White-Coat Hypertension as a Risk Factor for the Development of Home Hypertension

The Ohasama Study

Takashi Ugajin, MS; Atsushi Hozawa, MD, PhD; Takayoshi Ohkubo, MD, PhD; Kei Asayama, MD; Masahiro Kikuya, MD, PhD; Taku Obara, MS; Hirohito Metoki, MD; Haruhisa Hoshi, MD, PhD; Junichiro Hashimoto, MD, PhD; Kazuhito Totsune, MD, PhD; Hiroshi Satoh, MD, PhD; Ichiro Tsuji, MD, PhD; Yutaka Imai, MD, PhD

Background: White-coat hypertension is a condition characterized by elevated blood pressure (BP) in medical settings combined with normal ambulatory-recorded BP or self-measured BP at home (home BP). However, it is unknown whether this condition represents a transient state in the development of hypertension outside medical settings.

Methods: We followed up 128 subjects with white-coat hypertension (home BP <135/85 mm Hg and office BP ≥140/90 mm Hg) for 8 years and compared the risk of progression with home hypertension (home BP ≥135/85 mm Hg or start of treatment with antihypertensive medication) with 649 sustained normotensive subjects (home BP <135/85 mm Hg and office BP <140/90 mm Hg) using data from population-based home BP measurement projects in Japan.

Results: During the 8-year follow-up period, 60 subjects (46.9%) with white-coat hypertension and 144 (22.2%) with sustained normotension progressed to home hypertension. The odds ratio of subjects with white-coat hypertension for progression to home hypertension (adjusted for possible confounding factors) was significantly higher than for subjects with sustained normotension (odds ratio, 2.86; $P<.001$). This association was observed independent of baseline home BP levels.

Conclusion: The results from the present 8-year follow-up study demonstrate that white-coat hypertension is a transitional condition to hypertension outside medical settings, suggesting that white-coat hypertension may carry a poor cardiovascular prognosis.

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Author Affiliations: Departments of Clinical Pharmacology and Therapeutics (Messrs Ugajin and Obara and Drs Asayama, Metoki, Totsune, and Imai), Public Health (Drs Hozawa and Tsuji), Planning for Drug Development and Clinical Evaluation Health (Drs Ohkubo, Kikuya, and Hashimoto), and Environmental Health Sciences (Dr Satoh), Tohoku University Graduate School of Medicine and Pharmaceutical Sciences, Tohoku University 21st Century Center of Excellence (COE) Program "Comprehensive Research and Education Center for Planning for Drug Development and Clinical Evaluation," Sendai, Japan (Drs Ohkubo, Asayama, Metoki, Hashimoto, Totsune, Satoh, and Imai); and Ohasama Hospital, Iwate, Japan (Dr Hoshi).

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WHITE-COAT HYPERtension (WCHT) is a condition characterized by an elevated blood pressure (BP) in a medical setting, combined with normal self-measured or ambulatory-recorded BP. In contrast, sustained hypertension is the presence of an elevated BP regardless of setting or circumstance.[1] However, the clinical relevance of WCHT has not been established, and it is controversial whether this condition involves an increased cardiovascular risk. Results from cross-sectional and prospective studies have been contradictory; some had found increased cardiovascular risk in patients with WCHT,[2-6] whereas others did not.[7-11]

It is also unknown whether this condition represents a transient state in the development of hypertension outside medical settings. One small and short-term study [12] reported a similar rate of transition to ambulatory hypertension (high BP during ambulatory readings) in subjects with sustained normotension (SNT) (normal BP during office and ambulatory readings) and in subjects with WCHT. Although 2 other studies[13,14] reported a high rate for the development of ambulatory hypertension in subjects with WCHT, these studies did not have normotensive control subjects for comparison. Thus, these studies[13,14] failed to demonstrate that WCHT was truly a transient state compared with SNT or that it posed a greater risk for progression to hypertension outside medical settings.

Self-measurements of BP at home (home BP measurements) make it possible to obtain multiple measurements over a long observation period under relatively controlled conditions.[15-17] It has been reported that multiple measurements eliminate observer bias and regression dilution bias; therefore, home BP measurements are more reliable than conventional BP measurements taken in medical settings (office BP).[15-17] A few studies have also reported that home BP measurements are better predictors of cerebrovascular and cardiovascular events compared with office BP.[18-20]

We have followed home BP measurements in a general population sample in Japan since 1987.[18,20-22] The present 8-year follow-up study, conducted with 777 normotensive subjects 40 years or older, aims to quantitatively determine the risk of transition to hypertension outside medical settings (at home) in subjects with WCHT and to compare the risk with that in subjects with SNT.

METHODS

DESIGN

This study was a part of a longitudinal observational study of subjects who have been participating in a BP measurement project in Ohasama, Japan. The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere.[18,20-22] The study protocol was approved by the institutional review board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government.

DEFINITION OF HYPERTENSION

Based on several guidelines,[15-17] subjects with a home systolic BP of 135 mm Hg or higher and/or a home diastolic BP of 85 mm Hg or higher were classified as having high home BP, while others were classified as having normal home BP. Similarly, those who had office systolic/diastolic BP of 140/90 mm Hg or higher were classified as having high office BP. White-coat hypertension was defined as the occurrence of high office BP and normal home BP. Sustained normotension was defined as the occurrence of normal office BP and normal home BP. Development of home hypertension (hypertension based on home BP measurements) was defined as either progression to high home BP or start of treatment with antihypertensive medication.

STUDY POPULATION

The selection of subjects for this study has been reported previously.[18] Briefly, the subjects were 40 years or older and were residents from 3 of 4 subdivisions of Ohasama (n=2716). Hospitalized persons (n=121) and persons with dementia or those who were bedridden (n=31) were excluded from the study. Individuals who worked out of town (n=575) were also excluded because the project involved consistent and routine ambulatory BP monitoring. Informed consent to participate in the study was given by 1957 of 1989 eligible individuals. Home BP measurements at baseline were conducted among 1913 subjects who collected their own BP data at least 3 days during the 4-week study period. This criterion was based on our previous observation that the average BP value obtained for the first 3 days was not significantly different from the values obtained for the entire study period.[21] We had previously confirmed that these 1913 subjects were a representative sample of the general population.[18] In the present analysis, to compare the risk for development of hypertension between WCHT and SNT, we excluded subjects who did not have office BP measured (n=124) or those who regularly used antihypertensive medication (n=582). We further excluded 235 subjects who had home hypertension at baseline. Thus, we followed up the remaining 972 participants.

HOME BP MEASUREMENTS

Physicians and public health nurses instructed subjects on how to perform home BP measurements.[21] Subjects were asked to measure their BP every morning within 1 hour of waking, while seated and rested for more than 2 minutes, for 4 weeks. The home BP of an individual was defined as the mean of all measurements obtained for that person. The mean (SD [range]) number of baseline home BP measurements was 23.2 (6.8 [3-60]). The clinical utility of those methods of home BP measurements in this project has been previously reported.[18,20-22] The same procedure was used for the follow-up home BP measurements.

OFFICE BP MEASUREMENTS

Annual health check-ups including BP measurements are available to all Japanese citizens 40 years or older once per year. Two consecutive measurements of BP are taken by a nurse or technician, using a semiautomatic device, after the subject has been seated at rest for at least 2 minutes.[21] The office (screening) BP was defined as the average of the 2 readings and was obtained in the same year as the initiation of home BP measurement.

BP MEASURING DEVICE

Home BP was measured with the HEM401C (Omron Healthcare Co Ltd, Kyoto, Japan), a semiautomatic device, based on the cuff-oscillometric method that generates a digital display of systolic and diastolic BP at baseline. We also used the HEM401C and HEM7471CN devices for measurement at follow-up measurement. The screening BP was measured with an USM-700F (UEDA Electronic Works Co Ltd, Tokyo, Japan), a fully automatic device, based on the Korotkoff sound technique (a microphone method). The circumference of the arm was less than 34 cm in most cases, so we used a standard armcuff for both BP measurements. All devices used in this study were validated[23,24] and satisfied the criteria of the Association for the Advancement of Medical Instrumentation.[25]

DATA COLLECTION AND ANALYSIS

Residential status in the town of Ohasama on October 31, 1999, was confirmed using the residents' registration cards, which were considered accurate and reliable because they are required for pension and social security benefits in Japan. Information on smoking status, obesity, family history of hypertension, and a history of hypercholesterolemia or diabetes mellitus was obtained from questionnaires sent to each household during the time of home BP measurements and from the medical records at Ohasama Hospital. Ohasama Hospital is the only hospital in the town, and more than 90% of the participants go there for regular checkups.

