULTS

During the average period of 8.6 years, 103 participants underwent urine collection 11.4 times in average. The characteristics of the subjects are shown in Table 1. The mean age was 58.2 ± 9.1 years at the first visit and 67.3 ± 9.3 years at the last visit. Body weight and mean BP at the last visit were significantly lower than that at the first visit. Plasma glucose at the last visit was also significantly lower than that at the first visit. On the other hand, serum creatinine at the last visit was significantly higher than that at the first visit. Urinary salt excretion at the last visit was significantly lower than that at the first visit (8.2 ± 3.1 vs. 9.6 ± 3.7 g/day, $p < 0.01$). Urinary salt excretion at the last visit was significantly lower than that at the first visit (8.2 ± 3.1 vs. 9.6 ± 3.7 g/day, $p < 0.01$).

TABLE 1 Characteristics of the subjects

	First visit	Last visit
Age (years)	58.2 ± 9.1	67.3 ± 9.3
Body weight (kg)	60.8 ± 10.4	59.8 ± 10.9**
Body mass index (kg/m^2)	24.1 ± 3.1	23.6 ± 3.2**
Systolic blood pressure (mmHg)	145 ± 17	130 ± 14**
Diastolic blood pressure (mmHg)	86 ± 12	69 ± 11**
Serum creatinine (mg/dl)	0.83 ± 0.33	0.96 ± 0.74*
Estimated GFR (ml/min/1.73m^2)	66.3 ± 16.7	64.5 ± 23.3
Plasma glucose (mg/dl)	106 ± 20	100 ± 15**
Serum total cholesterol (mg/dl)	210 ± 30	202 ± 29*
Proteinuria (g/day)	0.46 ± 1.22	0.24 ± 0.70†
Urinary salt excretion (g/day)	9.6 ± 3.7	8.2 ± 3.1**
Urinary potassium excretion (g/day)	2.0 ± 0.6	1.8 ± 0.6
Urinary creatinine excretion (mg/day)	1052 ± 327	929 ± 275**

Values are means ± SD.
†$p < 0.1$; *$p < 0.05$; **$p < 0.01$ vs. first visit.
Abbreviation: GFR - glomerular filtration ratio

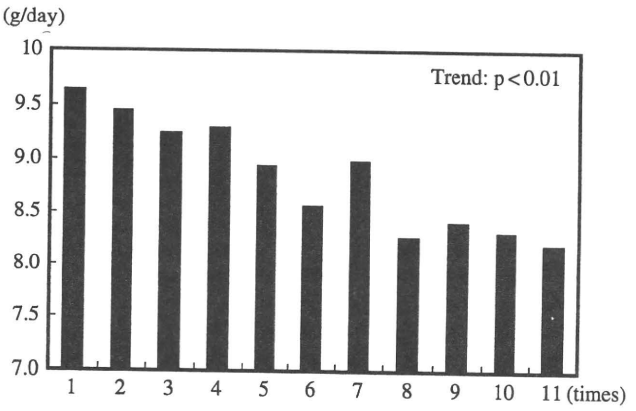


FIGURE 1 The trend in urinary salt excretion by the repeated measurements.

Urinary salt excretion almost steadily decreased during this period (Figure 1) and the maximum and minimum values were 13.4 ± 3.5 and 5.1 ± 1.8 g/day, respectively. There was no significant difference in the urinary potassium excretion during this period. The achievement rate of urinary salt excretion <6 g/day (100 mmol of sodium)/day significantly increased from 18.5% at the first visit to 26.2% at the last visit.

Comparisons of the baseline characteristics between the patients who decreased SBP of less than 15 mmHg (small SBP group, n = 54) and those who decreased more than 15 mmHg (large SBP group, n = 49) during the observation period are presented in Table 2. There were no significant differences between the two groups in the baseline urinary salt excretion. The levels of plasma glucose, serum creatinine, and proteinuria in the large BP group were significantly higher than those in the small BP group. The number of antihypertensive drugs in these two groups was similar.

Among 66 patients who showed poor salt restriction (urinary salt excretion of more than 8 g/day) at the first visit, 40 patients (60.6 %) continued to be poor at the last visit, while another 26 patients (39.4 %) successfully reduced their salt excretion to less than 8 g/day). The patients with improved salt restriction showed significantly lower BMI and SBP levels at the first visit compared to those of persistently poor salt restriction patients. However, the patients with higher salt excretion (urinary salt excretion of more than 8 g/day) at the last visit tended to need a greater number of antihypertensive drugs than those with lower salt excretion (urinary salt excretion of less than 8 g/day, 2.1 ± 1.0 vs. 1.8 ± 0.8, $p = 0.07$).

The prevalence of patients with good BP control significantly increased from 39.2% at the first visit to 70.8% at the last visit ($p < 0.01$, Figure 2). Similarly, the prevalence of patients with satisfactory BP control significantly increased from 13.7% at the first visit to

TABLE 2 Comparison of the characteristics between patients with large and small systolic blood pressure reduction

Blood pressure reduction	Small SBP <15 mmHg		Large SBP ≥15 mmHg	
	First visit	Last visit	First visit	Last visit
Number of patients	54	54	49	49
Age (years)	58.9 ± 7.9	68.2 ± 8.3	57.4 ± 10.3	66.3 ± 10.3
Male (%)	67	67	47	67
Body weight (kg)	60.1 ± 10.6	59.1 ± 10.5†	61.7 ± 10.2	60.1 ± 10.6†
Body mass index (kg/m^2)	24.1 ± 3.3	23.7 ± 3.2†	24.0 ± 2.8	23.4 ± 3.3†
Systolic blood pressure (mmHg)	137 ± 10	137 ± 12	154 ± 18**	122 ± 12††
Diastolic blood pressure (mmHg)	81 ± 6	70 ± 10††	91 ± 14**	69 ± 12††
Plasma glucose (mg/dl)	105 ± 13	99 ± 11††	107 ± 26**	102 ± 18
Serum total cholesterol (mg/dl)	209 ± 31	207 ± 28	212 ± 28	197 ± 29††
Serum triglyceride (mg/dl)	147 ± 107	115 ± 57†	149 ± 115	116 ± 55
Serum creatinine (mg/dl)	0.8 ± 0.2	0.9 ± 0.5	0.9 ± 0.4**	1.1 ± 0.9
Serum uric acid (mg/dl)	5.7 ± 1.5	5.5 ± 1.1	5.7 ± 1.5	5.6 ± 1.2
Proteinuria (g/day)	0.19 ± 0.27	0.18 ± 0.76	0.74 ± 1.71**	0.30 ± 0.63†
Urinary salt excretion (g/day)	9.2 ± 3.8	7.8 ± 3.0†	10.2 ± 3.5	8.6 ± 3.2†
Urinary potassium excretion (g/day)	2.0 ± 0.7	2.0 ± 0.7	1.9 ± 0.6	1.7 ± 0.5
Number of antihypertensive drugs	1.3 ± 0.9	1.9 ± 0.9††	1.1 ± 1.0	2.0 ± 1.0††

Values are means ± SD.
**p < 0.01 vs. small SBP; ††p < 0.01; †p < 0.05 vs. first visit.
Abbreviation: SBP - systolic blood pressure

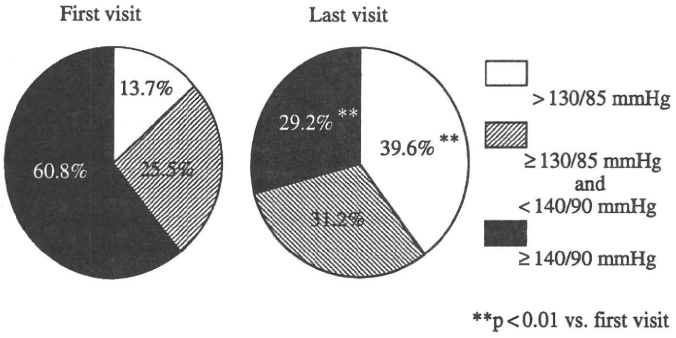


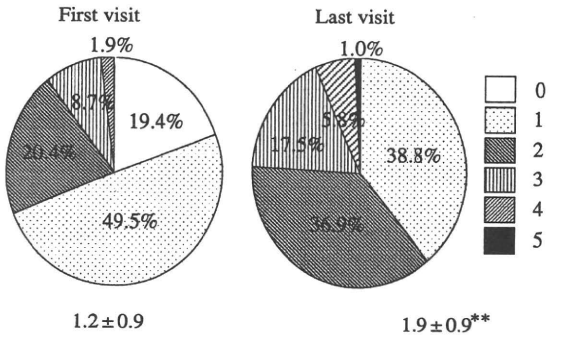
FIGURE 2 The trend in blood pressure control.

39.6% at the last visit (p < 0.01, Figure 2). During this period, the number of antihypertensive drugs significantly increased from 1.2 ± 0.9 to 1.9 ± 0.9 (p < 0.01, Figure 3). Figure 4 demonstrates the trend in the prescription of antihypertensive drugs during this period. Compared to the first visit, significant increases in the prescriptions of angiotensin II receptor antagonists (ARBs) and diuretics were observed at the last visit.

