Table 2 Age-specific prevalence of chronic kidney disease (CKD) stages in females

	Age						
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
GFR ≥90 ml/min/1.73 m^2							
N	7032	11161	17685	17819	7514	4633	681
Prevalence (%)	67.2	53.3	34.1	22.1	8.6	6.9	4.7
95% CI	66.3–68.1	52.7–54.0	33.7–34.5	21.8–22.4	8.4–8.8	6.7–7.1	4.4–5.0
GFR 60–89 ml/min/1.73 m^2							
N	3402	9575	32834	57354	67071	41410	7139
Prevalence (%)	32.5	45.8	63.3	71.1	76.6	61.4	49.2
95% CI	31.6–33.4	45.1–46.4	62.9–63.7	70.8–71.4	76.4–76.9	61.0–61.7	48.4–50.0
GFR 50–59 ml/min/1.73 m^2							
N	19	168	1206	4822	10601	15859	3385
Prevalence (%)	0.2	0.8	2.3	6.0	12.1	23.5	23.3
95% CI	0.0–0.3	0.7–0.9	2.2–2.5	5.8–6.1	11.9–12.3	23.2–23.8	22.6–24.0
GFR 40–49 ml/min/1.73 m^2							
N	2	13	98	521	1939	4333	2367
Prevalence (%)	0.0	0.1	0.2	0.6	2.2	6.4	16.3
95% CI	0.0–0.1	0.0–0.1	0.2–0.2	0.6–0.7	2.1–2.3	6.2–6.6	15.7–16.9
GFR 30–39 ml/min/1.73 m^2							
N	1	2	20	80	263	927	710
Prevalence (%)	0.0	0.0	0.0	0.1	0.3	1.4	4.9
95% CI	0.0–0.0	0.0–0.0	0.0–0.1	0.1–0.2	0.5–0.6	1.4–1.7	3.8–4.6
GFR <30 ml/min/1.73 m^2							
N	1	5	16	79	133	318	232
Prevalence (%)	0.0	0.0	0.0	0.1	0.2	0.5	1.6
95% CI	0.0–0.0	0.0–0.1	0.1–0.1	0.1–0.1	0.1–0.2	0.4–0.5	1.4–1.8

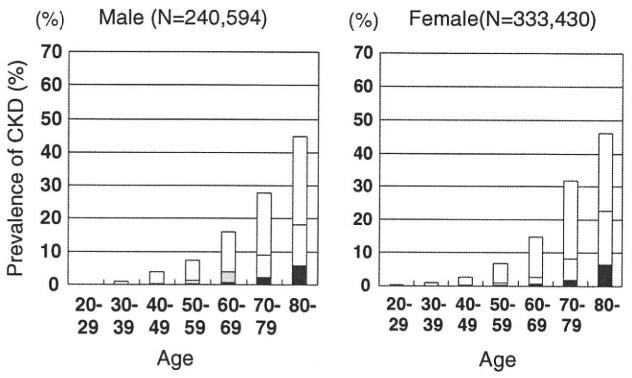

Fig. 2 Prevalence rates for CKD stages 3 to 5 for each age group in males and females in the study population. The prevalence of CKD (%) (as defined by <60 ml/min/1.73 m^2) for each age group was calculated separately for males and females in the study population. *White column* GFR 50–59 ml/min/1.73 m^2, *striped column* GFR 40–49 ml/min/1.73 m^2, *black column* GFR 40 or less ml/min/1.73 m^2

of CKD stages 1, 2, 3, 4 + 5 in the Japanese adult population in 2005 were 0.61, 1.71, 10.74, and 0.23 million, respectively (Table 3).

Prevalence of CKD stages 3–5 in proteinuric and hypertensive populations

The prevalence of CKD stages 3–5 was examined in proteinuric and hypertensive populations (Fig. 3A, B). The prevalence of CKD stages 3–5 was significantly higher in subjects with proteinuria ($P < 0.0001$) in all age groups, and in subjects with hypertension ($p < 0.01$ to $p < 0.0001$) in all age groups except for 80 years or older and in females in their 20s.

Prevalence of CKD stages 3–5 in the diabetic population

The prevalence of CKD stages 3–5 was examined in subjects with HbA1c ≥6.0 (Fig. 3C). The prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) was significantly lower in the diabetic population in some age groups (Fig. 3C), while its prevalence in subjects with reduced renal function (GFR <40 ml/min/1.73 m^2) was significantly higher in diabetic individuals in their 50s and 60s (Fig. 3D).

Table 3 Prevalence rates of CKD stages in Japanese adults (20 years or older), and estimated number of CKD cases per CKD stage based on the 2005 census

GFR (ml/min/1.73 m^2)	Total	Proteinuria (+)	Proteinuria (−)
Prevalence rate (%)			
GFR ≥90	27.8	0.6	27.2
60–89	61.6	1.7	60.0
30–59	10.4	0.8	9.6
<30	0.2	0.1	0.1
Stage 3			
50–59	7.6	0.4	7.2
40–49	2.3	0.3	2.0
30–39	0.6	0.1	0.4
Estimated number of Japanese adults in 2005			
GFR ≥90	28639274	605313	28033961
60–89	63576938	1708870	61868068
30–59	10743236	8238881	9919355
<30	236569	125190	111379
Stage 3			
50–59	7809261	425146	7384116
40–49	2363987	267158	2096828
30–39	569988	131577	438411

Prevalence of hyperfiltration in the diabetic population

The prevalence of subjects with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.05$ to $p < 0.0001$) at ages 30–79 (Fig. 4). The distribution of GFR in the diabetic population was shifted to higher values than for the population with HbA1c <6.0%. A representative figurefor ages 50–59 is shown in Fig. 5. The prevalence of hypertension with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.0001$) compared with the nondiabetic population (Fig. 5).

Comparison of GFR in the general population between Japan and the USA

The distribution of GFR across the whole Japanese population, calculated on the basis of the census from 2005, is shown in Fig. 6. Japan is an aging society, and the age pyramid for the population is shifted towards the elderly. An aging population tends to have low GFR, and this aging affects the distribution of GFR in the country. We recalculated the distribution of GFR by age adjusting the Japanese population to the 2005 US population estimate. As shown in Fig. 6, the distribution of GFR in the Japanese population is shifted to higher values after the correction for aging affects.

Discussion

In this study, we examined the prevalence of CKD for participants in a nationwide annual health check program in 11 prefectures of Japan using a new equation for estimating GFR from serum creatinine in the Japanese population [7]. The prevalence rates of CKD stages 1, 2, 3, and 4 + 5 in the study population of 574,024 were 0.6, 1.7, 10.4 and 0.2%, which resulted in predictions of 0.6, 1.7, 10.7 and 0.2 million patients, respectively, nationwide based on the census from 2005. Proteinuria resulted in a preponderance of declining GFR. The prevalence of concurrent CKD was significantly higher in the hypertensive population than in the population without hypertension, particularly in males. The diabetic population showed a preponderance of hyperfiltration, defined as GFR ≥120 ml/min/1.73 m^2.

The prevalence of CKD stages 1–5 has been reported for several countries (Fig. 7). According to the reliable and unbiased NHANES III surveys conducted from 1988 to 1994, from 1999 to 2000 [11], and from 1999 to 2004 [9], the prevalence of CKD remained the same between the first two surveys but increased for the third screening. For CKD stages 3 and stage 4, the prevalences were 4.2 and 0.19% in the first survey and 3.7 and 0.13% in the second survey, respectively [11]. In the third survey, the prevalences of CKD stages 1, 2, 3, 4 were 1.78, 3.24, 7.69, 0.35%, respectively (Fig. 7) [9], suggesting that the prevalence rates of CKD stages 3 and 4 increased in the USA. In Nord-Trondelag, a county in Norway, the prevalences were 4.2% for CKD stage 3 and 0.2% for CKD stages 4 + 5 [12]. The reported prevalence of CKD varies among countries in Asia. In Taiwan, about half a million participants were examined, and the MDRD equation was applied without correction using an ethnic coefficient; here, the prevalence rate of CKD was 11.9%, and those for CKD stages 1, 2, 3, 4, and 5 were 1.0, 3.8, 6.8, 0.2, 0.1%, respectively [13]. In Beijing, China, the prevalence of CKD was obtained using the original Chinese equation for estimating GFR, and the prevalences of CKD stages 1, 2, 3, 4 and 5 were 5.5, 3.3, 1.3, 0.0010 and 0.0003%, respectively [14]. Overall, about 10–13% of the population exhibited CKD in these countries. The different prevalences of CKD stages 1 and 2 among the countries appears to be mainly due to how proteinuria is defined. The definition of albuminuria differed considerably between countries. China defined albuminuria as 17 mg/g Cr [14], while the USA defined it as 30 mg/g Cr [9]. Taiwan defined proteinuria as (±) on dipstick test [13], while Japan defined a dipstick of (1+) as proteinuria. This difference in definition must affect the the prevalences of CKD stages 1 and 2 considerably. In addition, the methods used for creatinine measurement varied considerably among countries. We advocate the use of the