All data are given as mean (SD). The association between the baseline BP and the likelihood of progression to home hypertension was investigated using multiple logistic regression models, adjusted for age, sex, smoking status, obesity (body mass index [BMI; calculated as weight in kilograms divided by the square of height in meters] $\geq$25), family history of hypertension, and a history of hypercholesterolemia or diabetes mellitus. In all analyses, we treated the subjects with SNT as the reference group. Variables were compared using the unpaired, 2-tailed t test, χ^2 test, or analysis of variance, as appropriate. Differences of $P<.05$ were considered statistically significant. All analyses were conducted using the SAS package (version 8.2; SAS Institute Inc, Cary, NC).

RESULTS

FOLLOW-UP

Among the 972 subjects with WCHT or SNT, who did not take antihypertensive medication at the time of baseline sur-

Table 1. Characteristics of the Subjects at Baseline*

Risk Factor	All Subjects (N = 777)	Subjects With SNT (n = 649)	Subjects With WCHT (n = 128)	P Value†
Age, y	56.0 (8.7)	55.8 (8.5)	57.0 (9.5)	.13
Male	34.0	32.4	42.2	.03
History of smoking	19.4	19.9	17.2	.48
Obesity	20.1	19.0	25.8	.08
Family history of hypertension	34.9	33.6	41.4	.09
Hypercholesterolemia	7.2	7.7	4.7	.23
Diabetes mellitus	11.1	10.8	12.5	.57
Office BP, mm Hg				
Systolic	125.9 (15.8)	121.1 (11.3)	150.4 (12.2)	<.001
Diastolic	72.5 (10.3)	70.2 (8.5)	84.4 (10.5)	<.001
Home BP, mm Hg				
Systolic	116.0 (9.1)	114.9 (8.9)	121.5 (8.0)	<.001
Diastolic	70.4 (7.2)	69.8 (7.1)	73.5 (6.7)	<.001

Abbreviation: BP, blood pressure; SNT, sustained normotension; WCHT, white-coat hypertension.
*Data are given as mean (SD) or percentage of subjects unless otherwise specified.
†Statistical significance between normotensive subjects and subjects with WCHT was compared using the *t* test for continuous variables and the χ^2 test for categorical variables.

vey, 60 died or moved away from the town before the follow-up. Of the remaining 912 subjects, 777 (85%) took part in the follow-up home BP measurements. Mean duration of the period between the baseline and the follow-up home BP measurements was 8.2 (2.0) years. The mean number of follow-up home BP measurements was 23.7 (5.6).

BASELINE CHARACTERISTICS

The baseline characteristics of the subjects in each group are presented in **Table 1**. The mean (SD) age of the 777 subjects was 56.0 (8.7) years and the proportion of men was 34.0%. Mean (SD) office and home systolic/diastolic BP values were 125.9 (15.8)/72.5 (10.3) mm Hg and 116.0 (9.1)/70.4 (7.2) mm Hg, respectively. Of the 777 subjects, 649 (83.5%) were classified as having SNT, while the remaining 128 (16.5%) were classified as having WCHT. Office and home BP values and the proportion of men were significantly higher in subjects with WCHT than among subjects with SNT. Subjects with WCHT tended to be older and have higher proportions of obesity and a more prominent family history of hypertension than those with SNT.

RATE OF DEVELOPMENT OF HOME HYPERTENSION

Development of home hypertension was defined as either progression to high home BP or the start of treatment with antihypertensive medication. At baseline, 649 subjects had SNT and 128 subjects had WCHT. At the time of follow-up measurements, 144 subjects (22.2%) with SNT and 60 (46.9%) with WCHT developed home hypertension. The rate was significantly higher in subjects with WCHT ($P<.001$). The significantly higher rate of development of home hypertension in subjects with WCHT was observed for both hypertension defined by a home BP of 135/85 mm Hg or higher (71 [10.9%] of 649 subjects with SNT and 31 [22.7%] of 128 subjects with WCHT [$P<.001$]) and hypertension defined by the start of treatment with antihypertensive medication (73 [11.2%] of 649 subjects with SNT and 29 [24.2%] of 128 subjects with WCHT [$P<.001$]).

RATE OF DEVELOPMENT OF HOME HYPERTENSION BY BASELINE HOME BP LEVELS

Table 2 gives the rates of development of home hypertension, home BP values, and the magnitude of changes for home BP from baseline to follow-up. (Categories were divided according to baseline home systolic and diastolic BP values.) In subjects with WCHT, as well as those with SNT, rates for development of home hypertension showed a significant trend ($P<.001$), as the baseline home BP values increased across the categories (Table 2). Across a broad range of baseline home BP levels, compared with subjects with SNT, rates of development of home hypertension were higher in most subjects with WCHT (Table 2). In both groups, subjects with a baseline home systolic BP of 108 mm Hg or lower or a diastolic BP of 52 mm Hg or lower had a less than 5% chance of developing home hypertension (Table 2). Similar tendencies were observed regarding the rate for those who developed home hypertension defined by the start of treatment with antihypertensive medication (Table 2).

RISK OF DEVELOPMENT OF HOME HYPERTENSION

The odds ratio (OR) for WCHT to progress to home hypertension, adjusted for other factors, was significantly higher than that of SNT (OR, 2.86; $P<.001$) (**Table 3**). In this multivariate model, older age, male sex, and obesity also significantly predicted the development of home hypertension (Table 3). The significant OR of WCHT for progression to home hypertension was similarly observed for both hypertension defined by a home BP of 135/85 mm Hg or higher (OR, 3.09; 95% confidence interval [CI], 1.83-5.23 [$P<.001$]) and hypertension de-

Table 2. Rate of Development of Home Hypertension by Baseline Home BP Levels in Subjects With Sustained Normotension and White-Coat Hypertension

Home BP Categories	No. of Subjects (N=777)	Rate of Development of Home Hypertension, %		Baseline BP, mm Hg	Follow-up BP, mm Hg	ΔBP,† mm Hg
		Total	Treatment*			
Sustained Normotension						
Systolic BP, mm Hg						
≤108	143	3.5	1.4	102.7	109.4	6.7
109-114	170	15.3	10.6	111.6	117.3	5.7
115-119	141	26.2	12.1	117.0	121.8	4.8
120-124	97	32.0	15.5	122.0	125.7	3.7
125-129	63	41.3	20.6	126.6	129.2	2.6
130-134	35	54.3	22.9	131.6	134.2	2.6
Total	**649**	22.2	11.3	114.9	119.9	4.9
Diastolic BP, mm Hg						
≤52	9	0	0	50.6	61.9	11.4
53-64	140	9.3	5.0	60.5	68.1	7.6
65-69	140	15.0	9.3	67.3	71.5	4.2
70-74	190	23.7	13.2	71.7	74.1	2.4
75-79	108	36.1	19.4	76.7	78.1	1.4
80-84	62	41.9	11.3	81.3	80.6	−0.7
Total	**649**	22.2	11.3	69.8	73.4	3.6
White-Coat Hypertension						
Systolic BP, mm Hg						
≤108	6	0	0	103.7	110.2	6.5
109-114	22	18.2	13.6	111.4	118.6	7.2
115-119	21	52.4‡	23.8	117.4	125.8	8.4
120-124	25	44.0	16.0	121.8	131.5	9.6‡
125-129	34	58.8	23.5	127.0	132.3	5.3
130-134	20	70.0	45.0	132.4	131.3	−1.0
Total	**128**	46.9§	22.7§	121.5	127.5	6.0
Diastolic BP, mm Hg						
≤52	0	0	0	NA	NA	NA
53-64	13	30.8‡	23.1‡	61.5	65.7	4.1
65-69	23	34.8‡	13.0	66.6	73.6	7.1
70-74	29	41.4‡	24.1	72.2	74.5	2.3
75-79	38	50.0	21.1	77.2	79.3	2.2
80-84	25	68.0‡	32.0‡	81.9	83.2	1.3
Total	**128**	46.9§	22.7§	73.5	76.6	3.1

Abbreviations: BP, blood pressure; NA, not applicable.
*Rate of subjects defined as developed home hypertension by the start of treatment with antihypertensive medication in each home BP category.
†Follow-up home BP − baseline home BP.
‡$P<.05$ vs sustained normotension.
§$P<.01$ vs sustained normotension.

fined by the start of treatment with antihypertensive medication (OR, 2.71; 95% CI, 1.61-4.56 [$P<.001$]).