In univariate analysis, clinical factors associated with the BP reduction were body weight reduction, increased number of antihypertensive drugs, decrease in proteinuria and the female gender. The decrease in urinary salt excretion was not directly correlated with BP reduction. In the multivariate analysis for the dependent variables of BP reduction, body weight reduction and an increased number of antihypertensive drugs were detected as significant independent variables (p < 0.01 and p < 0.05, respectively).

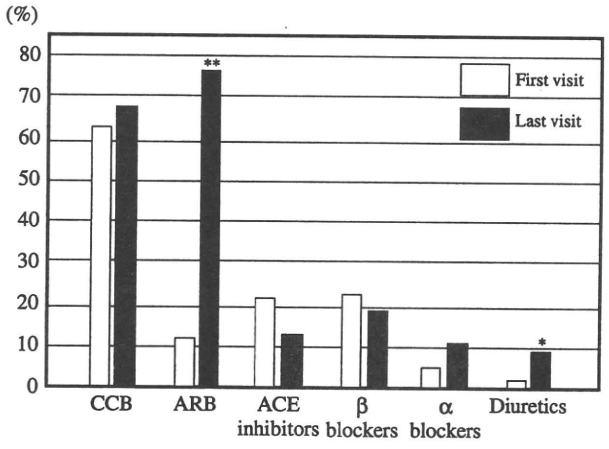
DISCUSSION

The present study demonstrates that long-term compliance with salt restriction is still insufficient in Japanese



**p<0.01vs. first visit

FIGURE 3 The trend in the number of antihypertensive drugs.



**p < 0.01, *p < 0.05 vs. first visit

FIGURE 4 The trend in the use of antihypertensive drugs.

hypertensive patients, while BP control status has been improved.

The JNC 7 and JSH 2009 recommend sodium reduction to a level of no more than 6 g (100 mmol of sodium)/day in hypertensive patients (6,7); however, the rate of achievement <6 g/day of salt excretion was still unsatisfactory in the present study. Since urinary salt excretion at the last visit was significantly lower than that at the first visit, repeated monitoring of urinary salt excretion, along with providing feedback to patients and follow-up counseling, seem to be important and practical ways to achieve a reduction of salt intake in individual hypertensives (8,11). Considering our previous observation that the salt intake is similar between the salt-conscious and salt-unconscious patients (12), monitoring the salt excretion is quite important. The National Nutrition Survey in Japan showed that the average salt intake decreased from 12.7 g/day in 1998 to 10.6 g/day in 2007. Thus, the decrease of urinary salt excretion in the present study seems to be attributable not only to the repeated monitoring of urinary salt excretion and advice to reduce their salt intake to the level of <6 g/day by trained dieticians and doctors but also to the trend of salt intake in the general Japanese population.

Another finding of the present study is that the rate of patients with appropriate BP control significantly increased during the observation period. This improvement seems to be attributable, at least in past, to the increased use of ARBs and diuretics. The JSH 2009 recommends the use of low doses of diuretics to achieve strict BP control (7). In the present study, the reduction in the urinary salt excretion was not directly associated with the BP reduction. Alternatively, body weight reduction and an increased number of antihypertensive drugs were associated with BP reduction in this period. Increased body weight has reported to be a strong risk factor for hypertension, and weight loss has been proposed as an effective, nonpharmacologic means for the primary prevention of hypertension (13). We have previously reported that patients with metabolic syndrome show higher urinary salt excretion and need more antihypertensive drugs to manage their BP (14). Effectiveness of sodium reduction and weight loss in the treatment of hypertension is also confirmed by TONE study (15). Taken together, dietary counseling focusing not only on sodium restriction but also on the body weight reduction seems to be important.

The limitation of our study is that the subjects are hypertensive outpatients who have been followed at a specialized hypertension clinic and the number of subjects may not be large. Therefore, the present findings may not indicate the precise current status of salt restriction and BP control in the hypertensive patients of the Japanese general population.

In conclusion, the compliance with salt restriction proposed by guidelines is insufficient in Japanese hypertensive patients. Although repeated measurements decreased urinary salt excretion, body weight reduction and intensive antihypertensive treatment were major determinants for the improved BP control.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

[1] Cailar G, Ribstein J, Mimran A. Dietary sodium and target organ damage in essential hypertension. *Am J Hypertens* 2002;15:222–229.

[2] Cook NR, Cutler JA, Obarzanek E, et al. for the trials of Hypertension Prevention Collaborative Research Group. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: Observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007;334: 885–888.

[3] Altshul AM, Grommet JK. Food choices for lowering sodium intake. *Hypertension* 1982;4(suppl III):116–III–120.
[4] Intersalt Cooperative Research Group. Intersalt: An international study of electrolyte excretion and blood pressure. Result for 24 hour urinary sodium and potassium excretion. *BMJ* 1988;297:319–328.
[5] Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals. *Arch Intern Med* 2001;161: 685–693.
[6] Chobanian AV, Bakris GL, Black HR, et al. 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 on High Blood Pressure. *Hypertension* 2003;42:1206–1252.
[7] Ogihara T, Kikuchi K, Matsuoka H, et al. on behalf of the Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension: The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). *Hypertens Res* 2009;32:4–107.
[8] Ohta Y, Tsuchihashi T, Onaka U, Eto K Ueno M. Long-term compliance of salt restriction in Japanese hypertensive patients. *Hypertens Res* 2005;28:953–957.
[9] Kawano Y, Ando K, Matsuura H, Tsuchihashi T, Fujita T, Ueshima H. Report of working group for dietary salt reduction of the Japanese Society of Hypertension: (1) Rationale for salt reduction and salt-restriction target level for the management of hypertension. *Hypertens Res* 2007;30:879–886.
[10] Tochikubo O, Uneda S, Kaneko Y. Simple portable device for sampling a whole day's urine and its application to hypertensive outpatients. *Hypertension* 1983;5:270–274.
[11] Miura S, Yamaguchi Y, Urata H, et al. Efficacy of a multicomponent program (Patient-Centered Assessment and Counseling for Exercise plus Nutrition [PACE + Japan]) for lifestyle modification in patients with essential hypertension. *Hypertens Res* 2004;27:859–864.
[12] Ohta Y, Tsuchihashi T, Ueno M, Onaka U, Tominaga M, Eto K. Relationship between the awareness of salt restriction and the actural salt intake in hypertensive patients. *Hypertens Res* 2004;27:243–246.
[13] 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.
[14] Ohta Y, Tsuchihashi T, Arakawa K, Onaka U, Ueno M. Prevalence and lifestyle characteristics of hypertensive patients with metabolic syndrome followed at an outpatient clinic in Fukuoka, Japan. *Hypertens Res* 2007;30:1077–1082.
[15] Whelton PK, Appel LJ, Espeland MA, et al. for the 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 (TONE). *JAMA* 1998;279:839–846.

INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Clustering of Cardiovascular Risk Factors and Blood Pressure Control Status in Hypertensive Patients

Yuko Ohta, Takuya Tsuchihashi, Uran Onaka and Eri Hasegawa

Abstract

Objective Hypertensive patients have multiple risk factors such as chronic kidney disease (CKD) and hyperuricemia in addition to components of metabolic syndrome. The morbidity of cardiovascular diseases is expected to increase synergistically by clustering of them. In the present study, we assessed the clustering of cardiovascular risk factors and blood pressure (BP) control status in hypertensive patients.

Methods and Patients Subjects were 699 treated hypertensive patients (mean age: 65 ± 12 years; males 297, females 402) who had been followed at National Kyushu Medical Center, Fukuoka, Japan. We assessed the status of BP control and the presence of comorbidity including obesity, diabetes mellitus (DM), dyslipidemia, CKD and hyperuricemia.

Results Average BP level and the number of antihypertensive drugs were 133 ± 11/74 ± 10 mmHg and 2.0 ± 1.1, respectively and the average number of cardiovascular risk factors was 1.5 ± 1.1. No comorbid risk factors were found in 18.7% of the patients. On the other hand, 34.2%, 28.9% and 18.2% of the patients had one, two or more than three risk factors, respectively. There were no significant differences in BP among these groups, while patients with three or more risk factors needed a greater number of antihypertensive drugs than those with other groups. Patients with three or more risk factors group showed significantly higher body mass index, serum LDL cholesterol, triglyceride, plasma glucose and serum uric acid levels compared to those with other groups ($p<0.05$, respectively). They also showed significantly lower serum HDL cholesterol and estimated GFR levels compared to those in other groups ($p<0.05$, respectively).

Conclusion These results suggest that the majority of the treated hypertensive patients are complicated with additional cardiovascular risk factors and the patients with clustering risk factors required a greater number of antihypertensive drugs. Integrative management of BP as well as comorbid risk factors should be encouraged.