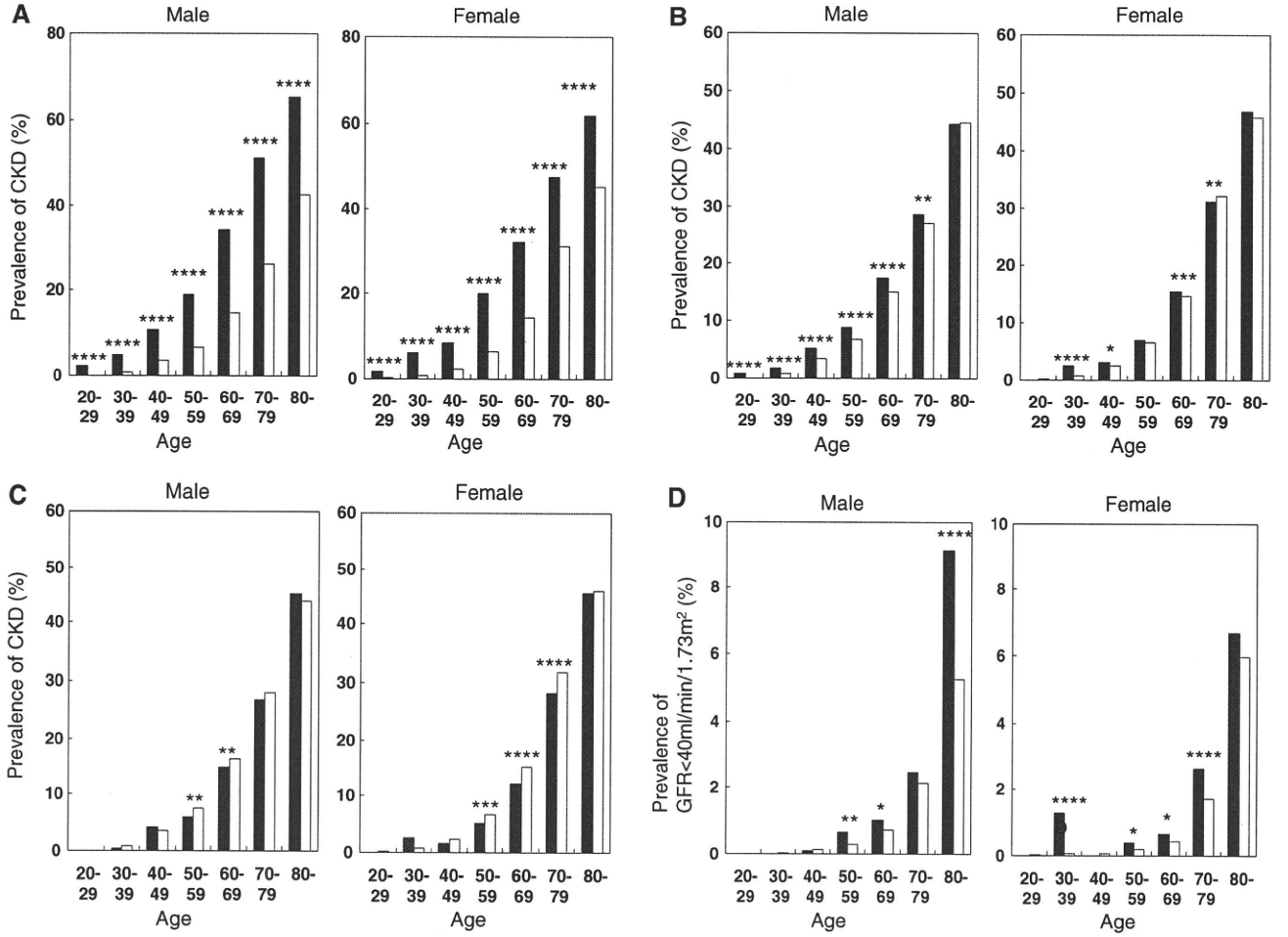

Fig. 3 Prevalence of CKD in proteinuria, hypertensive and diabetic populations. The prevalence of CKD (defined by GFR <60 ml/min/1.73 m^2) in the proteinuric population, shown by the *black column*, was compared with that in the population without proteinuria, shown by the *white column*, for each generation (**a**). Proteinuria was defined as 1+ or more by dipstick test. Prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) in the hypertensive population, shown by the *black column*, was compared with that in the population without hypertension, shown by the *white column*, for each generation (**b**). Hypertension was defined as a blood pressure of 140/90 mmHg or over. Prevalences of GFR <60 ml/min/1.73 m^2 and of GFR <40 ml/min/1.73 m^2 in the diabetic population (*black columns*) are compared with that in the nondiabetic population (*white columns*) (**c**, **d**). Diabetes was defined as HbA1c ≥6.0%. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$ versus individuals without cormobidity of proteinuria (**a**), hypertension (**b**), or diabetes (**c**, **d**)

following in order to compare the prevalence of CKD among different countries. First, the definition and method of measuring proteinuria must be unified across countries. Albuminuria or albuminuria-to creatinine ratio, which is scientifically more reliable than the dipstick test, should be used for proteinuria. Repeated measurements are recommended. Second, the serum creatinine that is used to estimate GFR should be measured by isotope diluted mass spectrometry (IDMS)-traceable creatinine assay. Third, the equation used to estimate GFR for each ethnic group must be established. Another alternative is to establish an IDMS-traceable MDRD equation [15] with an ethnic coefficient. The measurement of proteinuria by dipstick test and serum creatinine is accurate enough for daily practice and screening, but international comparisons of the prevalence of CKD should be done by a unified standard method involving the measurement of albuminuria and serum creatinine with an IDMS-traceable creatinine assay.

Our aging society results in a decline in the average GFR in this country. More than 20% of the Japanese population is over 60 years old, and the elderly population (over 75 years old) is much higher than in other countries. Because of this increased average age, the prevalence of CKD is higher in Japan. In fact, the distribution of the age-adjusted eGFR was shown to be similar for Japan and the USA (Fig. 6).

The prevalence of proteinuria increased as GFR decreased (Table 3) in this study. However, the prevalences of proteinuria in CKD stages 3 and 4 + 5 were 7.7 and 52.9%, respectively. In data from a mass health

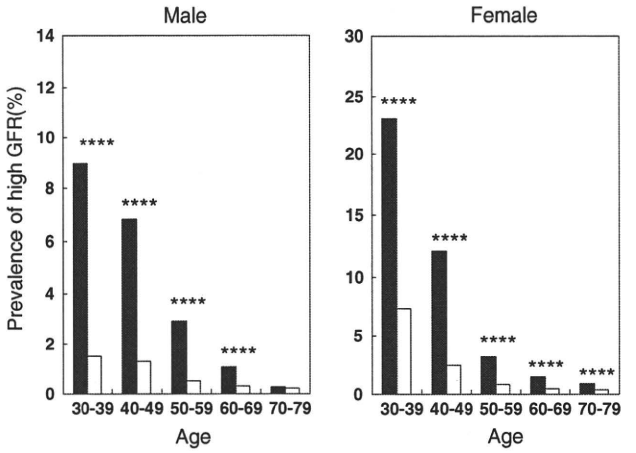

Fig. 4 Prevalence of GFR ≥120 ml/min/1.73 m^2 in the diabetic population. Individuals with diabetes as defined by HbA1c ≥6.0% are represented by the *black column*. Individuals with HbA1c <6.0% are represented by the *white column*. ****$p < 0.0001$ versus individuals with HbA1c <6.0%

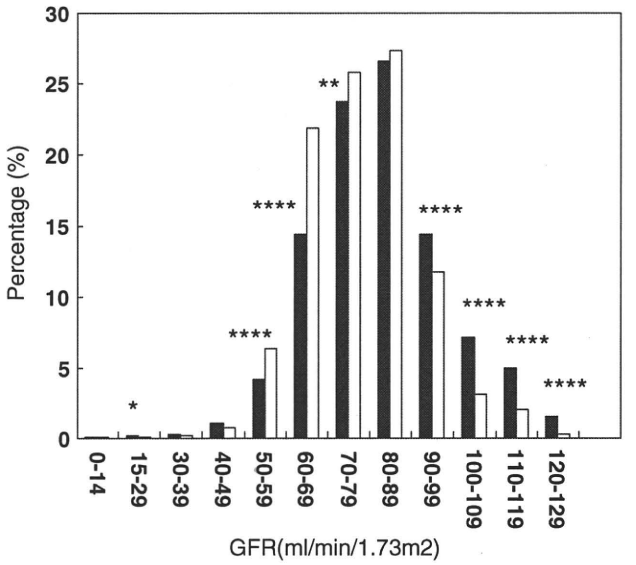

Fig. 5 Distribution of estimated GFR in populations with HbA1c ≥6.0% and HbA1c <6.0%. Distributions of estimated GFR are shown separately for diabetic individuals (defined as HbA1c ≥6.0%) and for individuals with HbA1c <6.0%. The population with diabetes is represented by the *black column*, and individuals with HbA1c <6.0% are represented by the *white column*. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ versus individuals with HbA1c <6.0%

screening in Okinawa, proteinuria (defined as a dipstick urinalysis result of 1+ or more) was a strong predictor of ESKD [16]. The rate of decline of GFR in individuals with proteinuria was more than twofold faster than that in individuals without proteinuria [17]. This may suggest that most of CKD stage 3 and half of Japanese stage 4 + 5 CKD patients without proteinuria may progress slowly to ESKD and may not even reach ESRD during their