Because higher home BP values at baseline were associated with a significantly higher rate of development for home hypertension (Table 2), we adjusted for home systolic/diastolic BP values separately, in addition to the previously mentioned factors. Although higher home BP levels were significantly and independently associated with the risk of home hypertension in the multivariate model (home systolic BP: OR (per 1−mm Hg increase), 1.11; 95% CI, 1.08-1.14 [$P<.001$]; home diastolic BP: OR (per 1−mm Hg increase), 1.10; 95% CI, 1.07-1.13 [$P<.001$]), WCHT remained a significant predictor of home hypertension (adjusted home systolic BP: OR, 1.81; 95% CI, 1.16-2.82 [$P=.009$]; adjusted home diastolic BP: OR, 2.36; 95% CI, 1.55-3.61 [$P<.001$]). Subgroup analysis of home BP levels at baseline also showed similar results (in subjects with a home BP lower than 125/80 mm Hg[26]: OR of WCHT, 2.24; 95% CI, 1.25-4.01 [$P=.007$]; in subjects with a home BP of 125/80 mm Hg or higher and lower than 135/85 mm Hg: OR of WCHT, 1.84; 95% CI, 0.94-3.60 [$P=.08$]). There was no significant interaction between the subgroup of home BP levels and the presence of WCHT on the risk of development of home hypertension ($P=.90$).

COMMENT

This 8-year follow-up study demonstrated that WCHT was a significant predictor of the development of home hypertension, independent of other confounding factors and baseline home BP levels. The risk of developing home hypertension was consistently higher in subjects with WCHT than in those with SNT, starting at a threshold of 108/58 mm Hg and across a broad range of base-

line home BP levels. Our results indicate that WCHT could pose a greater risk for progression to hypertension outside medical settings even if home BP values were within completely normal range.

Some studies reported that WCHT is associated with hyperreactivity to stress and higher sympathetic nerve activity.[27-29] Because stress has been reported to be an independent risk factor in the development of hypertension,[30,31] it is possible that a higher reactivity to stress in medical environments leads to WCHT, which in turn contributes to higher rates of progression to home hypertension in subjects with WCHT.

Only 1 study has ever compared the risk of developing hypertension outside medical settings in subjects with WCHT with those with SNT[12]; results showed that the transition to ambulatory hypertension occurred in a similar way in subjects with SNT and in subjects with WCHT. Those results were inconsistent with our findings; however, in that study the follow-up period was shorter (3.5 years) and the sample size was too small (36 subjects with WCHT and 56 subjects with SNT) to reliably determine the risk of WCHT. In the present study, we followed 649 subjects with SNT and 128 subjects with WCHT for 8-years and found high risk in subjects with WCHT.

Although 3 prospective studies reported the prognostic significance of WCHT compared with normotensive control subjects, the results were controversial: 2 studies[7,10] with short duration follow-up periods (mean of <5 years) showed similar lower cardiovascular risk for subjects with WCHT compared with normotensive control subjects, but 1 study[2] with a longer follow-up (10 years) demonstrated higher risk in subjects with WCHT compared with normotensive controls. In a recent 3-year follow-up study[19] of hypertensive patients taking antihypertensive medication, cases of isolated uncontrolled hypertension at the office had a similar risk of cardiovascular events compared with subjects with sustained controlled hypertension. These results and the present 8-year follow-up results suggest that WCHT could potentially represent a cardiovascular risk after 10 or more years. We are pursuing follow-up with research subjects to find the answer to this hypothesis.

To define WCHT, BP information obtained outside medical settings (home BP measurements or ambulatory BP monitoring) is necessary. Ambulatory BP monitoring provides a wide variety of BP information outside medical settings, and thus it may offer a more reliable definition of WCHT. However, because ambulatory BP monitoring is not easily achieved in typical clinical settings, it is not necessarily practical as a method to determine WCHT. On the other hand, home BP measurements are now widely recommended by professionals who practice in clinical settings in most developed countries[15-17] (in Japan, 30 million devices for self BP measurement at home have been distributed[32]). For these reasons, we based the definition of WCHT on actual and practical home BP measurements. However, applicability of the present findings to WCHT using a definition based on ambulatory BP remains to be investigated.

Development of home hypertension was defined as either progression to high home BP or start of treatment with antihypertensive medication at follow-up. Because subjects with WCHT had a higher office BP level, it is possible that the higher risk of developing hypertension might be attributable to receiving antihypertensive medication according to high office BP levels. However, WCHT showed a significant risk for progression to home hypertension by the definition of home BP levels as well as the start of treatment with antihypertensive medication. Furthermore, the rate of developing home hypertension, defined by the start of treatment with antihypertensive medication, was consistently higher in subjects with WCHT than in those with SNT, across a broad range of baseline home BP levels. Therefore, these findings suggest that WCHT is a transitional condition leading to home hypertension irrespective of high office BP levels. The objective of this study was to investigate home BP, and therefore no office BP data were collected at the time of follow-up. We recommend that the evaluation of subjects with SNT who develop WCHT is a topic for future research.

Table 3. Multiple Logistic Regression Analysis for Risk Factors for the Development of Home Hypertension

Variable	OR (95% CI)	*P* Value
Age (per 10 y)	1.32 (1.09-1.60)	<.005
Male	1.78 (1.12-2.82)	.01
History of smoking (present)	0.90 (0.53-1.52)	.69
Obesity* (present)	1.76 (1.14-2.72)	.01
Family history of hypertension (present)	0.80 (0.54-1.19)	.27
Diabetes (present)	0.67 (0.37-1.20)	.17
Hypercholesterolemia (present)	1.35 (0.70-2.63)	.37
White-coat hypertension (present)	2.86 (1.90-4.31)	<.001

Abbreviations: OR, odds ratio; CI, confidence interval.
*Obesity was defined as a body mass index of 25 kg/m^2 or greater.

The present 8-year follow-up study based on home BP measurements demonstrated that subjects with WCHT had an approximately 2-fold higher risk of eventually manifesting home hypertension compared with those who had SNT. Although the prognostic significance of WCHT remains unclear, these results suggest that WCHT is not a totally benign condition. Further follow-up studies targeting cardiovascular outcomes are needed to clarify whether WCHT is a potentially dangerous condition. In the meantime, patients with WCHT should be carefully monitored.

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Correspondence: Yutaka Imai, MD, PhD, Department of Clinical Pharmacology and Therapeutics, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan (imai@tinet-i.ne.jp).
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3)今後の研究計画

家庭血圧・24時間自由行動下血圧は、これまで健診等で用いられてきた随時血圧よりも予後予測能が高いことは本研究においてすでに報告されている通りである。今後は、血圧レベルのみならず、日内変動・血圧短期変動などの詳細な血圧成分をもとに、頭部MRI、Pulse Wave Velocity, Augmentation Index, 指尖容積脈波、24時間ホルター心電図、頸動脈エコー、ミニメンタルテスト、クレアチニンクリアランス、尿中微量アルブミン、BNP、高感度CRP、フィブリノーゲン、リポプロテイン（a）などの臓器障害・生化学パラメーターとの関連、および高血圧発症リスク・循環器疾患罹患・死亡リスクを評価していく。

さらに、近年話題となっているメタボリックシンドロームについて、75g 糖負荷試験において得られた血糖値・インスリン値および腹部CTにより得られた内臓脂肪面積をもとに、臓器障害・生化学パラメーターとの関連、および高血圧発症リスク・循環器疾患罹患・死亡リスクとの関連を検討する予定である。

また、食事頻度摂取量に関する詳細な調査票データをもとに、栄養素や食品の組み合わせと高血圧等の脳心血管疾患危険因子発症・進展との関連、および、単一栄養素、食品と高血圧・動脈硬化の関連についての分析を行う。さらに、パーソナリティーの型等の個人的素因に関するデータに基き、生活習慣、個人的素因と食事摂取の関連についての分析も行う。