Key words: blood pressure control, hypertensive patients, clustering of cardiovascular risk factors

(Inter Med 49: 1483-1487, 2010)
(DOI: 10.2169/internalmedicine.49.3406)

Introduction

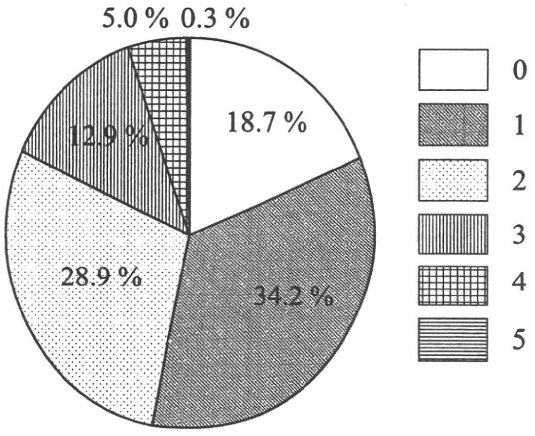
Hypertension is one of the most important risk factors for cardiovascular diseases (1, 2), and a number of randomized controlled trials have shown that antihypertensive treatment reduces cardiovascular mortality and morbidity (3, 4). Based on the findings obtained from these large-scale clinical trials, a recent guideline for the management of hypertension in the Japanese Society of Hypertension (JSH 2009) recommends active antihypertensive treatment to achieve strict blood pressure (BP) control (5). On the other hand, many patients with hypertension also have other risk factors for cardiovascular disease. In the Framingham Heart Study, almost 80% of patients with hypertension had at least one additional cardiovascular risk factor, while 30% of men and 32% of women with hypertension had three or more additional risk factors (6). We had previously reported the high prevalence of metabolic syndrome in Japanese hypertensive patients (7). However, other risk factors such as chronic kidney disease (CKD) and hyperuricemia may also contribute to cardiovascular disease (8, 9). The aim of this study was to investigate the clustering of cardiovascular risk factors and BP control status in hypertensive patients.

Division of Hypertension, Clinical Research Institute, National Kyushu Medical Center, Fukuoka
Received for publication January 25, 2010; Accepted for publication May 6, 2010
Correspondence to Dr. Yuko Ohta, yukoo@kyumed.jp

Table 1. Comparison of the Characteristic

	ALL	Number of clustering cardiovascular risk factors			
		0	1	2	≥3
N	699	131	239	202	127
Female (%)	57.5	56.5	65.3	58.9	41.7†‡
Age (years)	65 ± 12	65 ± 13	66 ± 11	64 ± 12	66 ± 11
Body Mass Index (kg/m^2)	24 ± 3	22 ± 2	23 ± 3*	25 ± 3*†	27 ± 3*†‡
Systolic BP (mmHg)	133 ± 11	131 ± 10	133 ± 11	133 ± 12	132 ± 11
Diastolic BP (mmHg)	74 ± 10	74 ± 8	75 ± 9	75 ± 10	73 ± 10
Number of antihypertensive drugs	2.0 ± 1.1	1.8 ± 0.9	1.9 ± 1.1	2.1 ± 1.1	2.6 ± 1.2*†‡
Serum LDL cholesterol (mg/dL)	121 ± 30	101 ± 22	121 ± 28*	131 ± 29*†	126 ± 32*†
Serum triglyceride (mg/dL)	135 ± 85	108 ± 72	123 ± 67	145 ± 88*†	169 ± 106*†
Serum HDL cholesterol (mg/dL)	58 ± 14	60 ± 14	60 ± 16	57 ± 13	54 ± 14*†
e GFR (mL/min/1.73m^2)	70 ± 20	81 ± 16	72 ± 17*	67 ± 21*†	58 ± 20*†‡
Serum glucose (mg/dL)	107 ± 27	99 ± 16	102 ± 19	109 ± 26*	121 ± 41*†‡
Serum uric acid (mg/dL)	5.5 ± 1.4	4.8 ± 1.1	5.2 ± 1.2*	5.7 ± 1.4*†	6.4 ± 1.4*†‡

Values are means ± SD, *p<0.05 vs. 0, †p<0.05 vs. 1, ‡p<0.05 vs. 2, BP; blood pressure



Risk factor: obesity, diabetes mellitus, dyslipidemia, chronic kidney disease, hyperuricemia

Figure 1. Number of cardiovascular risk factors in hypertensive patients.

Methods

Subjects were treated hypertensive patients who had been followed at National Kyushu Medical Center, Fukuoka, Japan. Subjects included 699 patients, 402 females and 297 males, mean age 65 ± 12 years. BP was measured with a sphygmomanometer with the patient seated. BP control status was assessed based on the average clinic BP of two clinical visits. "Good control" was defined as systolic BP (SBP) of <140 mmHg and diastolic BP (DBP) of <90 mmHg. "Satisfactory control" was defined as SBP of <130 mmHg and DBP of <85 mmHg. In addition, we assessed the presence of obesity, diabetes mellitus (DM), dyslipidemia, CKD and hyperuricemia.

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Obesity was defined ≥25 kg/m^2. DM was defined as fasting serum glucose ≥126 mg/dL, serum glucose ≥ 200 mg/dL at any time, HbA1c ≥6.5%, or the current use of hypoglycemic agents. Dyslipidemia was defined as serum LDL cholesterol ≥140 mg/dL and/or serum HDL cholesterol <40 mg/dL or the current use of lipid lowering drugs. Hyperuricemia was defined as serum uric acid ≥7 mg/dL or the current use of antihyperuricemic drugs. CKD was considered to be present if the patient had either a decreased estimated glomerular filtration ratio (eGFR) (<60 ml/min) or persistent proteinuria. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula (for men, $0.741 \times 175 \times \text{serum creatinine levels}^{-1.154} \times \text{age}^{-0.203}$; for women, $0.741 \times 175 \times \text{serum creatinine levels}^{-1.154} \times \text{age}^{-0.203} \times 0.742$).

This study was conducted following the guidelines of the National Kyushu Medical Center.

Statistical analysis

Values are presented as the mean ± standard deviation (SD). The differences in the variables were compared by one-way ANOVA followed by a Scheffe's multiple comparison test if necessary. A chi-square test was also utilized when appropriate. P values of less than 0.05 were considered significant.

Results

Subjects characteristics are presented in Table 1. Mean age was 65 ± 12 years, and 57.5% of the patients were female. Mean value of BMI was 24 ± 3 kg/m^2. Average BP level and the number of antihypertensive drugs were 133 ± 11/74 ± 10 mmHg and 2.0 ± 1.1, respectively. The average number of additional cardiovascular risk factors was 1.5 ± 1.1. Figure 1 shows the prevalence of clustering of cardiovascular risk factors. Among hypertensive patients, 18.7% had no additional risk factor except for hypertension. On the other hand, 34.2%, 28.9% and 18.2% had one, two or more than three additional risk factors, respectively. The prevalence of each risk factor according to the number of comorbid risk factors is shown in Fig. 2. Dyslipidemia was more frequently complicated in the patients with one additional

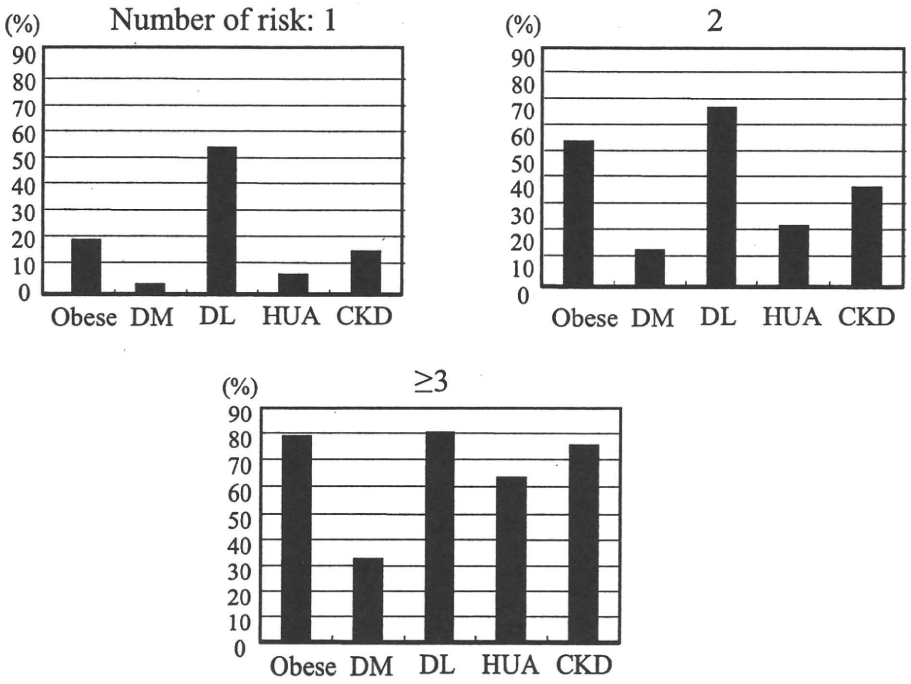


Figure 2. Comorbid disease according to the number of cardiovascular risk factors.