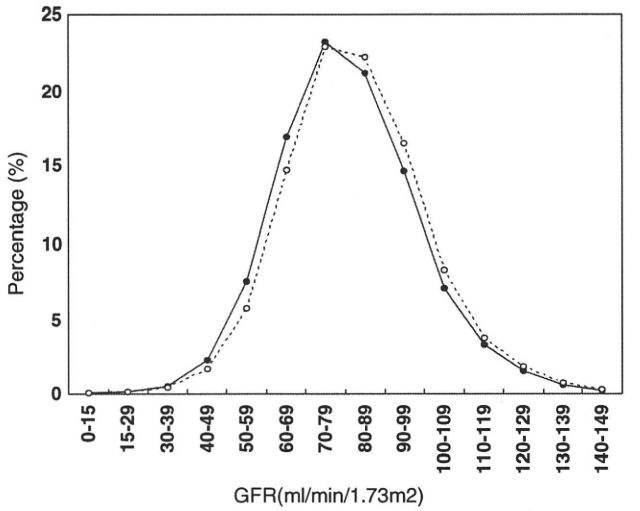

Fig. 6 Distribution of GFR in the Japanese general population. The distribution of estimated GFR for Japanese is shown by the *solid line*. We then recalculated the distribution of the GFR by age adjusting the Japanese population to the US population, as shown by the *dotted line*

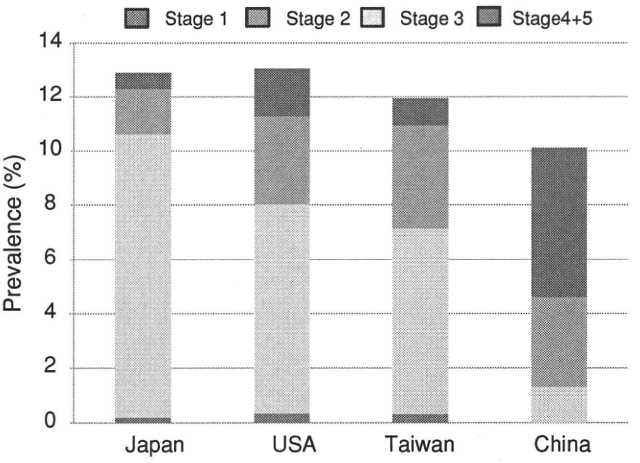

Fig. 7 Prevalences of CKD stages 1, 2, 3, and 4 + 5 in Japan, USA, Taiwan and China. The prevalence of each stage of CKD was obtained from previous publications. In Japan, the prevalence of CKD was estimated from accumulated data on 570,244 individuals aged 20 and over in the annual health check program in 2005. Proteinuria was evaluated by dipstick test, where 1+ and over was defined as proteinuria. In the USA, the prevalence of each stage of CKD was studied using data on nationally representative samples from 13,233 adults aged 20 and over taken from 1999 to 2004 [9]. The presence of albuminuria was estimated from the albumin-to-creatinine ratio, and microalbuminuria was defined as 30 mg/g creatinine. In Taiwan, the prevalence of each stage of CKD was estimated based on data from a private firm on 462,293 individuals aged 20 and over, obtained from 1994 to 2007 [13]. Proteinuria was evaluated by dipstick test, and (± or 1+) was defined as minimal proteinuria and (2+ and over) as overt proteinuria. In China, representative samples from 13,925 individuals aged 18 and older were analyzed [14]. Albuminuria was measured, and microalbuminuria was determined as ranging from 17 to 250 mg/g creatinine for males and from 25 to 355 mg/g creatinine for females

lifetimes. Further study is required to obtain risk stratifications for the stage 3 and 4 populations.

In the diabetic population, the prevalences of high GFR (GFR $\geq$120 ml/min/1.73 m^2) and low GFR (<40 ml/min/1.73 m^2) were higher than those in the population with HbA1c <6.0%, suggesting that diabetes shifts the distribution of GFR to the high and low ranges. We speculated that hyperfiltration plays a major role in this shift, and may contribute to the rapid decline in GFR in diabetic individuals. Hyperfiltration may aid the development of microalbuminuria in type 1 diabetic patients. Amin and colleagues reported a strong relationship between the risk for the development of microalbuminuria in individuals who had diabetes for five and ten years and the development of glomerular hyperfiltration in individuals who had diabetes for five years, independent of glycemic control [18].

The prevalence of CKD comorbid with other concurrent conditions in the Japanese population was similar to the corresponding prevalences in the US and Chinese populations. The prevalence of CKD was higher among hypertensive and diabetic individuals in the white US population, as previously reported [19]. The prevalence of CKD was reported to increase in hypertensive and diabetic populations in Chinese [20]. This study also supports the notion that prevalence of CKD comorbidity is higher in hypertensive and diabetic populations than in the normal population.

We previously reported that the rate of decline of GFR was more than twofold faster when the eGFR was less than 50 ml/min/1.73 m^2 in adults [17]. From the viewpoint of risk stratification for progression to ESKD, we estimated that 3.1% of the adult population (3.17 million) had GFR <50 ml/min/1.73 m^2 in 2005 (Table 3). Presence of proteinuria is a strong risk factor for ESKD and CVD. From Table 3, 2.74 million (2.7%) of the adult population have proteinuria and GFR >50 ml/min/1.73 m^2. Taken together, the CKD population with risk of progression to ESKD is predicted to be 5.91 million, 5.8% of the adult population in 2005.

The limitations of the present study are as follows. First, the study cohort was a proportion of the general population that participated in an annual health check program; it was not representative of the whole Japanese population. Second, the serum creatinine was not measured at a single laboratory, so the values of serum creatinine may have drifted. Third, we only measured proteinuria once. Therefore, the presence of proteinuria was confirmed, not persistent proteinuria.

In conclusion, about 13% of Japanese adult population, approximately 13.3 million people, were predicted to have CKD in 2005. From the viewpoint of risk stratification to progression to ESKD, about 5.8% of the adult population—approximately 6 million people—who have proteinuria or GFR <50 ml/min/1.73 m^2 are estimated to have CKD in Japan.

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ORIGINAL ARTICLE

Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy

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Abstract
Background Tonsillectomy and steroid pulse (TSP) therapy was proposed as a curative treatment for IgA nephropathy by Hotta et al. (Am J Kidney Dis 38:736–742, 2001) based on data that about 50% of patients achieved clinical remission (CR) of urinary abnormalities.

Materials and methods As a primary survey, we sent a questionnaire and letter to 848 hospitals in Japan, each of which employed a Fellow of the Japanese Society of Nephrology between October and December of 2006, in order to gather information about the prevalence and efficacy of TSP therapy for patients with IgA nephropathy. As a secondary survey, we collected data from both low- and

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high-CR-rate groups to determine which factors predicted resistance to TSP therapy.

Results A total of 2,746 patients received TSP therapy between 2000 and 2006. The CR rates, calculated by measuring urinary criteria 6 and 12 months after TSP therapy, were 32.0% (347/1,085) and 45.6% (452/991), respectively. Analysis of the 30 hospitals in which TSP therapy had been performed on at least ten patients revealed that the CR rates varied from below 10% to 100%. A secondary survey of ten hospitals revealed that, after correction of the CR rate from each hospital, patients could be categorized into three groups: those with a low CR rate (122 patients in four hospitals), a middle CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals). The CR rate of all patients ($N = 303$) was 54.1%. A comparison of patient data between the low- and high-CR-rate groups showed a significant difference in age at onset (years; $P = 0.05$), amount of proteinuria (g/day; $P = 0.02$), total protein (g/dl; $P = 0.02$), pathological grade ($P = 0.009$), and prognostic score as described by Wakai et al. [Nephrol Dial Transplant 21:2800–2808, 2006, ($P = 0.04$)]. Univariate analysis revealed that there was a significant difference between non-CR and CR subgroups in duration from diagnosis until TSP therapy (6.9 ± 6.8 versus 5.3 ± 5.2 years; $P = 0.02$), amount of proteinuria (1.5 ± 1.6 versus 0.8 ± 0.8 g/day; $P < 0.0001$), serum creatinine (0.99 ± 0.40 versus 0.87 ± 0.34 mg/dl; $P = 0.006$), pathological grade ($P = 0.0006$), and Wakai et al.'s prognostic score (37.4 ± 17.8 versus 28.1 ± 15.1; $P < 0.0001$). A multivariate logistic analysis demonstrated that resistance to TSP therapy depends on age at onset, amount of proteinuria, hematuria grade, and pathological grade, and a score predicting resistance to TSP therapy could be derived by the formula: $[(-0.0330) \times (\text{age}) + (0.4772) \times \log(\text{amount of proteinuria}) - (0.0273) \times (\text{hematuria grade: 0, 1, 2, and 3}) + (0.7604) \times (\text{pathological grade: 1, 2, 3, and 4}) - 0.1894]$. A receiver operating characteristic (ROC) curve showed that patients with a resistance score of greater than -0.02 easily resist TSP therapy (sensitivity 69%, specificity 75%, positive likelihood ratio 2.76).

Conclusion TSP therapy shows promise as a treatment that can bring about CR of urinary abnormalities, but unfortunately the average CR rate is about 50% at 1 year after treatment. Predictive factors for resistance to TSP therapy are age at onset, amount of proteinuria, hematuria grade, and pathological grade. The present study suggests that patients with either early-stage or mild to moderate IgA nephropathy easily achieve CR following TSP therapy, whereas patients with late-stage or severe disease are prone to TSP therapy resistance.

Keywords IgA nephropathy · Tonsillectomy · Steroid pulse therapy · Resistance to tonsillectomy and steroid pulse therapy

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Introduction

IgA nephropathy is the most common type of glomerulonephritis in the world, and is characterized by mesangial proliferation with predominantly IgA deposition. A study of patient prognosis showed that, 20 years after disease onset, about 30% of patients had undergone spontaneous remission with a normalized urinalysis and stable kidney function, about 30% had retained stable kidney function but persistent urinary abnormalities, and almost 40% had experienced a progressive course that necessitated dialysis. On the other hand, renal survival rate 20 years after diagnosis is about 60% [1, 2].