この他、冷凍保存してある大迫住民の白血球分画より抽出したDNAを遺伝解析し、高血圧、脂質、糖代謝に関する遺伝子を中心とした遺伝子型データとの相互作用を、具体的に検証する。

それとともに、家庭血圧導入を主体とした予防的介入の効果についての、医療経済学的な分析も行う予定である。

上記を通じ、生活習慣・遺伝情報の両面から循環器疾患発症のメカニズムを検討するとともに、日本人におけるきめ細かく無駄のない予防医学に貢献しうるエビデンス構築の一端を担いたいと考えている。

3．滋賀県におけるコホート研究について

分担研究者：　岡村 智教（滋賀医科大学社会医学講座福祉保健医学　助教授）
研究協力者：　中村 幸志（滋賀医科大学社会医学講座福祉保健医学　助手）

滋賀県内では、現在、滋賀医科大学社会医学講座福祉保健医学分野が中心となって実施したコホート研究が幾つかあり、代表的なものとして高島郡コホートや信楽町コホートがある。これらは循環器疾患の発症や死亡をエンドポイントした研究であり、前者は他の研究班として調査継続中であり、後者は本研究班に統合すべく現在、データクリーニング中である。これらとは別に、今年度、データ統合を行った滋賀県のコホート研究としては滋賀県国保コホートがある。本稿ではその概要と研究成果を述べる。

滋賀県国保コホートは、滋賀県内の7町1村における40-69歳の一般住民で、基本健康診査（以下、健診）受診した国民健康保険（以下、国保）加入者4,535名（男性1,939名、女性2,596名）を対象とした追跡調査である。1990年当時、この地域の総人口は82,155人であった。このうち40-69歳の人口は31,564人、その中で国保加入者は11,900人であった。従って、本対象集団はこの地域の40-69歳の国保加入者の約38%を占めていることになる。健診は老人保健法健診マニュアル（1987年）に準じて1989-1991年に実施された。健診項目には身長、体重、喫煙・飲酒習慣、血圧、血液生化学検査などが含まれている。本研究では対象者の保険点数（外来、入院別）を健診受診の翌年4月1日から2001年3月31日まで集計した。ただし、医療費（円）＝保険点数（点）×10円である。そして、国保保険証番号をキーにして健診データと国保のデータを結合させた。データの結合は滋賀県国保連合会内で行い、大学で分析する際には個人が特定できないように個人情報を消去し、連結不可能匿名化したデータセットを使用した。医療費は加入期間に応じて異なるため、死亡や社会保険への転出などの国保の受給資格を喪失した理由および年月日を把握し、対象者の国保加入期間を追跡期間として算出した。そして「追跡期間中の医療費(円)/国保加入期間(月)」をもとめ、これを医療費のデータとして分析に用いた。生活習慣や健診で見つかった異常所見と将来の医療費の関係を明らかにいていくことが、本コホート研究の目的である。その結果から、生活習慣の是正などによって、どの程度医療費を抑制できるのかを推定することができる。

なお、繰り返しになるが本研究は滋賀県国保連合会地域健康作り検討委員会の事業として行われ、研究成果を滋賀県内の市町村、国保診療施設、国保加入者に対して還元するためのパンフレット作成など、普及啓発事業を積極的に実施している。本研究は本邦でも数少ない医療費をエンドポイントした研究である。

次ページ以降に本年度の主な研究成果を提示する。

高血圧が医療費に及ぼす影響：
滋賀県国保コホートにおける10年間の追跡による検討

中村　幸志、岡村　智教、上島　弘嗣（滋賀医科大学社会医学講座福祉保健医学）

【 目的 】中高年の日本人では高血圧の頻度が高く、わが国の循環器疾患の最も重要な危険因子の一つである。循環器疾患の予防のためには長期にわたる血圧管理が必要であるが、コントロールが不十分な場合、循環器疾患の発症率が上昇するため、高血圧は医療費を上昇させる可能性があり、これを追跡調査によって明らかにすることを試みた。

【 方法 】滋賀県内の7町1村における40-69歳の国民健康保険加入者4,191名（男性1,819名、女性2,372名）を約10年間追跡した。この追跡対象者は高血圧未治療で、循環器疾患の既往のない者である。血圧値によって米国合同委員会第7次報告の分類に準じた4つのカテゴリーに分けて（「収縮期血圧（以下、SBP）120mmHg未満かつ拡張期血圧（以下、DBP）80mmHg未満；正常血圧」、「SBP120～139mmHg または DBP80～89mmHg；高血圧前症」、「SBP140～159mmHg または DBP 90～99mmHg；ステージ1高血圧」、「SBP160mmHg以上またはDBP100mmHg以上；ステージ2高血圧」）、各血圧カテゴリーの一人あたりの医療費と累積入院のオッズ比、総死亡のハザード比（正常血圧を基準）を評価した。高血圧者（前症、ステージ1、ステージ2）の医療費と正常血圧者の医療費の差額は高血圧に起因している可能性のある過剰医療費と考えられるが、これを高血圧関連医療費と定義して、血圧各群の集団としての高血圧関連医療費が対象集団の総医療費の中で占める割合を求めた。

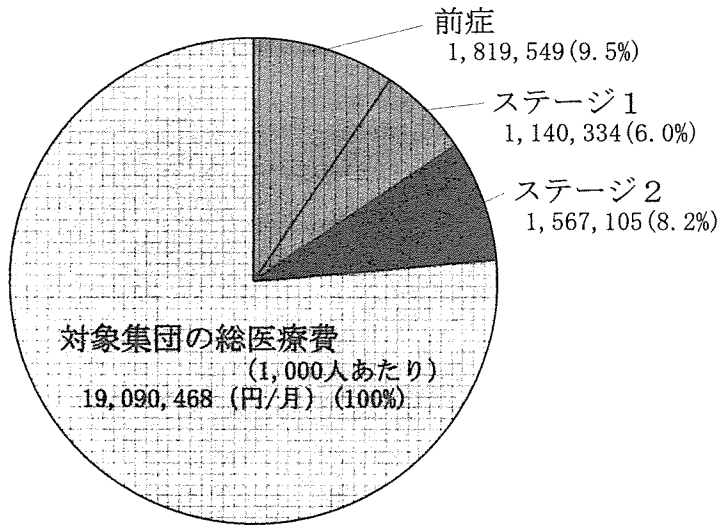
【 結果 】血圧値と医療費の間に正の段階的な関連がみられ、特に男性において著明であった。また、ほとんどの高血圧群（前症、ステージ1、ステージ2）において入院と総死亡は増加傾向を認めたが、男性のステージ2高血圧群においては入院も総死亡もかなり高くなっていた。集団としては、高血圧前症群、ステージ1高血圧群、ステージ2高血圧群の高血圧関連医療費に大きな差はなく、軽～中等症である高血圧前症群とステージ1高血圧群を合わせた高血圧関連医療費は重症のステージ2高血圧群よりもむしろ高くなった。また対象集団の高血圧関連医療費は対象集団の総医療費の23.7%を占めていると考えられた。

【 結論 】高血圧はその重症度を問わず医療費に大きな影響を及ぼすと考えられる。

表．一人あたり医療費，累積入院のオッズ比と総死亡のハザード比（滋賀県国保コホート）

血圧カテゴリー	対象者数	一人あたり医療費(円/月) 算術平均	幾何平均 *	累積入院 ケース数	オッズ比 (95%CI) *	総死亡 ケース数	ハザード比 (95%CI) *
男性							
正常	347	15,009	6,694	147	1.00	17	1.00
前症	858	18,973	6,995	399	1.10 (0.84-1.43)	63	1.33 (0.77-2.30)
ステージ1	450	22,378	8,325	215	1.05 (0.77-1.42)	32	1.21 (0.66-2.21)
ステージ2	164	45,947	15,756	105	1.96 (1.29-2.98)	27	3.19 (1.67-6.08)
			$p<0.01$				
女性							
正常	546	14,222	7,723	194	1.00	10	1.00
前症	1,135	17,944	7,848	438	1.04 (0.83-1.29)	26	1.23 (0.57-2.66)
ステージ1	527	16,998	7,801	194	0.85 (0.65-1.11)	14	1.32 (0.55-3.17)
ステージ2	164	23,332	9,887	76	1.14 (0.78-1.66)	4	1.06 (0.31-3.60)
			$p=0.18$				

* 年齢、BMI、喫煙、飲酒、総コレステロール、糖尿病を調整



図．対象集団における高血圧関連医療費（滋賀県国保コホート）

【 研究成果の公表 】

Nakamura K, Okamura T, Kanda H, Hayakawa T, Kadowaki T, Okayama A, Ueshima H. Impact of Hypertension on Medical Economics: A 10-Year Follow-Up Study of National Health Insurance in Shiga, Japan. Hypertens Res 2005; 28: 859-864.