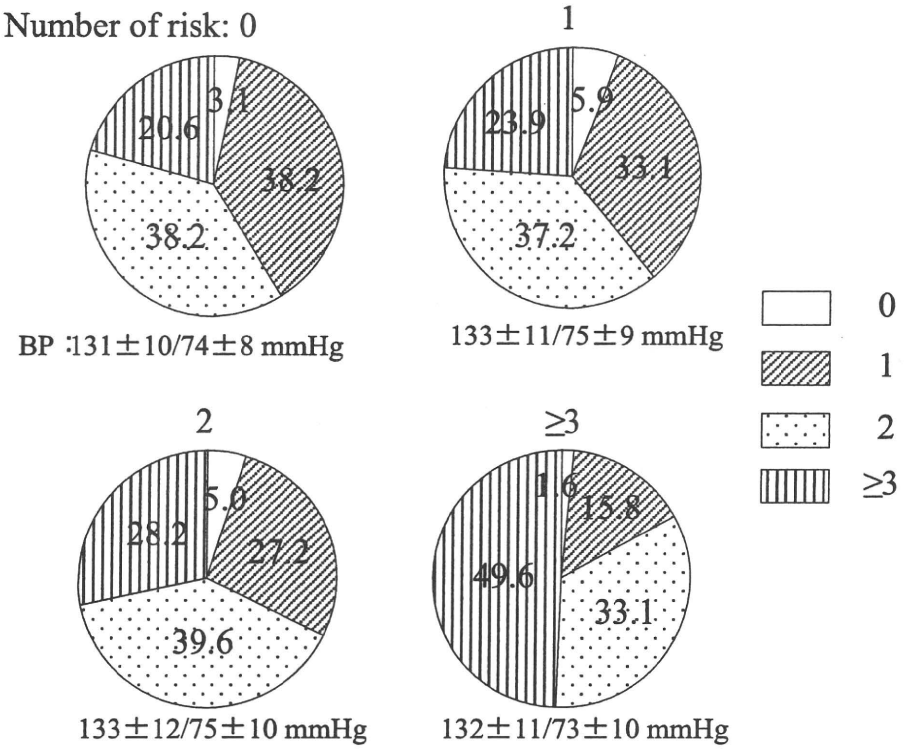


Figure 3. Number of antihypertensive drugs according to the number of cardiovascular risk factors.

risk factor. Similarly, dyslipidemia, obesity and CKD were complicated in the patients with two risk factors. There were no significant differences in BP among these groups, while patients with three or more risk factors group needed greater number of antihypertensive drugs than those with other groups (Table 1, Fig. 3). The achievement rate of good (<140/90 mmHg) and satisfactory (<130/85 mmHg) BP was 81.7% and 40.5%, respectively, in the patients without additional risk factors (Fig. 4). In contrast, BP in those with additional risk factors was less controlled. The patients with three or more risk factors group showed a significantly higher body mass index, serum LDL cholesterol, triglyceride, plasma glucose and serum uric acid levels compared to those in other groups ($p<0.05$, respectively). They also

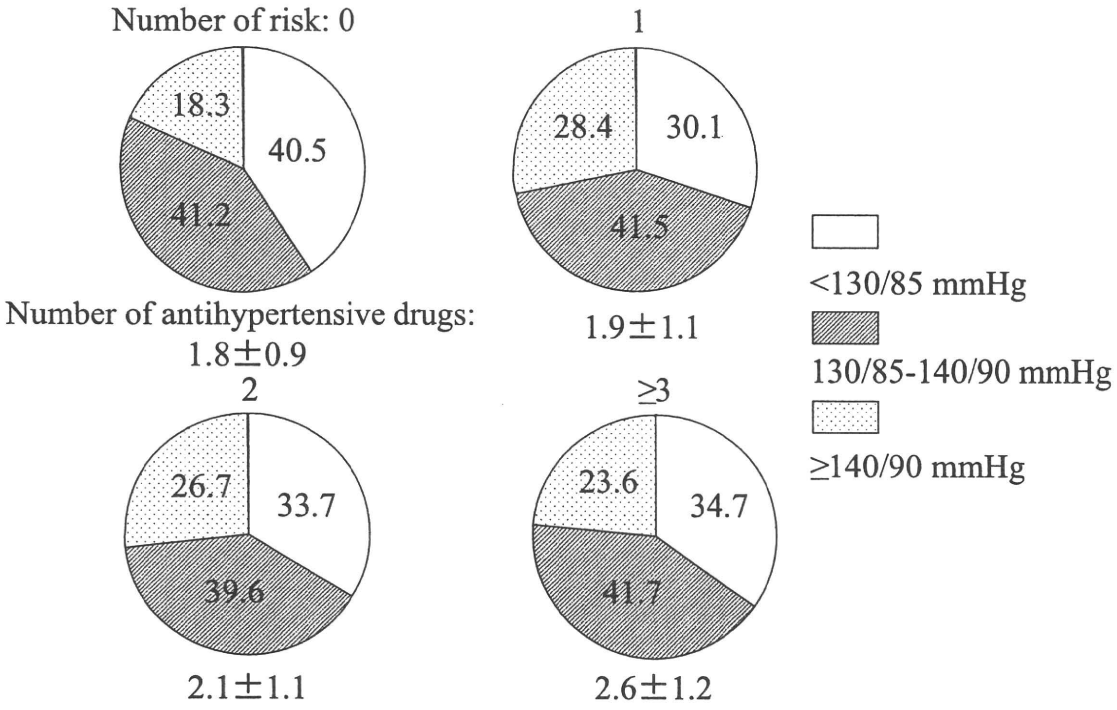


Figure 4. Blood pressure control status according to the number of cardiovascular risk factors.

showed significantly lower serum HDL cholesterol and eGFR levels compared to those in other groups ($p<0.05$, respectively). In addition, the prevalence of diuretics in the patients with three or more risk factors group was higher compared to those in other groups. Hyperuricemia was more frequently complicated in the patients taking diuretics compared to those without (32.9% vs 19.3%, $p<0.01$). Furthermore, the prevalence of DM and obesity in the patients with three or more risk factors group was higher compared to those in other groups. As expected, the prevalence of DM was also higher in the patients with obesity (49.4% vs 35.3%, $p<0.05$).

Discussion

The American and European guidelines as well as the Japanese guidelines emphasize the importance of the management of high risk patients, such as patients with multiple risk factors or DM (5, 10, 11). However, the control status of BP in the hypertensive patients with DM/CKD remains inadequate. Several surveys have reported that the proportion of DM patients with controlled BP varied from 4% to 20% (12-14) and the proportion of CKD patients with controlled BP was 29% (15). Although BP control status in our hypertensive patients with multiple risk factors seems somewhat better than that seen in previous studies, strict goal BP levels were not achieved in a significant number of the patients.

Among our hypertensive patients, 81.3% had one or more and 18.2% had three or more additional risk factors, suggesting the clustering of cardiovascular risk factors in the hypertensive patients. This observation is compatible with the previous finding that almost 80% of patients with hypertension had at least one additional cardiovascular risk factor, while 30% of men and 32% of women with hypertension had three or more additional risk factors in the Framingham Heart Study (6). Another study reported that more than 50% of hypertensive patients were complicated with DM, dyslipidemia, or obesity (16). There might be some differences in the prevalence based on study populations and definitions of risk factors, as well as the inclusion of patients with preexisting cardiovascular disease. Each component of metabolic syndrome has been reported to be associated with cardiovascular disease and the risk increases in incremental fashion with the number of components of metabolic syndrome (16-21). The patients with either hypertension or DM components in the formation of a diagnosis of metabolic syndrome had the greatest risk for cardiovascular disease (18, 20), however, it was also suggested that lowering uric acid and lipid can reduce cardiovascular risk (22-24). Because the clustering of three or more metabolic syndrome components increases the incidence of cardiovascular disease, the identification and management of additional risk factors as well as aggressive treatment to achieve recommended BP goals, should be encouraged to prevent cardiovascular events in hypertensive patients.

The limitation of our study includes the definition of dyslipidemia. Elevated LDL-C and high TG/low HDL-C may play different role in the pathogenesis of atherosclerosis, however, we did not analyze these patients separately since the number of patients with low HDL-C was small and TG levels were not necessarily determined at fasting condition.

In conclusion, the prevalence of cardiovascular risk fac-

tors, such as obesity, DM, dyslipidemia, CKD and hyperuricemia was high in hypertensive patients. In addition, the patients with clustering additional risk factors needed a greater number of antihypertensive drugs. More intensive intervention for not only BP but also for other complicated risk factors should be required in hypertensive patients.