Steroid pulse therapy using intravenous administration of 1,000 mg/day prednisolone has been reported to be efficacious at preventing disease progression, with 98% of steroid pulse therapy patients remaining stable 10 years after diagnosis as compared with 65% of placebo-treated patients [3].

There are controversial results about the efficacy of tonsillectomy alone for IgA nephropathy patients. Rasche et al. [4] reported that the renal survival rate of a tonsillectomy group was almost 60% that of a control group at 10 years. On the other hand, Xie et al. [5] demonstrated that the renal survival rate of a tonsillectomy group 20 years after diagnosis was 89.6% compared with 63.7% in a control group, even though there was no significant difference between groups at 10 years.

A retrospective study by Hotta et al. [6] revealed that tonsillectomy and steroid pulse (TSP) therapy induced clinical remission (CR), or absence of urinary abnormalities, in 48% of patients after an observation period of 82.3 ± 38.2 months. Furthermore, the renal survival rate of patients who achieved CR was 100% at 10 years, compared with 77.4% of the group who did not achieve CR.

Following the publication of the above results in 2001, TSP therapy began to be widely used in Japan before a consensus had been reached. The purpose of this study is to determine the prevalence of TSP therapy for patients with IgA nephropathy in Japan, and to identify the factors that predict resistance to TSP therapy 1 year after treatment.

Methods

Primary survey about prevalence of TSP therapy

We sent a questionnaire about TSP therapy for IgA nephropathy patients to 848 Fellows of the Japanese Society of Nephrology. The recipients of the survey worked in hospitals, excluding outpatient and dialysis clinics, between October 27 and December 28, 2006. The questionnaire included the items listed below.

Q1 Have you ever treated IgA nephropathy patients with tonsillectomy and steroid pulse (TSP) therapy? Please continue if you answered "yes."

Q2 When did you start TSP therapy for IgA nephropathy patients?

Before 2000, how many cases did you have?
In 2000, how many cases did you have?
In 2001, how many cases did you have?
In 2002, how many cases did you have?
In 2003, how many cases did you have?
In 2004, how many cases did you have?
In 2005, how many cases did you have?
In 2006, how many cases did you have?

Q3 How many of the patients who received TSP therapy achieved CR within 6 months of starting treatment?

Q4 How many of the patients who received TSP therapy achieved CR within 12 months of starting treatment?

If you answered "no" in Q1

Q4 Are you currently planning to begin TSP therapy for patients with IgA nephropathy?

CR criteria were determined by urinary analysis.

Remission of proteinuria was defined as negative (−) or trace (±) protein on urine dipstick, while remission of occult hematuria was specified as absence of blood on dipstick and urinalysis. CR was defined as complete resolution of both proteinuria and hematuria.

Secondary survey of hospitals in which more than ten patients with IgA nephropathy received TSP therapy

We collected clinical and laboratory data from ten hospitals whose CR rate was over 70% or below 30%, in order to clarify the predictive factors for resistance to TSP therapy. This data included patient age, sex, duration from diagnosis to TSP therapy, grade of proteinuria on dipstick, amount of proteinuria, hematuria grade on dipstick, systolic blood pressure, diastolic blood pressure, serum creatinine, serum total protein, pathological activity score, and prognostic score as outlined by Wakai et al. [7]. We also collected information about the individuals who performed the tonsillectomies and about the steroid amount and pulse timing used in TSP therapy.

Statistical analysis

1. Numerical data are expressed as mean ± standard deviation (SD) and categorical data are reported as proportions. The baseline characteristics of the two patient groups, including age, amount of proteinuria, systolic and diastolic blood pressures, serum creatinine, total protein, and prognostic score [7], were compared using Student's t test, while Fisher's test was used to assess sex, and Mann–Whitney's U test was used to assess urinary occult blood reaction and pathological grade. All P values were two-sided, with $P < 0.05$ indicating statistical significance.
2. A stepwise logistic regression model was performed using each of the predictor variables. All analyses were performed with SAS® software version 9.1 (SAS Institute, Inc., Cary, NC, USA). A receiver operating characteristic (ROC) curve analysis was used to determine the cutoff point on the items which showed significant difference.

Results

Prevalence of TSP therapy in Japan

Of the 848 fellows queried, 317 replied on behalf of the hospitals at which they worked. Despite the response rate of 37.4%, we believe that the present data provides a solid foundation for conclusions about TSP therapy use nationwide because responding hospitals provided the primary source of kidney disease care in their local communities.

1. The number of hospitals performing TSP therapy

Of the 317 responding hospitals, 128 (40.4%) performed TSP therapy for patients with IgA nephropathy.

2. The number of patients receiving TSP therapy in Japan

In 2000 and 2001, an annual total of 140 and 160 patients received TSP therapy, respectively, which included 100 patients per year at Sendai Shakaihoken Hospital. After 2002, the total number of patients treated annually with this modality increased gradually to 220 in 2002, 340 in 2003, 520 in 2004, 690 in 2005, and 620 in 2006. The total number of patients who received TSP therapy between 2000 and 2006 reached 2,746 (Fig. 1).

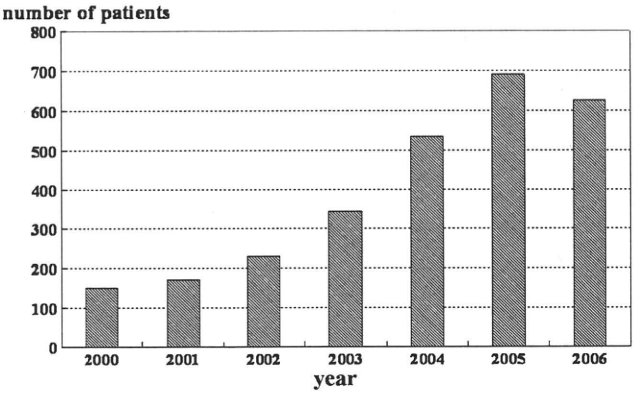

Fig. 1 Prevalence of TSP therapy in Japan. More than 600 IgA nephropathy patients per year received TSP therapy in 2005 and 2006. The total number of patients who have received TSP therapy since 2000 has now reached 2,746

Table 1 CR rate of tonsillectomy and steroid pulse therapy in patients with IgA nephropathy

Months after tonsillectomy	Patient number	Patients in clinical remission	Clinical remission rate (%)
6	1085	347	32.0
12	991	452	45.6

CR rate 1 year after TSP therapy

Of the 2,746 patients who received TSP therapy between 200 and 2006, 1,081 and 991 were evaluated for CR by urinary criteria at 6 and 12 months after TSP therapy, respectively. To eliminate any bias, this analysis excluded the 100 patients per year who received TSP therapy at Sendai Shakaihoken Hospital. The CR rates at 6 and 12 months were 32% (347/1,085) and 45.6% (452/991), respectively (Table 1).

Distribution of CR rate at the 30 hospitals performing TSP therapy on more than ten patients

Figure 2 demonstrates that the CR rate varied from less than 10% to greater than 90% at different hospitals. The high-CR-rate group (greater than 70% CR) consisted of six hospitals, the average-CR-rate group (31–60% CR rate) consisted of 16 hospitals, and the low-CR-rate group (below 30% CR) consisted of 8 hospitals.

Secondary survey

We collected patient data from ten hospitals at which the CR rate was over 70% or below 30%, although the CR rates in four out of the ten hospitals increased or decreased to between 50% and 70% after the addition of new patients.

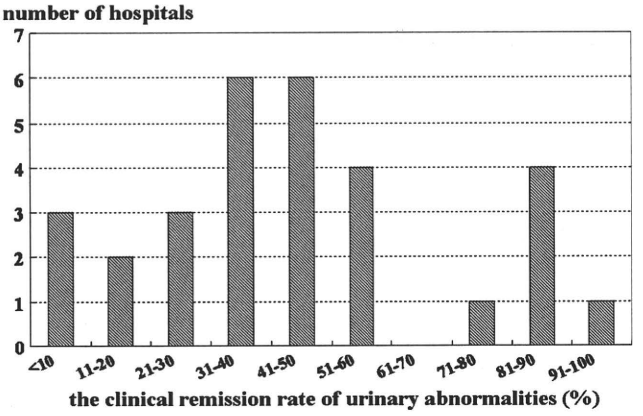

Fig. 2 The distribution of the CR rate at the 30 hospitals performing TSP therapy on more than ten patients. The *X*-axis defines the CR rate (%) and the *Y*-axis indicates the number of hospitals

We divided the ten hospitals into three groups, those with a low CR rate (122 patients in four hospitals), a moderate CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals).

Detailed information about tonsillectomy surgeons and intravenous steroid amount and administration times

There was no difference in surgeons between the low-CR-rate and high-CR-rate groups, because both groups included physicians whose experience levels varied from younger doctors in their third postgraduate year to oto-laryngology specialists who had performed over 200 tonsillectomies each. There was also no significant difference in the amount of intravenous methylprednisolone administered, as all hospitals used 500 mg/day for 3 days as described in Hotta's original report [6]. In the low-CR-rate group, one hospital administered one course of steroids and three hospitals dispensed three courses, while in the high-CR-rate group two hospitals administered three courses. Thus, we found no significant difference between groups in either the surgeons who performed the tonsillectomies nor in the steroid pulse therapy protocols.