Original Article

Impact of Hypertension on Medical Economics: A 10-Year Follow-Up Study of National Health Insurance in Shiga, Japan

Koshi NAKAMURA, Tomonori OKAMURA, Hideyuki KANDA*[1], Takehito HAYAKAWA*[2], Takashi KADOWAKI, Akira OKAYAMA*[3], and Hirotsugu UESHIMA, for the Health Promotion Research Committee of the Shiga National Health Insurance Organizations*[4]

Hypertension and related cardiovascular diseases may lead to an increase in medical costs for patients. We attempted to clarify the relationship between hypertension and long-term medical costs by a cohort study utilizing existing data as well as baseline blood pressures and medical costs over a 10-year period. The participants included 4,191 Japanese National Health Insurance beneficiaries aged 40–69 years, living in one area, who were not taking anti-hypertensive medication and did not have a history of major cardiovascular disease. They were classified into four categories according to their blood pressure. We evaluated the mean medical costs per month, cumulative hospitalization, and all-cause mortality for each blood pressure category. Hypertension-related medical costs attributable to hypertensive individuals, as compared to normotensive individuals, were estimated. There was a positively graded correlation between blood pressure and personal total medical costs, especially for men. The odds ratio for cumulative hospitalization and hazard ratio for all-cause mortality in severe hypertensive men were also higher than those in normotensive men. However, the hypertension-related medical costs for mild to moderate hypertensives were higher than those for severe hypertensives. The hypertension-related medical costs for all hypertensives accounted for 23.7% of the total medical costs for the Japanese population. In conclusion, high blood pressure was a useful predictor for excess medical costs; moreover, concomitant hypertension, regardless of the grade, increased the medical costs of Japanese National Health Insurance beneficiaries. (*Hypertens Res* 2005; 28: 859–864)

***Key Words*: hypertension, medical costs, Japan, National Health Insurance**

Introduction

Hypertension is a major risk factor for cardiovascular disease (*1–3*). In Japan, the mortality rate from cardiovascular disease, especially stroke, is high (*4*). Furthermore, stroke patients often become bed-ridden (*4*, *5*) and need long-term hospitalization or home nursing care. In 2001, the medical costs of cardiovascular disease, including hypertension, in the Japanese population aged 45–69 years, was 20.4% of the total

From the Department of Health Science, Shiga University of Medical Science, Otsu, Japan; *[1]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; *[2]Department of Public Health Science, Shimane University School of Medicine, Izumo, Japan; and *[3]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan.

*[4]Members of the committee are listed in the Appendix.

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Address for Reprints: Koshi Nakamura, M.D., Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu 520–2192, Japan. E-mail: ksnkmr@belle.shiga-med.ac.jp

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national medical costs, which was greater than those of any other disease group (*4*).

Although there have been several cohort studies regarding the relationship between hypertension and medical costs (*6*), the follow-up periods of these studies were short, and the populations were limited to Westerners. The objective of the present study was to clarify the relationship between hypertension and long-term medical costs in the general Japanese population.

Methods

Study Design and Participants

To clarify the relationship between hypertension and long-term medical costs, we conducted a cohort study utilizing medical cost data from Japanese beneficiaries of National Health Insurance who were living in a single area. Medical insurance is compulsory for everyone living in Japan and consists of two systems: the first system is for employees and their dependants, and the National Health Insurance system is for self-employed people such as farmers and fishermen, as well as those who are retired, and their dependants (*4*). The National Health Insurance system covers 34.7% of the total Japanese population (*4*).

Participants in the study included 4,535 National Health Insurance beneficiaries aged 40–69 years living in 7 rural towns and one village in Shiga Prefecture, West Japan, who underwent a baseline survey in 1989–1991. The study was performed as part of a research project conducted by the Health Promotion Research Committee of the Shiga National Health Insurance Organizations. After excluding participants taking anti-hypertensive medication and those with a history of major cardiovascular disease at baseline, 4,191 participants were considered eligible for the present analysis.

National Health Insurance claims were linked with baseline survey data files at the Shiga National Health Insurance Organizations. The participants' names were deleted from the linked data in order to protect their privacy. Thus, we analyzed the data without identifying individual participants. The study was approved by the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 16–15).

Data Collection

The baseline survey, conducted from 1989–1991, was performed using standardized methods according to the Manual for Health Check-ups under the Medical Service Law for the Aged in 1987 (*7*). Blood pressure was measured using a standard mercury sphygmomanometer on the right arm of each participant in the sitting position after at least a 5-min rest. Body height and body weight were measured, and body mass index was calculated as body weight (kg) divided by the square of body height (m^2). The smoking and drinking habits of the participants, use of anti-hypertensive medication, and any history of major cardiovascular disease or diabetes were evaluated from interviews with well-trained public health nurses. Serum total cholesterol was measured by an enzymatic method.

Referring to the seventh report of the Joint National Committee (*8*), the participants were classified into four categories: systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg (normotension), systolic blood pressure 120–139 mmHg or diastolic blood pressure 80–89 mmHg (pre-hypertension), systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg (stage 1 hypertension), and systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg (stage 2 hypertension).

We calculated the medical cost per person in each blood pressure category over a 10-year period. We obtained medical insurance costs for each participant beginning from April in the year following the health check-up to March 2001, using the monthly claim history files of the Shiga National Health Insurance Organizations. Costs were expressed in Japanese yen (*i.e.* 100 Japanese yen=0.89 US dollars or 0.73 euro, at the foreign exchange rate on August 1, 2005). Data obtained regarding the medical costs for each participant differed depending upon the period of enrollment in National Health Insurance. Therefore, information on beneficiaries who withdrew from the National Health Insurance system or those who died was obtained using monthly claim files. The medical cost for each participant was divided by the period of enrollment, and was expressed as costs per month of the follow-up period. If a beneficiary withdrew or died, the follow-up period was terminated at that point. For a beneficiary who withdrew and then re-enrolled in National Health Insurance, the follow-up period was reinitiated. Reasons for withdrawal from the National Health Insurance system included moving to an area outside of Shiga Prefecture or transfer to another insurance system.

Data Analysis

Because medical costs are generally different for men and women, sex-specific analyses were performed (*9*). Logarithmic transformations of actual medical costs were performed to normalize the distribution, and the results were expressed as geometric means. For the participants with 0 yen (per month), logarithmic transformations were performed by replacing 0 yen with 1 yen. There were 5 men and 10 women with total medical costs of 0 yen and 6 men and 10 women with outpatient medical costs of 0 yen. For comparison of the total medical costs and outpatient medical costs per person in each blood pressure category, we performed an analysis of covariance, which included age, body mass index, smoking habit (non-smoker or current smoker), drinking habit (non-, current occasional or current daily drinker, using two dummy variables with non-drinkers as a reference), serum total cholesterol, and history of diabetes as covariates. Due to the fact

Table 1. Baseline Risk Characteristics of 4,191 National Health Insurance Beneficiaries in Shiga, Japan, in 1989–1991, Grouped by Sex and Blood Pressure