References

1. Kannel WB. Fifty years of Framingham study contributions to understanding hypertension. J Hum Hypertens **14**: 83-90, 2000.
2. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. Lancet **352**: 1801-1807, 1998.
3. PROGRESS Collaborative Study Group. Randomised trial of perindopril based blood pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet **358**: 1033-1041, 2001.
4. Zanchetti A, Hansson L, Clement D, et al. Benefit and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? J Hypertens **21**: 797-804, 2003.
5. Ogihara T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2009). Hypertens Res **32**: 3-107, 2009.
6. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. Am J Hypertens **13**(Suppl): 3S-10S, 2000.
7. Ohta Y, Tsuchihashi T, Arakawa K, et al. Prevalence and lifestyle characteristics of hypertensive patients with metabolic syndrome followed at an outpatient clinic in Fukuoka, Japan. Hypertens Res **30**: 1077-1082, 2007.
8. Ninomiya T, Kiyohara Y, Kubo M, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. Kidney Int **68**: 228-236, 2005.
9. Alderman MH, Cohen H, Madhavan S, et al. Serum Uric Acid and Cardiovascular Events in Successfully Treated Hypertensive Patients. Hypertension **34**: 144-150, 1999.
10. Chobanian AV, Bakris GL, Black HR, et al. 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 **42**: 1206-1252, 2003.
11. Mancia G, De Backer G, Dominiczak A, et al. management of arterial hypertension of the European Society of Hypertension; European Society of Cardiology: 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens **25**: 1105-1187, 2007.
12. Katayama S, Inaba M, Morita T, et al. Blood pressure control in Japanese hypertensives with or without type 2 diabetes mellitus. Hypertens Res **23**: 601-605, 2000.
13. Souçek M, Widimský J, Lánská V. Control of hypertension in patients with hypertension, diabetes, and impaired fasting glucose by Czech primary care physicians. Kidney Blood Press Res **29**: 366-372, 2006.
14. Boero R, Prodi E, Elia F, et al. How well are hypertension and albuminuria treated in type II diabetic patients? J Hum Hypertens **17**: 413-418, 2003.
15. Ohta Y, Tsuruya K, Fujii K, et al. Improvement of blood pressure control in hypertensive patients with renal diseases. Hypertens Res **30**: 295-300, 2007.
16. Weycker D, Nichols GA, O'Keeffe-Rosetti M, et al. Risk-factor clustering and cardiovascular disease risk in hypertensive patients. Am J Hypertens **20**: 599-607, 2007.
17. Ninomiya T, Kubo M, Doi Y, et al. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population. The Hisayama Study. Stroke **38**: 2063-2069, 2007.
18. Kadota A, Hozawa A, Okamura T, et al. Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity. Diabetes Care **30**: 1533-1538, 2007.
19. 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 **28**: 203-208, 2005.
20. Rodriguez-Colon SM, Mo J, Duan Y, et al. Metabolic syndrome clusters and the risk of incident stroke. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke **40**: 200-205, 2009.
21. Iso H, Sato S, Kitamura A, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke **38**: 1744-1751, 2007.
22. Puig JG, Martínez MA. Hyperuricemia, gout and the metabolic syndrome. Curr Opin Rheumatol **20**: 187-191, 2008.
23. Mabuchi H, Kita T, Matsuzaki M, et al. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease. -Secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT)-. Circ J **66**: 1096-1100, 2002.
24. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. Lancet **361**: 1149-1158, 2003.

CLINICAL RISK FACTORS IN REGIONAL BRAIN ISCHEMIA USING SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

To the Editor: Single photon emission computed tomography (SPECT) brain perfusion imaging has been widely used to diagnose older patients with Alzheimer's disease and other dementia[1,2] and to study cerebrovascular diseases and focal epilepsy and even to determine brain death.[3] Because SPECT provides a qualitative estimate of regional cerebral blood flow (rCBF) according to the radiotracer accumulating in different areas of the brain, the neurological disorders that are tightly coupled with brain metabolism can be detected. Therefore, it is postulated that the rate of delivery of nutrients, which not only the brain disease itself determines, but which other factors such as local circulation and blood components also influence, affects hypoperfusion.

Ninety-five older patients (53 men, 42 women) with suspected stroke were randomly enrolled to undergo the SPECT study. There were no significant differences in age and sex distribution. The SPECT procedure and data analysis, which an experienced technician and two specialists in SPECT blindly performed, were detailed elsewhere.[4] The results of SPECT were shown as two parts: average blood perfusion in two hemispheres (mL/min per 100 g of brain tissue) and regional cerebral perfusion in each brain lobe. For the former, average blood perfusion was defined as positively low perfusion when less than 40 mL/min per 100 g of brain tissue. In addition, all of the diagnostic information was collected from the case history, and information on the blood variables obtained within 3 days of the SPECT detection included red blood cell count (RBC), hemoglobin (Hb), aspartate transaminase, alanine aminotransferase, lactate dehydrogenase (LDH), total protein, albumin, blood urea nitrogen, creatinine, fasting blood glucose (FBG), glycosylated Hb (HbA1c), total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. Data were expressed as means ± standard errors. Statistical analysis was performed using the chi-square test, the Student *t*-test, analysis of variance, and the Bonferroni test.

Cerebral ischemia was found in 67 patients, of whom 91.0% had bilateral hemisphere ischemia, especially the men (male, 58.2%; female, 32.8%; $P = .03$) and patients aged 75 and older (≥ 75, 61.2%; <75, 29.8%, $P < .001$). Local ischemia was always detected when patients were diagnosed with cerebral infarction, hypertension, type 2 diabetes mellitus, cervical syndrome, Alzheimer's disease, coronary heart disease, insomnia, carotid artery stenosis, heart failure, reflux esophagitis, arrhythmia, anemia, cerebral hemorrhage, brain atrophy, or depression. Hypoperfusion in the left lobes was significantly more frequent than in the right lobes in patients diagnosed with cerebral infarction (left, 33.6%; right, 26.6%; $P = .03$), hypertension (left, 29.1%; right, 18.4%; $P < .001$), and Alzheimer's disease (left, 18.4%; right, 12.2%; $P = .01$). Moreover, differences were also found in the relationship between blood variables and local hypoperfusion. As shown in Table 1, older patients were at greater risk for local hypoperfusion with lower RBC, Hb, and serum albumin and higher FBG, HbA1c, and LDH.

Lines of evidence have shown that SPECT brain perfusion imaging should be considered to be a preferred test for the diagnosis of some brain diseases since it was introduced as an instrument for the evaluation of rCBF in the early 1980s,[1,3] but a frequent shortcoming of these reports is that the most-typical cases were chosen, and normal older subjects were chosen as controls. Although this improved confidence in the clinical standard of validation, it limited the utility of the results. For example, most older adults with Alzheimer's disease have one or more concomitant diseases, such as cerebrovascular disease, cardiovascular disease, and metabolic disease.

Although the sex and age differences in cerebral blood perfusion are still largely unexplored, it should be considered

Table 1. Blood Variables Collected from Patients with No, Left, and Right Lobe Ischemia According to Single Photon Emission Computed Tomography

Blood Variable	Mean ± Standard Error			*F* Value	*P*-Value
	No Ischemia	Left Ischemia	Right Ischemia		
Red blood cell count (× 10^9/mL)	4.3 ± 0.1	3.7 ± 0.1	3.9 ± 0.1	3.43	.03
Hemoglobin, g/dL	13.9 ± 0.2	12.2 ± 0.1	12.4 ± 0.2	4.24	.01
Aspartate transaminase, U/L	21.4 ± 1.2	25.6 ± 1.1	25.5 ± 1.2	0.56	.57
Alanine aminotransferase, U/L	17.5 ± 1.6	24.4 ± 2.1	24.2 ± 2.1	0.43	.65
Lactate dehydrogenase, U/L	158.9 ± 4.2	207.2 ± 5.0	217.2 ± 6.2	4.31	.01
Total protein, g/dL	6.7 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	0.07	.93
Albumin, g/dL	4.3 ± 0.0	3.7 ± 0.1	3.7 ± 0.1	3.18	.04
Blood urea nitrogen, mg/dL	17.4 ± 1.2	15.1 ± 0.5	16.2 ± 0.7	1.08	.34
Creatinine, mg/dL	0.91 ± 0.05	0.75 ± 0.02	0.71 ± 0.04	1.88	.16
Fasting blood glucose, mg/dL	113.8 ± 5.7	165.1 ± 5.2	157.8 ± 4.8	3.37	.04
Glycosylated hemoglobin, %	4.8 ± 0.2	6.2 ± 0.1	6.1 ± 0.2	3.69	.03
Total cholesterol, mg/dL	204.6 ± 10.4	194.3 ± 3.6	186.0 ± 4.1	1.71	.18
High-density lipoprotein cholesterol, mg/dL	53.7 ± 2.2	53.2 ± 2.8	52.0 ± 3.4	0.04	.96
Low-density lipoprotein cholesterol, mg/dL	105.0 ± 7.6	99.2 ± 4.1	103.8 ± 4.1	0.35	.71
Triglycerides, mg/dL	116.6 ± 11.2	112.1 ± 5.4	103.8 ± 7.3	0.53	.59

in the intervention for patients by combining with other factors. For Japanese people, it has been reported that rCBF is higher in women than in men aged 60 and older and declined significantly with age.[5] The possible foundation might be associated with physical activity such as housework performed by older women but not older men in Japan. More physical activity is associated with greater cerebral blood volume and a lower risk for developing some dementia diseases;[6] hence it is plausible that older women had higher blood perfusion than men younger than 75 in this study. In addition, vascular risk factors, such as hypertension,[7] diabetes mellitus,[8] and even coronary heart disease[9] also negatively affect rCBF. Moreover, SPECT scans were always performed after intravenous injection of the RBC tracer (e.g., 99mTc-labeled RBC) and plasma tracer (e.g., 99mTc-labeled human serum albumin). Hence, the levels of RBC, Hb, and serum albumin could also affect the results of SPECT.