Comparison of patient data between low- and high-CR-rate groups

A comparison of patient data between the low- and high-CR-rate groups showed a significant difference in age at onset (30.3 ± 11.1 versus 33.5 ± 13.7 years; $P = 0.05$), amount of proteinuria (1.3 ± 1.4 versus 0.9 ± 0.7 g/day; $P = 0.02$), total protein (6.7 ± 0.6 versus 6.5 ± 0.6 g/dl; $P = 0.02$), pathological grade ($P = 0.009$), and prognostic score as described by Wakai et al. [7] (34.5 ± 15.9 versus 28.8 ± 21.3; $P = 0.04$) (Table 2).

Table 2 Patient profile among the low-, middle-, and high-CR-rate groups and a comparison of patient data between the low- and high-CR-rate groups

	Low-CR-rate group CR rate 30.3%	Middle-CR-rate group CR rate 57.7%	High-CR-rate group CR rate 79.6%	*P*
Number of patients	122	78	103	
Male/female	52/70	41/37	37/66	n.s.
Age (years)	30.3 ± 11.1	40.6 ± 15.1	33.5 ± 13.7	0.05
Years until TSP therapy	7.2 ± 6.2	4.4 ± 5.2	5.9 ± 5.6	n.s.
Proteinuria (g/day)	1.3 ± 1.4	1.2 ± 1.6	0.9 ± 0.7	0.02
Hematuria (0: 1+: 2+: 3+)	7:12:30:73	4:10:25:39	4:25:20:54	n.s.
Systolic BP (mm Hg)	118 ± 16	123 ± 14	121 ± 15	n.s.
Diastolic BP (mm Hg)	73 ± 14	75 ± 11	72 ± 11	n.s.
Cr (mg/dl)	0.94 ± 0.36	0.91 ± 0.27	0.93 ± 0.44	n.s.
TP (g/dl)	6.7 ± 0.6	6.7 ± 0.5	6.5 ± 0.6	0.02
Pathological grade (I: II: III: IV)	6:14:47:55	2:15:40:21	4:32:41:26	0.009
Prognostic score by Wakai et al. [7]	34.5 ± 15.9	32.6 ± 14.1	28.8 ± 21.3	0.04

Table 3 Comparison of non-CR and CR subgroup patient data in all patients who received TSP therapy

	All patients		*P*
	CR rate 54.1%		
	Non-CR	CR	
Number of patients	139	164	
Male/female	61/78	69/95	n.s.
Age	33.1 ± 13.2	34.8 ± 14.1	n.s.
Years until TSP therapy	6.9 ± 6.8	5.3 ± 5.2	0.02
Proteinuria (g/day)	1.5 ± 1.6	0.8 ± 0.8	<0.0001
Hematuria (0: 1+: 2+: 3+)	11:19:33:76	4:28:42:90	n.s.
Systolic BP (mm Hg)	121 ± 15	119 ± 15	n.s.
Diastolic BP (mm Hg)	75 ± 15	72 ± 11	n.s.
Cr (mg/dl)	0.99 ± 0.40	0.87 ± 0.34	0.006
TP (g/dl)	6.6 ± 0.6	6.7 ± 0.6	n.s.
Pathological grade (I: II: III: IV)	5:14:64:56	7:47:64:46	0.0006
Prognostic score by Wakai et al. [7]	37.4 ± 17.8	28.1 ± 15.1	<0.0001

Analysis of factors predicting resistance to TSP therapy

The CR rate was 54.1% in all patients ($N = 303$). In comparing data from patients in the non-CR and CR subgroups, a significant difference was observed in duration from diagnosis until TSP therapy (6.9 ± 6.8 versus 5.3 ± 5.2 years; $P = 0.02$), amount of proteinuria (1.5 ± 1.6 versus 0.8 ± 0.8 g/day; $P < 0.0001$), serum creatinine (0.99 ± 0.40 versus 0.87 ± 0.34 mg/dl; $P = 0.006$), pathological grade ($P = 0.0006$), and prognostic score (37.4 ± 17.8 versus 28.1 ± 15.1; $P < 0.0001$) (Table 3).

Table 4 Stepwise logistic regression analysis of non-CR 1 year after TSP therapy

	Coefficients	OR	95% CI	*P* value
Age at onset	−0.0330	0.97	0.95–0.99	0.003
Amount of urinary protein (log) (g/day)	0.4772	1.61	1.23–2.12	<0.001
Hematuria	−0.2731	0.76	0.56–1.04	0.08
Pathological grade	0.7604	2.14	1.50–3.06	<0.001

Intercept −0.1894

Multivariate logistic analysis

The factors predicting resistance to TSP therapy were identified as age at onset, amount of proteinuria, hematuria grade, and pathological grade (Table 4). Resistance correlated positively with the score derived from the following formula: [(−0.0330) × (age) + (0.4772) × log (amount of urinary protein) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894].

Efficacy [3] and limitation of the resistance score

An ROC curve analysis revealed that patients with a resistance score of greater than −0.02 in the current study more easily resisted TSP therapy (sensitivity 69%, specificity 75%; Fig. 3).

Discussion

The present study demonstrates five points. The first is that about 600 IgA nephropathy patients per year received TSP

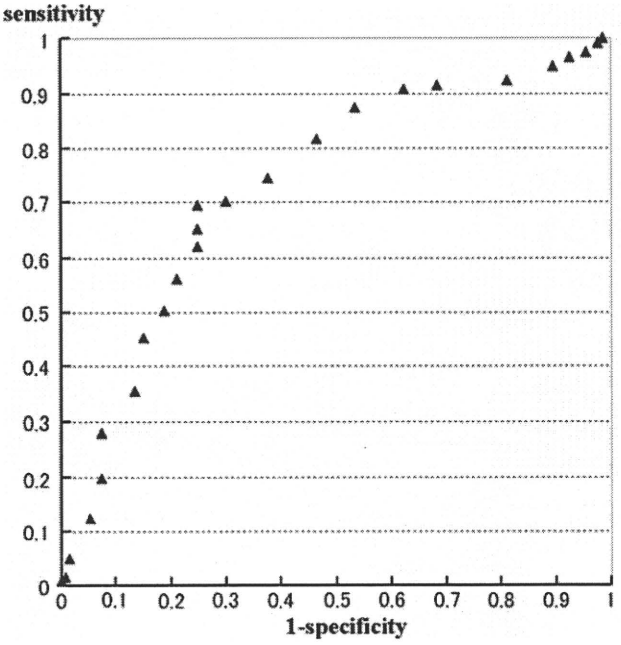

Fig. 3 Resistance correlated positively with the score derived from the following formula: [(−0.0330) × (age) + (0.4772) × log (amount of urinary protein) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894]. The cutoff value is −0.02, with a sensitivity of 69%, specificity of 75%, and positive likelihood ratio of 2.76

therapy in Japan since 2001, at which time the efficacy of TSP therapy was reported in an international journal. The second is that the CR rate 1 year after TSP therapy was almost 50%, which confirms the data of original report. The third is that CR rates ranged from 10% to 100% in each hospital that performed TSP therapy on at least ten patients. The fourth is that low- and high-CR-rate groups differed considerably in age at onset, amount of proteinuria, total protein, pathological grade, and Wakai et al. prognostic score. This suggests that the indication criteria for TSP therapy in the high-CR-rate group may differ from that in the low-CR-rate group. The fifth point is that the factors that predicted resistance to TSP therapy are age at onset, amount of proteinuria, hematuria grade, and pathological grade.

The aim of the present study, namely the identification of the factors predicting resistance to TSP therapy, differed from that of Hotta's original report, which aimed to establish which factors led to clinical remission in all IgA nephropathy patients. The present study revealed that younger patients with massive proteinuria, mild hematuria, and a severe pathological grade easily resist TSP therapy. It should be noted that these factors were already included in the prognostic scoring system developed by Wakai et al. Our results suggest that patients with late-stage or severe IgA nephropathy are likely to resist TSP therapy, and conversely patients with early or mild to moderate disease easily achieve CR following TSP therapy. An ROC curve of the predictive score for resistance to TSP therapy shows that, when the score is more than −0.02, the sensitivity is almost 70%, the specificity is 75%, and the positive likelihood ratio is 2.76. It is still unclear whether responsiveness to TSP therapy depends on how early the treatment is given, or on other factors, for instance genetic characteristics, or on a combination of these. A retrospective analysis by Hotta's group suggested that TSP therapy may be more effective for patients in the early stages of the condition, based on data that patients with serum creatinine level of less than 2.0 mg/dl responded well to the treatment [8]. There are several medical decisions; one is whether TSP therapy should be performed for patients with early or mild to moderate grade nephropathy so as to induce clinical remission, and the other is whether TSP therapy should be used for patients with a progressive type of IgA nephropathy. Further study should clarify the indications for TSP therapy in patients with IgA nephropathy.

Regarding clinical remission of urinary abnormalities, TSP therapy is still the most promising treatment, with a maximum CR rate of almost 50%, compared with 10–20% seen in steroid pulse therapy as reported by Pozzi et al. [3]. According to Hotta's original report about TSP therapy, the renal survival rate following treatment is estimated as 90% at 10 years, 71% at 16 years, and 66% at 20 years, with 48% (157/329) of patients achieving complete remission of urinary abnormalities and 52% (172/329) resisting the therapy. The fact that almost half of enrolled patients showed a poor prognosis demonstrates that TSP therapy is not a curative treatment for all patients with IgA nephropathy. Regardless, we must evaluate various therapies based on the renal survival rate after longer periods, such as 20 years, not on the CR rate assessed shortly after treatment. Further prospective randomized controlled trials in which the primary end point is the renal survival rate at 20 years, or cohort studies having large number of patients, are needed to clarify the efficacy of TSP therapy.