	Blood pressure category				*p* value
	Normal	Pre-	Stage 1	Stage 2	
Men					
No. of participants	347	858	450	164	
(Distribution [%])	(19.1)	(47.2)	(24.7)	(9.0)	
Age (years)*	51.7±8.4	53.1±8.2	54.9±8.2	56.5±7.0	<0.01
Blood pressure (mmHg)*					
Systolic	110.5±6.4	128.6±6.4	142.9±7.7	167.8±14.2	<0.01
Diastolic	68.4±5.9	79.0±6.1	87.6±6.9	99.0±9.8	<0.01
Body mass index (kg/m^2)*	21.4±2.3	22.5±2.5	23.0±2.8	24.0±3.0	<0.01
Smoking habit (%)†					0.49
Non-smoker	35.7	40.3	38.4	40.9	
Current smoker	64.3	59.7	61.6	59.1	
Drinking habit (%)†					<0.01
Non-drinker	27.4	19.5	20.3	12.9	
Occasional drinker	24.3	23.1	17.9	15.9	
Daily drinker	48.3	57.4	61.8	71.2	
Total cholesterol (mg/dl)*	180.0±31.5	189.1±34.4	190.3±37.7	189.1±37.4	<0.01
History of diabetes (%)†	3.2	4.8	4.4	3.7	0.63
Women					
No. of participants	546	1,135	527	164	
(Distribution [%])	(23.0)	(47.9)	(22.2)	(6.9)	
Age (years)*	51.6±8.1	53.8±7.9	56.1±7.6	58.3±7.2	<0.01
Blood pressure (mmHg)*					
Systolic	111.0±5.8	128.3±6.2	145.0±7.0	166.3±11.4	<0.01
Diastolic	68.7±5.8	77.8±6.2	85.7±7.0	94.2±9.0	<0.01
Body mass index (kg/m^2)*	21.9±2.7	22.8±2.8	23.9±3.1	24.5±2.9	<0.01
Smoking habit (%)†					0.16
Non-smoker	95.0	96.5	97.1	98.1	
Current smoker	5.0	3.5	2.9	1.9	
Drinking habit (%)†					0.72
Non-drinker	78.4	80.0	78.2	82.6	
Occasional drinker	17.3	16.5	17.0	13.0	
Daily drinker	4.3	3.5	4.8	4.4	
Total cholesterol (mg/dl)*	193.5±33.7	202.5±34.2	209.5±35.4	210.6±41.5	<0.01
History of diabetes (%)†	0.5	1.9	2.7	3.7	0.02

Mean±SD. *One way analysis of variance. †χ^2 test.

that there were 953 men and 1,470 women with inpatient medical costs of 0 yen, no logarithmic transformations were performed. The odds ratio in each blood pressure category, as compared to the lowest category (normotension), was calculated using a logistic regression model for cumulative hospitalization during the follow-up period. The logistic regression model was utilized, because the date of initial hospitalization was not available. The hazard ratio was calculated using a Cox proportional hazards model for all-cause mortality.

The analyses were repeated, dividing the entire follow-up period into the first half and the latter half, because a single blood pressure measurement at baseline could potentially show different associations between medical costs or all-cause mortality after stratification of the follow-up period.

Finally, we defined and calculated hypertension-related medical costs attributable to pre-, stage 1, and stage 2 hypertensive participants, as compared to those of normotensive participants. The hypertension-related medical costs were estimated as follows: (arithmetic mean of total medical costs in pre-, stage 1 and stage 2 hypertension – arithmetic mean of total medical costs in normotension) × number of pre-, stage 1 and stage 2 hypertensive participants, respectively. Furthermore, we examined the percentages of pre-, stage 1, and stage 2 hypertension-related medical costs for the whole population when both sexes were combined. The total medical cost of the entire population was expressed in Japanese yen per 1,000

Table 2. Medical Costs per Person, Cumulative Hospitalization and All-Cause Mortality Grouped by Sex and Blood Pressure Category, after a 10-Year Follow-Up, from 1990 to 2001, in National Health Insurance in Shiga, Japan

Blood pressure category	No. of participants	Medical costs per person (Japanese yen per month)					Cumulative hospitalization		All-cause mortality	
		Total		Outpatient		Inpatient				
		Arithmetic mean	Adjusted geometric mean‡	Arithmetic mean	Adjusted geometric mean‡	Arithmetic mean	No.	Adjusted odds ratio§ (95% CI)	No.	Adjusted hazard ratio¶ (95% CI)
Men										
Normal	347	15,009	6,694	7,940	4,846	7,068	147	1.00	17	1.00
Pre-	858	18,973	6,995	9,023	4,846	9,962	399	1.10 (0.84–1.43)	63	1.33 (0.77–2.30)
Stage 1	450	22,378	8,325	11,452	5,665	10,926	215	1.05 (0.77–1.42)	32	1.21 (0.66–2.21)
Stage 2	164	45,947	15,756	17,436	9,302	28,511	105	1.96 (1.29–2.98)	27	3.19 (1.67–6.08)
			$p<0.01$		$p<0.01$					
Women										
Normal	546	14,222	7,723	8,804	6,039	5,507	194	1.00	10	1.00
Pre-	1,135	17,944	7,848	9,826	6,106	8,110	438	1.04 (0.83–1.29)	26	1.23 (0.57–2.66)
Stage 1	527	16,998	7,801	11,498	6,419	5,500	194	0.85 (0.65–1.11)	14	1.32 (0.55–3.17)
Stage 2	164	23,332	9,887	14,258	7,662	9,074	76	1.14 (0.78–1.66)	4	1.06 (0.31–3.60)
			$p=0.18$		$p=0.12$					

‡Multivariate analysis of covariance adjusted for age, body mass index, smoking habit, drinking habit, serum total cholesterol and a history of diabetes. §Multivariate analysis of a logistic regression model adjusted for age, body mass index, smoking habit, drinking habit, serum total cholesterol and a history of diabetes. ¶Multivariate analysis of a Cox proportional hazards regression model adjusted for age, body mass index, smoking habit, drinking habit, serum total cholesterol and a history of diabetes. CI, confidence interval.

persons per month.

The statistical analysis package SPSS 11.0J for Windows was used for statistical processing. All probability values were two-tailed, and the significance level was set at $p<0.05$.

Results

Most of the baseline risk characteristics of the participants were positively associated with blood pressure, as shown in Table 1. For men, the mean systolic and diastolic blood pressures at baseline were 132.2±17.3 mmHg (mean±SD) and 80.9±10.8 mmHg, respectively. For women, the mean systolic and diastolic blood pressures were 130.6±16.5 mmHg, 78.6±9.7 mmHg, respectively. The mean age and body mass index at baseline were 53.6±8.2 years and 22.6±2.7 kg/m^2 for men, and 54.1±8.0 years and 23.0±3.0 kg/m^2 for women, respectively.

The total number of person-years was 37,775; the mean follow-up period was 9.0 years. Mean total medical costs per month were higher in the higher blood pressure categories, as shown in Table 2. Among men, a significant difference in mean total medical costs was observed. However, this result was not seen among women. For men, both the odds ratio for cumulative hospitalization and the hazard ratio for all-cause mortality in participants with stage 2 hypertension were significantly higher than those in normotensive participants.

When the analyses were repeated, the pattern of results obtained by dividing the entire follow-up period into a first half and a latter half was generally similar to that shown in Table 2 (stratified data not shown in the table).

The hypertension-related medical costs per month attributable to pre-, stage 1, and stage 2 hypertensive participants were calculated to be 3,401,492 yen, 3,316,041 yen, and 5,073,770 yen for men, respectively; and 4,224,237 yen, 1,463,100 yen, and 1,493,965 yen for women, respectively (data not shown in the table).

The percentages of pre-, stage 1, and stage 2 hypertension-related medical costs for the whole population (*i.e.*, both sexes combined), with costs expressed in Japanese yen per 1,000 persons per month, are shown in Fig. 1. The hypertension-related medical costs for combined pre- and stage 1 hypertensive participants were higher than those for stage 2 hypertensive participants. The hypertension-related medical costs for all hypertensive participants accounted for 23.7% of the total medical costs.