This study found that age, sex, some blood variables, and concomitant diseases significantly influenced the average value of hemisphere blood perfusion and rCBF, which was in part in accordance with previous studies.[5–9] Therefore, it is important that these factors be taken carefully into account for patient enrollment in SPECT studies. Physicians should be aware of risk factors in regional brain ischemia for older patients.

*Rui Chen, MD, PhD**
Union Hospital
Huazhong University of Science and Technology
Wuhan, China

Kanazawa Medical University
Ishikawa, Japan
Himi Municipal Hospital
Toyama, Japan

*Fengxia Liang, MD, PhD**
Hubei University of Traditional Chinese Medicine
Wuhan, China

Kei-Ichiro Ishigami, MD, PhD
Tsugiyasu Kanda, MD, PhD
Kanazawa Medical University
Ishikawa, Japan

Himi Municipal Hospital
Toyama, Japan

Li Zeng, MD
Kanazawa Medical University
Ishikawa, Japan

Atsushi Saito, MD
Masayuki Hasegawa, MD
Naohiro Yamashita, MD
Tomohiko Itoh, MD
Toshikazu Kigoshi, MD
Yoichi Izumi, MD
Noboru Takekoshi, MD
Kanazawa Medical University
Ishikawa, Japan
Himi Municipal Hospital
Toyama, Japan

Shigeto Morimoto, MD, PhD
Kanazawa Medical University
Ishikawa, Japan

*These authors contributed equally to this work.

ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: All authors contributed to this letter.

Sponsor's Role: None.

REFERENCES

1. Bergman H, Chertkow H, Wolfson C et al. HM-PAO (CERETEC) SPECT brain scanning in the diagnosis of Alzheimer's disease. J Am Geriatr Soc 1997;45:15–20.
2. Read SL, Miller BL, Mena I et al. SPECT in dementia: Clinical and pathological correlation. J Am Geriatr Soc 1995;43:1243–1247.
3. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment of brain SPECT. Neurology 1996;46:278–285.
4. Hanyu H, Sakurai H, Hirao K et al. Unawareness of memory deficits depending on cerebral perfusion pattern in mild cognitive impairment. J Am Geriatr Soc 2007;55:470–471.
5. Takeda S, Matsuzawa T, Matsui H. Age-related changes in regional cerebral blood flow and brain volume in healthy subjects. J Am Geriatr Soc 1988;36:293–297.
6. Scarmeas N, Luchsinger JA, Schupf N et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627–637.
7. Efimova IY, Efimova NY, Triss SV et al. Brain perfusion and cognitive function changes in hypertensive patients. Hypertens Res 2008;31:673–678.
8. Schmidt R, Launer LJ, Nilsson LG et al. Magnetic resonance imaging of the brain in diabetes: The Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes 2004;53:687–692.
9. Ouchi Y, Yoshikawa E, Kanno T et al. Orthostatic posture affects brain hemodynamics and metabolism in cerebrovascular disease patients with and without coronary artery disease: A positron emission tomography study. Neuroimage 2005;24:70–81.

CENTENARIAN STROKE TREATED WITH REHABILITATION THERAPY

To the Editor: A 104-year-old, right-hand-dominant man who awoke with aphasia and right-sided weakness was admitted to the emergency department in February 2006. He had a previous history of hypertension, lacunar cerebellum stroke, implanted cardiac pacemaker, and urothelial carcinoma stage G2 pT1 (treated by transurethral resection in 2005). Before admission, he had been independent in activities of daily living (ADLs) (Barthel Index: 100/100) and able to ambulate independently with a walking stick. He enjoyed an active lifestyle, including walking every day. He had no cognitive alterations.

On hospital admission, he had severe motor deficit with right hemiplegia, mixed aphasia, and delirium. Computerized tomography showed an acute infarct in the left anterior middle cerebral artery. Physical therapy was not initially indicated because of delirium, severe flaccid right-sided weakness, and lack of sitting balance.

He was admitted to a subacute care unit for follow-up. He required major assistance (2 people) to stand, lacked sitting balance, and was completely dependant for personal

Geriatrics Gerontology INTERNATIONAL 1st Impact Factor in June 2010 Medline Indexed

Geriatr Gerontol Int 2011; **11:** *3–7*

COMMISSION REPORT

Survey on geriatricians' experiences of adverse drug reactions caused by potentially inappropriate medications: Commission report of the Japan Geriatrics Society

Masahiro Akishita,[1] Hiroyuki Arai,[2] Hidenori Arai,[3] Takashi Inamatsu,[4] Masafumi Kuzuya,[5] Yusuke Suzuki,[5] Shinji Teramoto,[6] Katsuyoshi Mizukami,[7] Shigeto Morimoto[8] and Kenji Toba;[9] Working Group on Guidelines for Medical Treatment and Its Safety in the Elderly

[1]Department of Geriatric Medicine, The University of Tokyo, Tokyo, [2]Department of Geriatric Medicine, Tohoku University, Sendai, [3]Department of Geriatric Medicine, Kyoto University, Kyoto, [4]Tokyo Metropolitan Geriatric Hospital, Tokyo, [5]Department of Geriatric Medicine, Nagoya University, Nagoya, [6]National Hospital Organization Tokyo Hospital, Tokyo, [7]Department of Psychiatry, Tsukuba University, Tsukuba, [8]Department of Geriatric Medicine, Kanazawa Medical University, Kanazawa, and [9]National Center for Geriatrics and Gerontology Hospital, Obu, Japan

Aim: The Japan Geriatrics Society (JGS) developed the guidelines for medical treatment and its safety in the elderly and the list of potentially inappropriate medication use, a Japanese version of the Beers list, in 2005. The JGS working group in collaboration with the Japan Broadcasting Corporation conducted the survey to geriatricians to investigate their experiences of adverse drug reactions (ADR) caused by potentially inappropriate medications.

Methods: In September 2008, the survey mails were sent to all the JGS certified geriatricians ($n = 1492$). The questionnaire consisted of 1 year of experiences of ADR of any type, past experiences of ADR by the use of antipsychotic benzamides, hypnotic benzodiazepines, digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and additional drugs, and their attitudes to reduce the dose/number of drugs for the prevention of ADR.

Results: A total of 425 geriatricians responded (response rate 29%). Seventy-two percent experienced ADR within 1 year. Past experiences of ADR were reported by 79% for antipsychotic benzamides, 86% for hypnotic benzodiazepines, 70% for digoxin and 37% for vitamin D_3. Free responses included frequent ADR by non-steroidal anti-inflammatory, antihypertensive, antiplatelet, anti-arrhythmic, antidiabetic and antidepressant drugs. Reduction of drugs for ADR prevention was attempted by 93%.

Accepted for publication 28 Apr 2010.

Correspondence: Dr Masahiro Akishita MD PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: akishita-tky@umin.ac.jp

doi: 10.1111/j.1447-0594.2010.00631.x

Conclusion: This survey showed that most geriatricians experience ADR and take preventive measures for ADR. The results can be used for education and the development of new guidelines. **Geriatr Gerontol Int 2011; 11: 3–7.**

Keywords: adverse drug reactions, Beers list, geriatrician, polypharmacy, side-effect.

Introduction

Adverse drug reactions (ADR) are more frequent and severe in the elderly than in young adults. A recent systematic review[1] of prospective observational studies reported that 10.7% of hospital admissions were associated with ADR in elderly patients, while 6.3% were so in young adults. Surveys performed in acute care hospitals in Japan also showed that inpatients aged 70 years or older were 1.5-fold more likely to develop ADR than those under 60 years of age,[2] and that the ADR incidence among elderly inpatients was 6–15%.[3] It has been reported from Western countries that ADR occur in more than 10% of outpatients or nursing home residents.[4]

Although many factors relate to the high ADR incidence in the elderly, overdoses resulting from age-related changes of pharmacokinetics/pharmacodynamics and polypharmacy may be of critical importance.[2–4] Because the evidence for the elderly is limited, practical guidelines to medical treatment and its safety are required in the field of geriatric medicine.