Acknowledgments We thank the Fellows of the Japanese Society of Nephrology who responded to our questionnaire. This work was supported by a grant (to H.I.) from the Progressive Renal Diseases Research Project of the Ministry of Health, Labour and Welfare of Japan. Drs. Kikuchi K, Ito Y, Yamaji I, Fukazawa S, Kawada T, Sakurai T, Wada A, Nagane Y, Sato H, Taguma Y, Wakui H, Konta T, Degawa N, Masakane I, Yamagata K, Kobayashi M, Ebihara I, Nakamura S, Oda T, Tukamoto Y, Ishizuka A, Shiraga H, Imasawa T, Seki T, Takemoto F, Matsushita K, Shibata T, Murakami M, Takahashi T, Wakai S, Ando M, Mishio Y, Hayashi M, Sasaki S, Okada T, Nitta K, Higuchi C, Funahiki K, Tamura K, Yasuda H, Yoshimura A, Takizawa R, Suwabe T, Hayaasa J, Yokota S, Sato M, Jinguuji Y, Higuchi M, Nakao I, Yoshida H, Araki H, Yoshimura M, Wada T, Koni I, Yamamoto T, Kasai K, Tomita M, Fukuda M, Inaguma D, Naruse T, Yamashita H, Asada Y, Sugimoto T, Isono M, Mukoyama M, Mori Y, Komatsu H, Tsuji H, Ishimura E, Imai E, Inoue T,

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Conflict of interest statement None declared.

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Original Paper

Gaps Between Hypertension Treatment Guidelines and Clinical Practice in Japan: Baseline Survey Results From Fukushima Research of Hypertension (FRESH)

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This observational study assessed the achievement of treatment goals, as defined by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). These goals are: <140/80 mm Hg in elderly patients (65 years and older), <130/80 mm Hg in patients with diabetes or kidney disease, and <130/85 mm Hg in younger patients (younger than 65). From July 2006 to May 2007, 72 physician members of the Fukushima Hypertension Conference enrolled a total of 3320 patients from Fukushima Prefecture, Japan. The median age of the patients was 71 years and 46% were male. The success rate was 27% among patients with diabetes mellitus or renal disease, 30% among those younger than 65 years, and 66% among the elderly without the diseases. Factors significantly associated with an increased risk of failure to achieve goals were obesity, dyslipidemia, family histories of diabetes mellitus or hypertension, and number of antihypertensive drugs used. The presence of atherosclerotic complications decreased the risk. This study revealed low achievement rates, identified the importance of weight control and family histories, and indicated a need for better management to prevent complications. J Clin Hypertens (Greenwich). *2009;11:333–341.* ©*2009 Wiley Periodicals, Inc.*

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According to the World Health Organization (WHO),[1] reported cardiovascular disease (CVD) was the most common cause of death worldwide in 2005, accounting for approximately 30% of all deaths, with the main causes of death among individuals 60 years and older being ischemic heart disease followed by cerebrovascular disease.[2] Prevention of CVD is emphasized in both developed and developing countries.[1,2] Hypertension affects approximately 1 billion people worldwide[3] and is estimated to account for 6% of deaths worldwide.[4] It is among the most important modifiable risk factors for CVD, and also the most common reason for outpatient office visits to physicians.[5]

Hypertension management consists of several components, including the screening of elevated blood pressure (BP), lifestyle interventions and evaluation for pharmaceutical treatment, continued

medical follow-up, and adherence to treatment.[6,7] For several decades, many projects and studies have been conducted to clarify the factors associated with BP levels,[7–10] based on established treatment guidelines.[3,11,12] Major guidelines include the 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 the European Society of Cardiology (ESC) (ESH/ESC 2007)[11] from Europe, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[3] from the United States, and the 2003 WHO/International Society of Hypertension (ISH) Statement on Management of Hypertension (WHO/ISH).[12] These reports have produced concise, evidence-based manuals for the most effective and convenient therapy for hypertensive patients, although there are some differences between them regarding recommended first choice drugs and combinations of drugs. These guidelines provide clear and practical treatment algorithms, indicating goal BPs that take into consideration a patient's risk factors: <130/80 mm Hg for patients with diabetes mellitus or chronic kidney disease and 140/90 mm Hg for those without the diseases. Intensive and strict BP control among hypertensive patients with diabetes mellitus and/or chronic kidney disease is emphasized,[3,11,13] because hypertension is a known risk factor for these outcomes.[13] Furthermore, diabetes mellitus often leads to atherosclerotic disorders[14,15] and chronic kidney disease, which is defined as either renal damage or decreased kidney function for 3 months or longer,[16,17] and causes CVD.[18,19]

In Japan, the Japanese Society of Hypertension[20] first published the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2000) in 2000, which was revised as JSH 2004 in 2004. The guidelines explain the measurement and clinical evaluation of BP as well as basic principals of treatment and lifestyle modification. It also indicates adequate BP goals according to individuals' risk factors, which is similar to previously published guidelines. The average BPs of the Japanese population have decreased between 1961 and 1990 among both men (from 143.2/83.0 mm Hg to 134.3/82.9 mm Hg) and women (from 143.3/82.2 mm Hg to 128.4/77.6 mm Hg) aged 30 to 69 years.[21] During the same period, the incidence of stroke has significantly decreased in response to health promotion activities and introduction of new antihypertensive drugs.[20–22] Nevertheless, there are more than 30 million hypertensive patients in Japan,[23] and it is the second most common disease among those categorized within the metabolic syndrome.[24]

Although a few studies reported robust achievement rates based on 140/90 mm Hg as a goal BP level,[25–27] there have been no reports from Japan assessing the rates toward individualized BP goals, and the present study was the first trial to evaluate these rates in a community. The aim of our study was to assess success rates in achieving treatment goals as defined by JSH 2004 in one prefecture in Japan. We will also explore the factors associated with these success rates, including patients' and physicians' characteristics.

RESEARCH DESIGN AND METHODS

The present study was a prospective cohort study carried out in Fukushima Prefecture, Japan, from July 2006 to May 2007. Fukushima Prefecture is located in the northern region of Japan, with a population of about 2 million. From March to April 2006, we called physician-members of the Fukushima Hypertension Conference to solicit participation in this study. The Fukushima Hypertension Conference was established in 1997 and there were 120 members as of April 2006.

Participants in our study had hypertension and had received antihypertensive medication for at least 3 months and visited a participating physician during the baseline survey period (July 2006). In the baseline survey, the physician enrolled the first 10 consecutive patients who were eligible and willing to participate in our study.[28] The enrollment continued until the total number of registered patients reached 50 for each physician. Even if the number of enrolled patients did not reach 50, the recruitment was stopped on the last day of July 2006. The research date was not announced to patients prior to the survey, and appointments for medical consultation were made according to their requests as usual. Enrolled patients were monitored for 1 year in 3-month intervals.

In the baseline survey, the registered patient's clinical data was copied from medical files to survey sheets. The data included the patient's age, sex, height, weight, waist circumference, family histories (hypertension, diabetes mellitus, dyslipidemia, heart disease, stroke, renal disease, and premature CVD), alcohol consumption, current smoking habits, systolic and diastolic BPs, whether home BP measurement was instructed, duration of hypertension treatment, usage of antihypertensive drugs, and presence of metabolic disorders (diabetes mellitus,

dyslipidemia), end-organ damage, and CVDs (brain, heart, kidney, blood vessel, hypertensive, and diabetic retinopathy). The status of renal disease and diabetes mellitus was obtained from physician reports. In Japan, diabetes mellitus is defined based on the Japan Diabetes Society, Diabetes Treatment Guideline 2008–2009.[29] Renal disease is defined based on the Japanese Clinical Practice Guidebook for Diagnostic and Treatment of Chronic Kidney Disease.[16] As for methods to measure BP, we asked physicians to maintain their usual practices and report BP measurements on each day the patients were surveyed. Follow-up surveys (October 2006, January 2007, and April 2007) collected hypertension-related information. As for physicians' characteristics, the following information was collected in the baseline survey: age, sex, place of employment, main specialty, number of hypertensive patients (per month), and measurer, timing, place, and method of BP measurement. The present report used data from the baseline survey and conducted analyses on achievement toward treatment goals and its associated factors.

All data were entered into a computer and analyzed using SPSS version 14 (SPSS Inc, Chicago, IL). We classified participants into 3 groups according to the JSH 2004: elderly patients 65 years and older without diabetes mellitus or renal disease, young or middle-aged patients without diabetes mellitus or renal disease, and patients with diabetes mellitus or renal disease. The success rates were calculated following treatment goals for each group indicated in JSH 2004: <140/90 mm Hg for elderly patients without diabetes mellitus or renal disease, <130/80 mm Hg for patients with the diseases, and <130/85 mm Hg for young or middle-aged patients without the diseases. For the analysis of factors associated with failure to achieve the treatment goals, we computed odds ratios (ORs) and 95% confidence intervals (CIs) for each item using univariate logistic regression. Significant factors in the univariate analysis ($P<.05$) were then entered into a multivariate logistic regression analysis.