Discussion

In the present study, there was a positively graded correlation between blood pressure and personal total medical costs, especially among men. However, the hypertension-related medical costs attributable to mildly to moderately hypertensive individuals (combined pre- and stage 1 hypertensives) were higher than those attributable to severely hypertensive

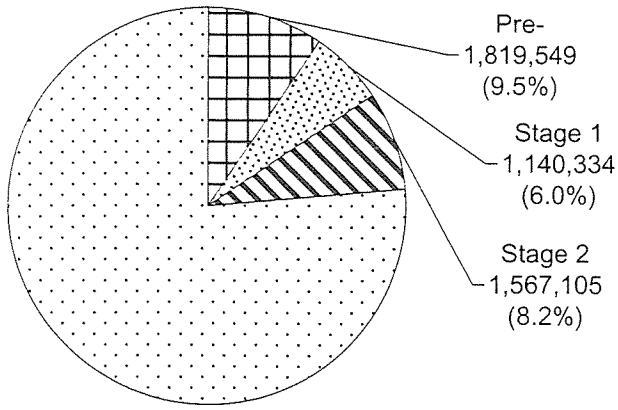

Fig. 1. *Medical costs (Japanese yen per 1,000 persons per month) and percentages of pre-, stage 1, and stage 2 hypertension-related medical costs for the whole population (19,090,468 Japanese yen per 1,000 persons per month [100%]), after a 10-year follow-up period from 1990 to 2001, enrolled in National Health Insurance in Shiga, Japan (men and women combined).*

individuals (stage 2 hypertensives). The hypertension-related medical costs attributable to all hypertensive individuals accounted for 23.7% of the total medical costs.

Cardiovascular mortality after hospitalization for events related to hypertension, such as stroke, may increase medical costs. From an individual viewpoint, medical costs increase as blood pressure increases. However, from the viewpoint of the entire population, mild to moderate hypertension has a large impact on medical economics, because the number of mildly to moderately hypertensive individuals is much greater than that of severely hypertensive individuals. We would expect a 23.7% reduction in total medical costs of the population if each individual were to become normotensive by making lifestyle modifications such as reducing dietary sodium intake, decreasing body weight, and reducing alcohol intake (*8*, *10–20*). Furthermore, it is apparent that anti-hypertensive medications can lower the risk of cardiovascular mortality in hypertensive individuals (*21*). However, the roles played by anti-hypertensive medications in the reduction of hypertension-related medical costs remain to be determined.

The present study has several limitations. Although the participants were selected from a community-based population with a relatively typical health status (*4*), they were limited to National Health Insurance beneficiaries in one area of Shiga Prefecture (*4*). The socio-economic status and lifestyle of these beneficiaries may have had an effect on their health. Additionally, the excess medical costs attributable to hypertension may be associated with metabolic syndrome, which is characterized by a combination of hypertension, high body mass index, diabetes, hyperlipidemia, and other features (*22*). Interestingly, the mean body mass index for those with stage 2 hypertension was the highest among the four blood pressure categories for both sexes, and the prevalence of participants with a history of diabetes with stage 2 hypertension was also the highest among women. However, the present study clearly revealed that hypertension is an important predictor of medical costs in a Japanese population with an extremely low mean body mass index compared to that of Western populations (*23*). In the present study, the details regarding the participants' medical diagnosis (*e.g.*, stroke), medical treatment, and cause of mortality were not available. Thus, it remained unclear which disease in particular directly increased medical costs and events among the hypertensive participants. Furthermore, the extent to which anti-hypertensive medications were effective at reducing hypertension-related medical costs remained unclear with respect to the entire population. Further studies are thus warranted in order to answer such questions. Finally, the results of the present study may not be directly relevant or adaptable to Western populations.

In conclusion, high blood pressure can be a useful predictor of excess medical costs; moreover, hypertension, regardless of grade, may increase the total national medical costs in Japan. In order to reduce hypertension-related medical costs, efforts should be made to prevent hypertension on the basis of both a high-risk strategy and a population strategy.

Acknowledgements

The present study was performed as part of the research project of the Health Promotion Research Committee of the Shiga National Health Insurance Organizations. We are grateful to the Shiga National Health Insurance Organizations.

Appendix

The Health Promotion Research Committee of the Shiga National Health Insurance Organizations

Chairman: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science).
Participating Researchers: Shigeo Yamashita (Kohoku General Hospital), Tomonori Okamura (Department of Health Science, Shiga University of Medical Science), Yoshinori Tominaga (Kohka Public Hospital), Kazuaki Katsuyama (Otsu Public Health Center), Fumihiko Kakuno (Nagahama Public Health Center), Machiko Kitanishi (Higashiomi City Yokaichi Public Health Center).
Associate Researchers: Koshi Nakamura (Department of Health Science, Shiga University of Medical Science), Hideyuki Kanda (Department of Hygiene and Preventive Medicine, Fukushima Medical University).
Secretary Members: Yukio Tobita, Kanehiro Okamura, Kiminobu Hatta, Takao Okada, Michiko Hatanaka (the Shiga National Health Insurance Organizations).

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血清 Alanine Aminotransferase 値と Body Mass Index の組み合わせによる死亡と医療費に対する予測能；滋賀県国保コホートにおける 10 年間の追跡による検討

中村　幸志、岡村　智教、上島　弘嗣（滋賀医科大学社会医学講座福祉保健医学）

【 目的 】血清 Alanine Aminotransferase（以下、ALT）は日常診療で肝疾患のスクリーニングとして利用されており、その上昇要因としてはウィルス性肝炎、アルコール性肝炎、脂肪肝などが考えられる。肥満を伴う血清 ALT の高値は脂肪肝の可能性が高いが、近年、脂肪肝はメタボリックシンドロームを介して循環器疾患の危険因子と考えられており、その結果、肥満を伴う血清 ALT の上昇は死亡率や医療費の上昇要因と考えられる。このように、血清 ALT 値が総死亡や医療費に及ぼす影響は Body Mass Index（以下、BMI）によって修飾される可能性があり、これを追跡調査によって明らかにすることを試みた。

【 方法 】滋賀県内の 7 町 1 村における 40-69 歳の国民健康保険加入者 4,524 名を約 10 年間追跡した。血清 ALT 値によって５つのカテゴリーに分けて（ALT＜20、20≦ALT＜30、30≦ALT＜40、40≦ALT＜50、 50≦ALT（IU/L））、各 ALT カテゴリーの総死亡のハザード比（ALT＜20 を基準）と一人あたりの医療費を評価した。

【 結果 】血清 ALT 値と BMI の間には、総死亡と医療費に対する有意な交互作用がみられた。BMI が中央値（22.7kg/m^2）未満の対象者では、血清 ALT と総死亡および医療費の間に正の段階的な関連がみられた。50≦ALT の総死亡の調整ハザード比は 8.11（95%CI, 3.16-20.82）であった。しかし、BMI が中央値以上の対象者では、血清 ALT と総死亡および医療費の間に有意な差はみられなかった。

【 結論 】日本人における血清 ALT 高値と中央値未満の BMI の組み合わせは過剰な死亡や医療費と関連があり、ウィルス性肝炎や肝硬変などで栄養障害を呈する者などが多く含まれていた可能性がある。逆に、血清 ALT 高値と中央値以上の BMI の組み合わせに多いと思われる脂肪肝は日本人における死亡や医療費の上昇要因ではないと推測された。

表. 総死亡のハザード比と一人あたり医療費（滋賀県国保コホート）

血清ALT (IU/L) カテゴリー	対象者数	総死亡		一人あたり医療費(円/月)	
		ケース数	ハザード比(95%CI)*	算術平均	幾何平均 *
BMI中央値(22.7 (kg/m^2))未満					
ALT<20	2,056	100	1.00	19,882	7,864
20≤ALT<30	146	14	1.42 (0.80-2.52)	26,752	8,136
30≤ALT<40	28	1	0.91 (0.13-6.55)	46,559	13,227
40≤ALT<50	13	2	3.53 (0.85-14.61)	33,276	20,414
50≤ALT	17	5	8.11 (3.16-20.82)	62,956	29,882
			P for trend<0.01		P<0.01
BMI 中央値(22.7 (kg/m^2))以上					
ALT<20	1,832	78	1.00	19,391	8,866
20≤ALT<30	293	6	0.33 (0.14-0.77)	17,926	8,699
30≤ALT<40	72	4	0.88 (0.31-2.49)	20,382	10,883
40≤ALT<50	37	1	0.64 (0.09-4.65)	17,567	11,204
50≤ALT	30	3	1.38 (0.34-5.63)	23,640	9,605
			P for trend=0.91		P=0.49

* 年齢、性、BMI、喫煙、飲酒、収縮期血圧、高血圧治療、総コレステロール、糖尿病を調整

【 研究成果の公表 】

Nakamura K, Okamura T, Kanda H, Hayakawa T, Okayama A, Ueshima H. The Value of Combining Serum Alanine Aminotransferase Levels and Body Mass Index to Predict Mortality and Medical Costs: a 10-year Follow-up Study of National Health Insurance in Shiga, Japan. J Epidemiol 2006; 16: 15-20.