The Japan Geriatrics Society (JGS) has conducted educational activities through scientific sessions and official journals to reduce ADR. As part of activities, the ad hoc committee "Working group on guidelines for medical treatment and its safety in the elderly" was set up in 2003, and the JGS guidelines for medical treatment and its safety in the elderly were published in 2005.[5] In the guidelines, the list of medications that should be prescribed with special attention to elderly patients was reported and was put on the JGS website. This list, a Japanese version of the Beers list,[6,7] consists of 45 drugs or drug classes that may be harmful or less efficient, thus potentially inappropriate for elderly patients, and can be applied to reduce ADR and polypharmacy in clinical settings of geriatric medicine and nursing-care facilities.[5]

Although the mass media expressed an interest in these activities, the JGS should increasingly accumulate the evidence and make a proposal on pharmacotherapy of the elderly for public education. For this purpose, the JGS working group in collaboration with the Japan Broadcasting Corporation (NHK) conducted the survey to JGS certified geriatricians to investigate their experiences of ADR caused by potentially inappropriate medications. This commission report of the working group shows the survey results.

Methods

Mailing and collection of the questionnaire

In September 2008, the questionnaire was mailed by the NHK to all the JGS certified geriatricians ($n = 1492$) who appeared on the JGS website. In the cover letter, a brief introduction including the background and aim of the survey was described, followed by the statement that this survey was carried out in collaboration with the NHK and the JGS working group. The JGS version of the Beers list (Table 1 and detailed explanation) was included in the mail for options of additional drugs. The responder was asked to return the questionnaire to the NHK by fax without his/her name.

Questionnaire item

The questionnaire consisted of 1-year experiences of ADR of any type (yes/no question), past experiences (frequent, occasional or none) of ADR by the use of antipsychotic benzamides (sulpiride, sultopride), hypnotic benzodiazepines (flurazepam, haloxazolam, quazepam, triaxolam), digoxin (≥0.15 mg/day), vitamin D_3 (alfacalcidol ≥1.0 μg/day) and free additions, and their attitudes to reduce the dose/number of drugs for the prevention of ADR (yes/no question). In addition, free comments on the problems and approaches related to pharmacotherapy in the elderly were asked. The above four classes of drugs were chosen from the JGS version of the Beers list (Table 1) because these drugs were considered frequently prescribed to elderly patients.

Statistical analysis

The data are shown as the number and the percent of subjects. The χ^2-test was performed to analyze the associations between ADR experiences.

Results

A total of 425 geriatricians responded, resulting in a response rate of 28.5%. The response rate would have been 29.1% if the 30 subjects to whom the mails were not successfully delivered were excluded.

The summary of the results is shown in Table 2. Seventy percent of the geriatricians reported

Table 1 List of medications that should be prescribed with special attention to elderly patients (JGS version of the Beers list)

Class	Drug (generic name)
Antihypertensive (central sympathetic blocking agents)	Methyldopa
	Clonidine
Antihypertensive (rauwolfia)	Reserpine
Antihypertensive (short-acting calcium channel blockers)	Nifedipine
Vasodilator	Isoxsuprine
Cardiac glycoside	Digoxin (≥0.15 mg/day)
Anti-arrhythmic	Disopyramide
	Amiodarone
Antiplatelet	Ticlopidine
Hypnotic (barbiturates)	Pentobarbital
	Amobarbital
	Barbital
	Chlorpromazine, promethazine, phenobarbital
Hypnotic (benzodiazepines)	Flurazepam
	Haloxazolam
	Quazepam
	Triaxolam
Anxiolytic (benzodiazepines)	Chlordiazepoxide, diazepam
Antidepressants	Tricyclic (amitriptyline, imipramine, clomipramine)
	Maprotiline
Antipsychotic (phenothiazines)	Thioridazine, chlorpromazine, levomepromazine
Antipsychotic (butyrophenones)	Haloperidol, timiperone, bromperidol
Antipsychotic (benzamides)	Sulpride, sultopride
Anti-parkinsonian	Trihexyphenidyl
Antiepileptic	Phenobarbital
	Phenytoin
Narcotic analgesic	Pentazocine
Non-steroidal anti-inflammatory	Indometacin
	Diclofenac sodium, naproxen, piroxicam
Irritant laxative	Caster oil
Skeletal muscle relaxant	Methocarbamol
Soothing muscle relaxant	Oxybutynin
Intestinal antispasmodic	Butylscopolamine
	Propantheline
Anti-emetic	Metoclopramide
	Domperidone
Androgen	Methyltestosterone
Estrogen	Estrogens
Thyroid hormone	Dried thyroid
Hypoglycemics (1st-generation sulfonyl urea)	Chlorpropamide
	Acetohexamide
Hypoglycemics (biguanides)	Metformin
	Buformine
Iron	Fe (≥300 mg/day)
Vitamin D	Alfacalcidol (≥1.0 μg/day)

Doses in the parentheses are applicable for digoxin, Fe and alfacalcidol. This list with detailed explanation such as trade names and alternative drugs was enclosed in the questionnaire.

experiences of ADR within a year, even though non-responders ($n = 7$) were included in those without experience. Regarding past experiences of ADR, approximately a quarter of the geriatricians reported frequent ADR experiences by antipsychotic benzamides and hypnotic benzodiazepines. Seventy to eighty percent frequently or occasionally experienced ADR by these two classes of drugs and by digoxin, and

Table 2 Geriatricians' experiences of adverse drug reactions (ADR) and their attitudes to reduce drugs for the prevention of ADR ($n = 425$)

1. One-year experiences of ADR of any type ($n = 418$)			71.5%
2. Past experiences of ADR by use of the following drugs			
	Frequent	Occasional	Frequent + Occasional
(i) Antipsychotic benzamides ($n = 381$) (sulpiride, sultopride)	93 (24.4%)	207 (54.3%)	300 (78.7%)
(ii) Hypnotic benzodiazepines ($n = 386$) (flurazepam, haloxazolam, quazepam, triaxolam)	93 (24.1%)	241 (62.4%)	334 (86.5%)
(iii) Digoxin (≥0.15 mg/day) ($n = 382$)	33 8.6%)	234 61.3%)	267 69.9%)
(iv) Vitamin D_3 ($n = 373$) (alfacalcidol ≥1.0 μg/day)	14 (3.7%)	125 (33.5%)	139 (37.3%)
3. Past experiences of ADR (free responses; $n = 240$)			
Class of drugs	Frequent	Occasional	Frequent + Occasional
(i) Non-steroidal anti-inflammatory	60	34	94
(ii) Antihypertensive	19	27	46
(iii) Antiplatelet	17	21	38
(iv) Antidiabetic	19	15	34
(v) Anti-arrhythmic	13	17	30
(vi) Antidepressant	15	10	25
(vii) Anti-Parkinson	9	12	21
(viii) Warfarin	6	7	13
4. Reduction of the dose/number of drugs for the prevention of ADR ($n = 417$)			93.0%

Data in the parentheses indicate the number of responses to each questionnaire item. Each value indicates the number of cases and the percentage. Free responses to past experiences of ADR show the classes of drugs with more than 10 cases.

nearly 40% by vitamin D_3. Interestingly, the χ-square test showed that 1-year experiences of ADR of any type were significantly associated with ADR experiences by each of the four classes of drugs (data not shown), suggesting that some geriatricians frequently experience ADR of various types, and others do not. Free responses ($n = 240$) included common ADR by non-steroidal anti-inflammatory drugs; 25% of the responders reported frequent ADR and 39% reported frequent or occasional ADR. More than 90% of the geriatricians reported that they reduced the dose and number of drugs for the prevention of ADR.

Free comments on the problems and approaches related to pharmacotherapy in the elderly were summarized as follows: (i) lack of understanding about drug metabolism and ADR by doctors and patients, and need for their education; (ii) training of geriatricians who understand medical treatment in the elderly and are able to align prescriptions in a comprehensive manner; (iii) medication errors and a lack of prescription information derived from multi-consultations are problematic, thus a medication management and interdisciplinary collaboration system must be established; and (iv) because a medical fee system in which an easy medication is profitable rather than attentive listening may cause polypharmacy, guidelines and a new medical system to block this pathway should be created.

Discussion

In this questionnaire survey, although the mails were sent from the NHK, approximately 30% of the JGS certified geriatricians responded, expressing their high interest in medical treatment in the elderly. Seventy percent of them reported ADR experiences within a year, while more than 90% attempted to reduce the dose and number of drugs for the prevention of ADR.

Although most geriatricians reported ADR experiences, the prevalence should be carefully interpreted. First, sampling bias and overestimation are possible, because geriatricians who experienced more ADR and were conscious of ADR might have responded more actively. Second, there is a problem in reliability of ADR, because judgments of ADR including causality and severity may vary between geriatricians, and ADR experiences were dependent on memory rather than records. The questionnaire item concerning the frequency of ADR for individual drugs was also ambiguous. Because the frequency of ADR is related to the frequency of prescriptions, free responses included many common medications for elderly patients, such as non-steroidal anti-inflammatory drugs and antihypertensive drugs.