With regard to the analysis of physicians' characteristics and the success rates of their patients, we divided participating physicians into 2 groups using a median split of overall patient success rates (<45% vs ≥45%). The 2 groups were compared using the chi-square test and Fisher exact test for categoric items and Mann–Whitney test for continuous items.

This survey was conducted according to the Ethical Guideline for Epidemiological Studies established by the Japanese government,[30] and work was performed in accordance with the Declaration of Helsinki of 1975 (revised in 2000).[31]

RESULTS

Seventy-two of 120 members of the Fukushima Hypertension Conference enrolled patients into the study. In the baseline survey, 3358 hypertensive patients were initially registered. Of those registered, 38 patients were excluded due to missing data on BPs and nonmedication, and thus 3320 patients were entered into the present analysis. Median age of patients was 71 years (24–99 years) and the percentage of males was 46.1% (Table I). As for anthropometric measurements, median body mass index (BMI) was 24.3 (13.2–45.4), and median waist circumference was 87.6 cm (59.0–126.0 cm) for males and 85.0 cm (53.0–134.0 cm) for females. Among family histories, the prevalence of hypertension was most frequent (55.2%), followed by stroke (27.6%), diabetes mellitus (18.0%), and heart disease (15.3%). The prevalence of alcohol use (daily consumption) was 21.7%, and that of current smoking was 12.1%. The median systolic and diastolic BPs were 134 mm Hg (82–212 mm Hg) and 76 mm Hg (36–124 mm Hg), respectively. Sixty percent of patients were instructed to measure BPs at home, 43.6% of patients were treated by 1 antihypertensive drug, and the median duration of hypertension treatment was 8.0 years (0.5–60.0 years). The proportion of those with diabetes mellitus was 31.7% and that of dyslipidemia was 44.8%. Cardiovascular complications were reported in 21.5% of patients, neurological complications in 13.4%, and renal complications in 11.1%.

Table II shows various characteristics of the physicians assisting in this study. Seventy of 72 physicians completed the questionnaire. The proportion of males was 93.0% and median years after graduation from medical school was 24 years. The most frequent specialty among participating physicians was general internal medicine (n=35), followed by cardiology (n=17), gastroenterology (n=7), and endocrinology (n=7). The proportion of those working at hospitals was 52.9%, and 60.0% were located in urban areas (defined as cities with >100,000 residents). Median number of hypertensive patients per physician per month was 300. Eighty percent of physicians measured BPs by themselves, 82.9% during medical consultation, 82.9% in a consultation room, and 72.9% using mercury sphygmomanometer.

The median systolic and diastolic BPs were 134 mm Hg (84–190 mm Hg) and 75 mm Hg (36–120

Table I. Characteristics of Hypertensive Patients at Baseline

Variables	Median (Range) or No. (%)
Age, y	71 (24–99)
Male sex	1524 (46.1)
Anthropometric measurements	
Body mass index	24.3 (13.2–45.4)
Waist circumference, cm	
Male	87.6 (59.0–126.0)
Female	85.0 (53.0–134.0)
Family histories	
Hypertension	1805 (55.2)
Stroke	902 (27.6)
Diabetes mellitus	589 (18.0)
Heart disease	499 (15.3)
Dyslipidemia	132 (4.0)
Renal disease	123 (3.8)
Premature cardiovascular disease	47 (1.4)
Alcohol consumption (daily)	705 (21.7)
Current smoking	392 (12.1)
Hypertension-related factors	
Systolic blood pressure, mm Hg	134 (82–212)
Diastolic blood pressure, mm Hg	76 (36–124)
Instruction of home blood pressure measurement (yes)	1969 (59.6)
Duration of hypertension treatment, y	8.0 (0.5–60.0)
No. of antihypertensive drug used	
1	1449 (43.6)
2	1318 (39.7)
≥3	553 (16.7)
Metabolic disorders	
Diabetes mellitus	1050 (31.7)
Dyslipidemia	1484 (44.8)
Organ damage/cardiovascular disease	
Heart	713 (21.5)
Brain	445 (13.4)
Kidney	368 (11.1)
Peripheral vascular disease	249 (7.5)
Hypertensive retinopathy	150 (4.5)
Diabetic retinopathy	176 (5.3)

Table II. Characteristics of Physicians Participating in the Survey

Variables	Median (Range) or No. (%)
Male sex	65 (93.0)
Years after graduation from medical university, y	24 (8–44)
Main specialty	
General internal medicine	34 (48.6)
Cardiology	16 (22.9)
Gastroenterology	7 (10.0)
Endocrinology	7 (10.0)
Others	6 (8.5)
Medical office	
Hospital	37 (52.9)
Clinic	33 (47.1)
Location of medical office (urban[a])	
Urban[a]	42 (60.0)
Rural	28 (40.0)
Number of attending hypertension patients (No. per month)	300 (15–1500)
Measurer of BP	
Physician	56 (80.0)
Nurse	8 (11.4)
Patient	6 (8.6)
Timing of BP measurement	
During medical consultation	58 (82.9)
Waiting time	11 (15.7)
Others	1 (1.4)
Place of BP measurement	
Consultation room	58 (82.9)
Treatment room or waiting space	11 (15.7)
Others	1 (1.4)
Method of BP measure	51 (72.9)
Mercury sphygmomanometer	51 (72.9)
Automated sphygmomanometer	19 (27.1)
No. of registered patients	49.5 (14–51)
Achievement rate toward treatment goals	43.9 (14.3–82.0)

Abbreviation: BP, blood pressure. [a]Urban is defined as a city with a population of ≥100,000.

mm Hg) for elderly without diabetes mellitus or renal disease, 132 mm Hg (100–180 mm Hg) and 80 mm Hg (43–106 mm Hg) for those younger than 65 years without the diseases, and 134 mm Hg (82–212 mm Hg) and 76 mm Hg (39–124 mm Hg) for those with the diseases. Success rates toward treatment goals (defined by JSH 2004) were 66.0% for the elderly without diabetes mellitus or renal disease, 30.4% for those younger than 65 years without the diseases, and 26.7% for those with the diseases (Table III). We conducted an additional analysis among those younger than 65 years without the diseases according to JNC 7[3] (<140/90 mm Hg), whose target BP level differs from JSH 2004, and found the success rate to be 65.9%.

The Figure shows the number of antihypertensive drugs used. Monotherapy was most frequent among the elderly without diabetes mellitus or renal disease (47.7%), while bitherapy was most frequent among the patients with the diseases (40.9%). Median systolic and diastolic BPs were 132 mm Hg (82–190 mm Hg) and 77 mm Hg (36–120 mm Hg) among patients treated with monotherapy, 134 mm Hg (92–190 mm Hg) and

Table III. Median of Blood Pressure (BP) and Success Rates Toward Target BP Levels

	JSH 2004 Target BP Level, mm Hg	Median (Range) of Systolic and Diastolic BP, mm Hg	Success Rates, No. (%)
Elderly patients without diabetes mellitus or renal disease (n=1518)	<140/90	134 (84–190)/75 (36–120)	1002 (66.0)
Young or middle-aged patients without diabetes mellitus or renal disease (n=583)	<130/85	132 (100–180)/80 (43–106)	177 (30.4)
Patients with diabetes mellitus or renal disease (n=1212)	<130/80	134 (82–212)/76 (39–124)	324 (26.7)

Abbreviation: JSH 2004, Japanese Society of Hypertension Guidelines for the Management of Hypertension.

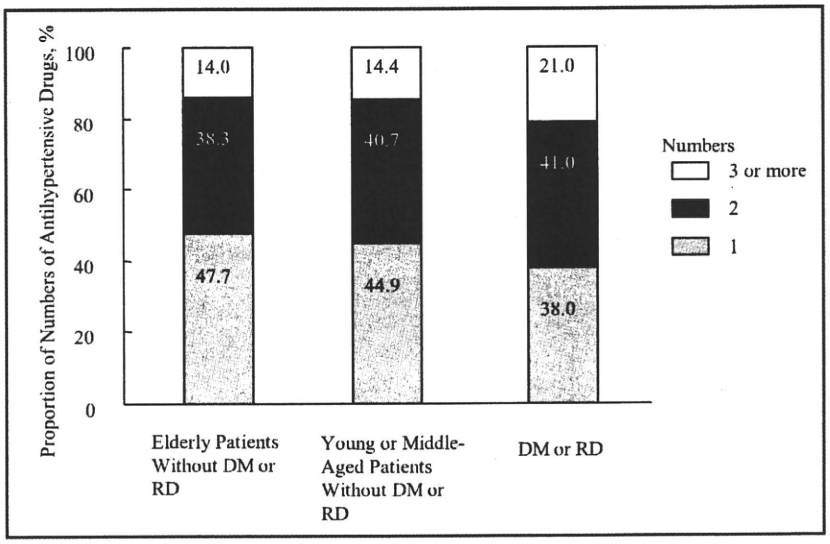

Figure. Numbers of antihypertensive drugs. DM indicates diabetes mellitus; RD, renal disease.

76 mm Hg (39–111 mm Hg) among those treated with bitherapy, and 135 mm Hg (96–212 mm Hg) and 76 mm Hg (41–124 mm Hg) among those treated with ≥3 drugs.