Original Article

The Value of Combining Serum Alanine Aminotransferase Levels and Body Mass Index to Predict Mortality and Medical Costs: a 10-year Follow-up Study of National Health Insurance in Shiga, Japan

Koshi Nakamura,[1] Tomonori Okamura,[1] Hideyuki Kanda,[2] Takehito Hayakawa,[3] Akira Okayama,[4] and Hirotsugu Ueshima[1] for the Health Promotion Research Committee of the Shiga National Health Insurance Organizations.*

BACKGROUND: Evidence suggests that the predictive value of serum alanine aminotransferase (ALT) levels for prognosis, measured by indices such as all-cause mortality and medical costs, may be modified by body mass index (BMI). However, the relationship between serum ALT and BMI has not been satisfactorily elucidated.
METHODS: Four thousand, five hundred and twenty-four community dwelling Japanese National Health Insurance beneficiaries, 40-69 years old, were classified into five categories according to their serum ALT levels (IU/L) (ALT<20, 20≤ALT<30, 30≤ALT<40, 40≤ALT<50 and 50≤ALT) and followed for 10 years. Hazard ratios for all-cause mortality, with reference to the lowest serum ALT category, and medical costs per person were evaluated for each serum ALT category after analyzing interactions between serum ALT levels and BMI for all-cause mortality and for medical costs.
RESULTS: A significant interaction between serum ALT levels and BMI was observed. In participants below the median BMI, positive, graded relationships were identified between serum ALT levels and all-cause mortality as well as between serum ALT levels and personal medical costs. The multivariate-adjusted hazard ratio in the "50≤ALT" category showed an approximately 8-fold increase. However, in the participants at or above the median BMI, no significant relationships between serum ALT levels and all-cause mortality or personal medical costs were identified.
CONCLUSIONS: In these Japanese participants, the predictive value of serum ALT levels for prognosis was more evident if BMI was taken into account. A combination of high serum ALT levels and below median BMI was associated with excess mortality and medical costs.
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Key words: Alanine Transaminase, Body Mass Index, Mortality, Health Expenditure.

Serum alanine aminotransferase (ALT) levels are useful indicators for certain liver diseases, such as viral hepatitis, alcoholic hepatitis, and fatty liver.[1] The serum ALT level is positively associated with all-cause or liver disease mortality,[2] even for ALT values within the clinically normal range.[3] Fatty liver is the most common liver disease and is associated with a slight-to-moderate elevation in serum ALT levels,[1] especially in individuals with a high body mass index (BMI).[4] Fatty liver alone rarely leads to an increase in mortality, because hepatic failure typically occurs only in a few such patients.[1,5] On the other hand, recent studies have

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[1] Department of Health Science, Shiga University of Medical Science.
[2] Department of Hygiene and Preventive Medicine, Fukushima Medical University.
[3] Department of Public Health Science, Shimane University School of Medicine.
[4] Department of Preventive Cardiology, National Cardiovascular Center.
* Members of the committee are listed in the Appendix
Address for correspondence: Koshi Nakamura, Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu City, Shiga 520-2192, Japan. (e-mail: ksnkmr@belle.shiga-med.ac.jp)

shown that fatty liver, which is a marker of visceral fat, is associated with the metabolic syndrome,[6,7] a major risk factor for cardiovascular disease.[8] Therefore, the prognostic value of serum ALT levels might be modified by BMI.

The objectives of the present study were as follows: (1) to clarify the predictive value of serum ALT level for all-cause mortality and for medical costs (a possible marker of chronic, non-fatal liver disease); and (2) to examine whether BMI modified the predictive value of the serum ALT level. To our knowledge, no such cohort study has ever been conducted.

METHODS

Study Design and Participants

A cohort study of Japanese National Health Insurance (NHI) beneficiaries residing in a single geographic area was undertaken with the objective of clarifying the relationships between baseline serum ALT levels and all-cause mortality or medical costs. Medical insurance is compulsory for everyone living in Japan and comprises two systems: the first system is for employees and their dependants; while the second system, the NHI, is for self-employed people (such as farmers and fishermen) and retirees, along with their dependants.[9] The NHI covers 34.7% of the overall Japanese population.[9]

The participants in the study cohort were 4,524 NHI beneficiaries, 40-69 years old, living in seven rural towns and one village in Shiga Prefecture, West Japan, who underwent a baseline survey in 1989-1991. In 1990, the study area had 82,155 residents, including 31,564 individuals aged 40-69 years old, of whom 11,900 were NHI beneficiaries.[10] Therefore, the study participants represented approximately 38% of all NHI beneficiaries aged 40-69 years old in the area. The present study was performed as part of the research work of the Health Promotion Research Committee of the Shiga NHI Organizations. NHI claims were linked with the baseline survey data files at the Shiga NHI Organizations. The participants' names were deleted from the linked data at the Shiga NHI Organizations, thereby protecting the confidentiality of the participants' identities during data analysis. The present study was approved by the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 16-15).

Data Collection

The baseline survey in 1989-1991 was performed using standardized methods according to the Manual for Health Check-ups under the Medical Service Law for the Aged issued by the Japan Public Health Association in 1987.[11] Serum ALT levels were measured by an ultraviolet method. Body height and body weight were measured, and BMI was calculated as body weight (kg) divided by the square of body height (m). Smoking and drinking habits, medications for hypertension, and diabetes mellitus history were evaluated from interviews with well-trained public health nurses. Ex-drinkers were classified as non-drinkers in the present study because we had no information on past drinking history. Blood pressure was measured once using a standard mercury sphygmomanometer on the right arm of each participant in the sitting position after at least a 5-minute rest. Serum total cholesterol levels were measured by an enzymatic method.

The participants were classified into five categories according to their baseline serum ALT levels (IU/L): "ALT<20", "20≦ALT<30", "30≦ALT<40", "40≦ALT<50", and "50≦ALT". In each serum ALT category, we evaluated the hazard ratio for all-cause mortality and medical costs per person after a 10-year follow-up.

We obtained information on beneficiaries who died or those who withdrew from the NHI system and the medical insurance costs for each participant from April in the year following the health check-ups until March 2001 using the monthly NHI claim history files of the Shiga NHI Organizations. Costs were expressed in Japanese *Yen* (i.e. 100 Japanese *Yen* = 0.91 US Dollars or 0.73 Euro, at the foreign exchange rate on September 1, 2005). Medical costs data for each participant differed depending upon the period of subscription to the NHI. Therefore, the medical cost for each participant was divided by the period of subscription, and expressed as costs per month of follow-up. If a beneficiary died or withdrew, follow-up was stopped at that point; if a beneficiary who had withdrawn subsequently re-enrolled in the NHI, follow-up was re-started. Reasons for withdrawal from the NHI included moving to areas outside of Shiga Prefecture and/or transfer to another insurance system.

Data Analysis

A Cox proportional hazards model was used to examine the association between serum ALT category or log-transformed serum ALT levels (test for linear trend) and all-cause mortality. The hazard ratio for all-cause mortality in each serum ALT category was compared to the lowest serum ALT category ("ALT<20"). This model incorporated the following variables as covariates: age, sex, BMI, smoking habit (non-smoker or current smoker), drinking habit (non-drinker, current occasional drinker, or current daily drinker, using two dummy variables and "non-drinker" as a reference), systolic blood pressure, medication for hypertension, serum total cholesterol and history of diabetes mellitus.

Personal total medical costs for each serum ALT category, separated into outpatient and inpatient costs, were expressed using arithmetic means. Furthermore, the cost data were logarithmically transformed to normalize the distribution, with the results expressed as geometric means, because the distribution of real medical costs revealed positive skewness. For the participants with 0 *Yen* (per month), the logarithmic transformations were performed by replacing 0 *Yen* with 1 *Yen*. There were 15 participants with total medical costs of 0 *Yen* and 16 participants with outpatient medical costs of 0 *Yen*. For comparisons of total and outpatient medical costs per person in each serum ALT category, we performed an analysis of covariance, using the same covariates listed above. Because there were 2,600 participants (57.5%) with