As described above, this survey was not designed to determine the incidence of ADR per patient or drug. The aim was to accumulate the opinions of JGS certified

geriatricians about ADR and pharmacotherapy, thus the results may have reflected their awareness of the issues. Taken together, it is reasonable that antipsychotic benzamides, hypnotic benzodiazepines and digoxin (≥0.15 mg/day) are included in the JGS version of the Beers list, because 70–80% of geriatricians reported ADR experiences by these drugs. This questionnaire also asked about ADR by vitamin D, which was not included in the lists of potentially inappropriate medications in Western countries.[6–8] Vitamin D_3 (alfacalcidol ≥1.0 μg/day) was included in the JGS list, because this class of drugs are frequently and carelessly used at high doses with calcium preparations for treatment of osteoporosis, leading to hypercalcemia. The result that 37% experienced vitamin D-related ADR justified the inclusion of vitamin D in the list. Regarding additional classes of drugs with more than 10 responses, some drugs of all classes but warfarin were also included in the JGS list. Each drug with many responses should be considered for inclusion when the list is updated.

It is not surprising but important that 93% of geriatricians reduced drugs for the prevention of ADR. This may be a result of educational activities by the JGS and may represent advanced performance of JGS certified geriatricians. Educational efforts and public information to reduce ADR should be strengthened.

The data are not available about what percentage of patients received interventions for drug reduction. We reanalyzed the data of the ADR survey conducted in five university hospitals,[3] and found that the number of drugs were decreased in 20% of inpatients ($n = 1002$) during hospital stay, although the reason for drug reduction is unknown. The investigation of five long-term care facilities[9] showed that one or more drugs were discontinued after admission in 40% of 581 patients on medications. It is noteworthy that the numbers of drugs included in the 1997 version of the Beers list[6] were decreased by 33% (from 61 to 41 cases) in this investigation, even though these drugs were not selectively discontinued. In the future, prospective studies to survey the frequency of drug reduction per patient for ADR prevention, and interventional studies, preferably randomized controlled trials, to investigate the efficacy of drug review/reduction using the JGS version of the Beers list needs to be performed.

Finally, free comments should be appreciated. Various problems and proposals raised from clinical practice are reasonable and were summarized as described in the results section. Other comments included the issue of drug dependency or fear of some patients, effectiveness-biased advertisements by pharmaceutical companies and disease-specific guidelines neglecting the individual difference, leading to the high ADR incidence and inappropriate medication management in elderly patients. Based on the results and comments obtained from this survey, the JGS and geriatricians should promote researches and accumulate the evidence concerning pharmacotherapy in the elderly to develop new guidelines and advance educational activities.

Acknowledgments

We thank the staff of the NHK TV program "Close-up Gendai", especially Mr Mamoru Ichikawa and Mr Tatsuo Yonehara for their full cooperation to complete this survey, and the 425 geriatricians who responded to this questionnaire.

References

1 Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 2008; **42**: 1017–1025.
2 Toba K, Akishita M, Mizuno Y *et al.* Adverse drug reaction in the elderly. *Jpn J Geriatr* 1999; **36**: 181–185.
3 Arai H, Akishita M, Teramoto S *et al.* Incidence of adverse drug reactions in geriatric units of university hospitals. *Geriatr Gerontol Int* 2005; **5**: 293–297.
4 Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; **160**: 2717–2728.
5 The Japan Geriatrics Society. *Guidelines for Medical Treatment and Its Safety in the Elderly 2005*. Tokyo: Medical View, 2005 (in Japanese).
6 Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531–1536.
7 Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; **163**: 2716–2724.
8 McLeod PJ, Huang AR, Tamblyn RM, Gayton DC. Defining inappropriate practices in prescribing for elderly people: a national consensus panel. *CMAJ* 1997; **156**: 385–391.
9 Mita Y, Akishita M, Tanaka K *et al.* Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. *Geriatr Gerontol Int* 2004; **4**: 146–150.

特集

血管石灰化とカルシウム

Review

糖尿病における血管石灰化と心血管イベント発症リスク

岩井 邦充*1) 森本 茂人*2)

糖尿病の疫学研究より，無症候性血管石灰化は高血糖で特徴づけられる前糖尿病状態から発症，進行し，やがては臓器虚血を引き起こすことが示唆されている。さらに動脈硬化性粥腫での内膜石灰化ばかりでなく，独自のメカニズムにより中膜石灰化も生じることがわかってきた。外膜での炎症が信号を発して，中膜の異所性骨形成を引き起こす機序が解明されている。一方，生体には骨化を阻止する因子も複数発見され，治療への応用が期待されている。

Regulatory Mechanisms and Practical Management in Vascular Calcification.

Arterial calcification and risk of cardiovascular events in diabetes mellitus.

Department of Geriatric Medicine, Kanazawa Medical University.

Kunimitu Iwai, Shigeto Morimoto

The cohort studies reported the subclinical vascular calcification including atheroslerosis starts during pre-diabetic state characterized by impaired fasting glucose. In the cardiovascular systems of diabetes mellitus there is an original mechanism to induce the medial calcification other than intimal calcification observed in the classical atherosclerosis. This is characterized as the ectipic osteogenesis induced by paracrine signals from inflammatory lesions in the adventitia. On the other hand, many internal systems have been discovered to inhibit vascular calcification.

はじめに

心臓血管系の粥状動脈硬化過程は高血圧，高脂血症，糖尿病などのリスクファクターが異なっていても，結局は同様の病理学的変化を示すものと思われてきた。しかも血管石灰化はこの過程のただの一現象にしかすぎないと思われてきた。しかし近年，血管石灰化を前糖尿病病態の指標と関連付けた疫学研究や，血管に存在する異所性骨化メカニズムの細胞生物学的研究が進み，これを覆す事実がいくつも報告されてきている。

*金沢医科大学老年病学高齢医学 1)(いわい・くにみつ) 2)教授(もりもと・しげと)

疫学研究

高血圧症，高脂血症および糖尿病は，心血管疾患の危険因子として知られ，日本を含む多くの先進国では，この心血管疾患が国民の死因の約1/3を占めている。心血管疾患の中で重要なのは脳梗塞，虚血性心疾患，閉塞性動脈硬化症であり，これらの原因は動脈硬化による血管閉塞による臓器虚血である。動脈硬化はさまざまな因子が多彩に絡み合った複合病変であるが，主に欧米での疫学調査からリスクファクターとして高血圧，高脂血症，糖尿病，喫煙，およびストレスが報告されてきた。わが国に目を移すと，糖尿病患者数は平成14年の厚生労働省糖尿病実態調査では約740万人で，予備軍を含めると1,600万人にのぼると推定され，慢性疾患のなかでも最多の疾患である。近年，その予備軍の急増が問題視されている。特に，食後高血糖状態，すなわち耐糖能異常は2型糖尿病の前状態と捉え，それ自体が心血管系疾患のリスクファクターになりうることがDECODE研究[1]，山形県の舟形町研究[2]等の大規模疫学調査で明らかにされた。臨床研究が進むにつれ，耐糖能異常のほかにも前糖尿病状態として肥満，空腹時高血糖，空腹時高インスリン血症，インスリン抵抗性，メタボリックシンドロームなどを有する患者が非常に多いことがわかってきた。さらに臨床的に明らかに糖尿病と診断された時点で，すでに臨床的に明らかな虚血性心疾患や脳梗塞を有していることも多いことがあげられる。これらの事実によって，糖尿病の疫学的危険因子としての厳密に独立した位置づけが容易には確定できなかった。

そこで，この疑問を厳密に解決することに成功したのは2002年のフラミンガムスタディである[3]。臨床的に虚血性心疾患と診断される以前から存在するはずの冠動脈硬化病変を前臨床的動脈硬化と定義し，前糖尿病状態との関係を解析した。前臨床的動脈硬化は電子ビームCTによる冠動脈石灰化で診断した。その結果予想どおり，正常耐糖能，空腹時高血糖/耐糖能異常，糖尿病と病的段階が上がるにつれ，冠動脈石灰化の程度も有意に強くなっていった。さらに，2009年のHeinz Nixdorf Recall Study[4]で臨床的糖尿病はなく，また臨床的冠動脈疾患を有しない症例において，空腹時血糖の上昇が冠動脈石灰化と相関することが証明された。すなわち，糖尿病が引き起こされるのと同じ病態によって冠動脈の石灰化も引き起こされ，長期間たって糖尿病および冠動脈疾患が完成してくることが示唆された。

次の段階としてこれらの遺伝的背景の解析に努力がそそがれている。2010年のHeinz Nixdorf Recall Studyの報告[5]によれば，興味深いことにすでにGenome-wide association study（GWAS）から糖尿病に関連することが明らかになっている一塩基多型（SNPs）の中で冠動脈石灰化と関連するものはcyclin-dependent kinase inhibitor 2A/2Bのみであり，IGFBP2，CDKAL1，SLC30A8，HHEX，TCF7L2などは関連しなかった。今後の展開が期待される。

細胞生物学研究

血管石灰化は病理学的に下記の3種類に分類される。

1．大動脈弁石灰化
2．粥状硬化性内膜プラーク石灰化
3．中膜石灰化（Monkeberg型硬化，medial artery calcification：MAC）

このなかで糖尿病にかなり特異的な石灰化は，中膜石灰化（MAC）であり，これは粥状硬化性病

GWAS：Genome-wide association study，MAC：中膜石灰化，SNPs：一塩基多型