The multivariate analysis showed that the factors significantly associated with failure to achieve treatment goals were waist circumference of ≥85 cm for men and ≥90 cm for women (OR, 1.26; 95% CI, 1.01–1.57) and usage of ≥3 antihypertensive drugs (OR, 1.96; 95% CI, 1.42–2.71) for the elderly group without diabetes mellitus or renal disease (Table IVa). For young and middle-aged patients without diabetes mellitus or renal disease, the significant factors were BMI ≥25 (OR, 1.74; 95% CI, 1.19–2.56), family history of hypertension (OR, 1.67; 95% CI, 1.14–2.45), cerebrovascular complication (OR, 0.33; 95% CI, 0.16–0.68), and hypertensive retinopathy (OR, 0.33; 95% CI, 0.12–0.91) (Table IVb). For patients with diabetes mellitus or renal disease, BMI ≥25 (OR, 1.34; 95% CI, 1.03–1.75), family history of diabetes mellitus (OR, 1.40; 95% CI, 1.04–1.87), dyslipidemia (OR, 1.41; 95% CI, 1.08–1.84), and cerebrovascular (OR, 0.62; 95% CI, 0.44–0.87) and vascular complications (OR, 0.48; 95% CI, 0.33–0.70) were significantly associated (Table IVc).

Table V shows the differences in characteristics between 2 groups of physicians categorized by overall success rates of their patients. The proportion of elderly patients without diabetes mellitus or renal disease was higher among physicians with higher success rates.

DISCUSSION

This community-based assessment of hypertension control among our patients in one prefecture in Japan showed excellent results with a median BP <140/90 mm Hg. Now given new target BP levels redefined by recent hypertension management guidelines,[3,11,20] we used the JSH 2004 to calculate the success rates among our patient population. Achievement rates were relatively pessimistic, especially among patients with diabetes mellitus or renal disease and those younger than 65 years without

Table IV. Association of Blood Pressure Achievement-Failure

Variables	No. (%)	Odds Ratio	95% Confidence Interval	*P* Value
(a) In elderly patients without diabetes mellitus or renal disease (multivariate logistic regression analyses)				
Waist circumference ≥85 cm for men, ≥90 for women	620 (42.1)	1.26	1.01–1.57	<0.05
No. of antihypertensive drugs used				
1	461 (38.0)	1.00 (Reference)		
2	496 (40.9)	1.15	0.91–1.46	
≥3	255 (21.0)	1.96	1.42–2.71	<0.05
(b) In young and middle-aged patients without diabetes mellitus or renal disease (multivariate logistic regression analyses)				
Body mass index ≥25	241 (42.8)	1.74	1.19–2.56	<0.05
Family history of hypertension (yes)	378 (66.4)	1.67	1.14–2.45	<0.05
Organ damage/cardiovascular disease				
Brain (yes)	33 (5.7)	0.33	0.16–0.68	<0.05
Hypertensive retinopathy (yes)	17 (2.9)	0.33	0.12–0.91	<0.05
(c) In patients with diabetes mellitus or renal disease (multivariate logistic regression analyses)				
Body mass index ≥25	582 (48.5)	1.34	1.03–1.75	<0.05
Family history of diabetes mellitus (yes)	379 (31.5)	1.40	1.04–1.87	<0.05
Dyslipidemia (yes)	656 (54.3)	1.41	1.08–1.84	<0.05
Organ damage/cardiovascular disease				
Brain (yes)	191 (15.8)	0.62	0.44–0.87	<0.05
Blood vessel (yes)	144 (11.9)	0.48	0.33–0.70	<0.05

Table V. Physician Characteristics of Blood Pressure Achievement Rates Toward Treatment Goals

	Achievement Rate Median (Range) or No. (%)[a]		*P* Value
Variables	<45% (n=38)	≤45% (n=32)	
Male sex	35 (92.1)	30 (93.8)	
Years after graduation from medical university	24 (8–40)	25 (11–44)	
Main specialty (internal medicine)	37 (97.4))	29 (90.6)	
Medical office (hospital)	23 (60.5)	14 (43.8)	
Location of medical office (urban[b])	25 (65.8)	17 (53.1)	
Number of attending hypertension patients (for one month)	300 (15–1500)	300 (32–1200)	
Measurer of BP (physician)	31 (81.6)	25 (78.1)	
Timing of BP measurement (during medical consultation)	32 (84.2)	26 (81.3)	
Place of BP measurement (consultation room)	32 (84.2)	26 (81.3)	
Method of BP measure (mercury sphygmomanometer)	28 (73.7)	23 (71.9)	
Proportion of registered patients, %			
Elderly patients without diabetes mellitus or renal disease	42.8 (0.0–74.0)	55.0 (0.0–84.0)	<0.01
Young and middle-aged patients without diabetes	18.6 (0.0–60.0)	13.3 (0.0–61.3)	
Patients with diabetes mellitus or renal disease	29.2 (4.0–100)	27.9 (2.0–100)	

Abbreviation: BP, blood pressure. [a]The chi-square test and Fisher exact test for categoric items and Mann–Whitney test for continuous items were used to assess the significance. [b]Urban is defined as a city with a population of ≥100,000.

diseases based on JSH 2004, although median BPs showed excellent results of <140/90 mm Hg.

Other factors associated with failure to achieve treatment goals included BMI, waist circumference, family histories, dyslipidemia, and usage of ≥3 antihypertensive drugs increased the risk of achievement failure, while presence of complications was paradoxically associated with success rates.

The success rate of elderly patients without diabetes mellitus or renal disease in our study was substantially higher compared with those of young and middle-aged patients. Likewise, a Japanese cross-sectional study reported that achievement rate toward goal BP (defined as <140/90 mm Hg) was 17.0% in patients younger than 60 years while it was 40.6% for patients 60 to 69 years, 54.4% for

patients 70 to 79 years, and 65% for patients 80 years and older.[32] In contrast, previous studies have reported advancing age as an independent predictor of inadequate BP control in the United States.[33,34] The discrepancies in achievement rates between the elderly and nonelderly in Japan and between the elderly in Japan and the United States could be explained in part by differences in health behaviors among the older generations. JNC 7 emphasizes the importance of the following 5 healthy lifestyles: weight reduction, improvement in dietary habits, dietary sodium restriction, increased physical activity, and appropriate alcohol consumption.[3] The proportions of those who exercise regularly, keep healthy weight, and do not smoke were higher in the elderly compared with the nonelderly according to a Japanese national survey.[35] In the United States, on the other hand, these proportions in the elderly are lower compared with the nonelderly.[36,37] Furthermore, BP level is correlated with cardiovascular mortality in the nonelderly,[10] which could result in a survivor effect causing a relatively elevated success rate among the Japanese elderly.

The study indicated that 2 markers of obesity, high BMI and waist circumference, were significantly associated with achievement failure among hypertensive patients with diabetes mellitus or renal disease, and young and middle-aged patients without the diseases. Several studies have reported a high prevalence of hypertension among obese individuals compared with nonobese individuals.[38–40] The sympathetic nervous system, sodium retention/salt sensitivity, and insulin resistance are thought to be involved in the etiology of hypertension accompanied by obesity.[20] As previous research emphasized,[41,42] body weight control is thus considered one of the most important therapeutic strategies in JSH 2004,[20] JNC 7,[3] and ESH/ESC 2007.[12] In other words, obesity is an important risk factor of failure to achieve treatment goals[33] as indicated in our results.

It is well-known that family histories of hypertension,[43] diabetes mellitus,[44] and dyslipidemia[45] are risk factors for hypertension. The number of these risk factors, as well as nonfavorable health behaviors, is associated with an increased incidence of hypertension and overall CVD severity. In Japan, family histories are usually recorded in standard medical files with other basic information and are checked in general clinical practice and routine health check-ups.

Interestingly, we found a positive association between history of organ and vascular complications and achieving treatment goals. It may be possible that both patient and physician become more aware of the need to maintain goal BP levels, once organ and vascular complications present. Previous studies have reported a similar association between history of CVD and improved BP control, explained by increased patient compliance and/or more aggressive treatment.[46,47] Supporting this hypothesis, Street and colleagues[48] also reported that physicians seeing patients with a critical disease paid more attention to their clients than physicians seeing patients with less severe conditions. Furthermore, a lack of disease awareness has been pointed out as a patient-related factor related to poor BP control.[49] Had patients been treated appropriately in the past, such a paradoxical result may not have been found, and presence of complications may have instead become a risk factor of inadequate BP control. Our results suggest the necessity of better management of hypertension prior to the onset of complications.

Using $\geq$2 drugs was a risk factor of achievement failure among our elderly patients without diabetes mellitus or renal disease. A previous report from the United States also showed that a multi-drug regimen was an independent risk factor of poor BP control,[46] and patients whose BP is difficult to control are more likely to be treated with multiple drugs. Additional analyses of our study showed that a multiple antihypertensive drug therapy correlates with higher number of vascular and/or organ damage, longer duration of hypertension treatment, and a family history of hypertension. These findings suggest that resistance to treatment persists among the elderly without diabetes mellitus or renal disease, despite physician adherence to treatment guidelines. Further analysis of follow-up data on change in antihypertensive drugs may provide additional insight on the relationship between different medications and BP control.

LIMITATIONS

Our study has some major limitations. First is a selection bias; the physicians who participated in our study were limited to members of the Fukushima Hypertension Conference, and participants were limited to hypertensive patients who visited these physicians. In addition, some important information on their characteristics and medical practices were not investigated, and the patient characteristics appeared as the only factor that differed significantly between 2 groups of physicians classified by their achievement levels. It is possible that participating members might be more aware about hypertension management compared with nonmembers.