measured in light clothing without shoes, and the BMI was calculated (kg/m^2).

Statistical analysis

All statistical analyses were performed with SPSS version 20.0J software (SPSS, Chicago, IL, USA). Data are expressed as mean ± SD. Clinical parameters and BP or metabolic values according to the BMI were compared using the Mann–Whitney *U* test, and categorical parameters were compared using the Chi squared test. Univariable and multivariable logistic regression analyses were used to examine the independent association of the level of eGFR with new-onset brain or heart attacks. In the multivariable analysis, associations were assessed with adjustments for age, sex, proteinuria, BMI, TG, and FPG, among others. Statistical significance was defined as $p < 0.05$.

Results

Correlation between BMI and new-onset brain or heart attacks

The distribution and prevalence of new-onset brain or heart attacks for each BMI category are shown in Fig. 1. The results show that the prevalence of new-onset brain or heart attacks increased according to an increase in BMI. However, the actual number of new-onset brain or heart attacks is higher in those with a BMI <24.5 kg/m^2 than ≥24.5 kg/m^2.

Comparison between subjects with BMI ≥ and < 25 kg/m^2

Subjects were divided into two groups, obese and non-obese, according to BMI < or ≥25 kg/m^2, respectively (Table 1). Age did not differ significantly between the groups. Among obese subjects, male sex and proteinuria (dipstick test ≥1+) were common. Compared with the non-obese subjects, obese subjects showed lower eGFR, higher systolic and diastolic BP, higher FPG, higher HbA1c, and higher TG.

The rates of new-onset brain or heart attacks were 3.1 and 4.0 % in the non-obese and obese subjects, respectively (Fig. 2). Chronic kidney disease (CKD) stages were classified as eGFR levels [9]; CKD stage G2 was set as a reference when multivariate logistic analysis was performed (Table 2). In the total population, stage G3a or G3b+ was a significant risk factor for CKD in a step-by-step manner. In the non-obese population, stage G3a or G3b+ was also significant. However, in the obese population, stage G1 or G3b+ was significant but not in stage G3a.

The multivariate logistic analysis data, except for the results of basal eGFR stratification, are shown in Table 2. The 2-year change of eGFR, male, older age, proteinuria, and higher BMI, BP, and TG levels were significant. In obese subjects, high-normal BP or worse was also a significant risk factor, while higher TG (≥150 mg/dl) and higher FPG (≥100 mg/dl) were not statistically significant, but their odds ratios were greater than one.

To clarify the significance of eGFR, the odds ratio of eGFR for new-onset brain or heart attacks was analyzed in incremental steps (Fig. 3). Estimated GFR was a significant risk factor for unadjusted analysis. In particular, the eGFR in the non-obese population remained significant after adjustment by age, sex, basal proteinuria, systolic BP, TG, low-density lipoprotein, and FPG, but was not significant in obese subjects.

Synergistic effect of eGFR and hypertension on brain or heart attacks differs according to BMI

Because high-normal BP or hypertension was found to be a strong risk factor, we checked the synergistic effect of

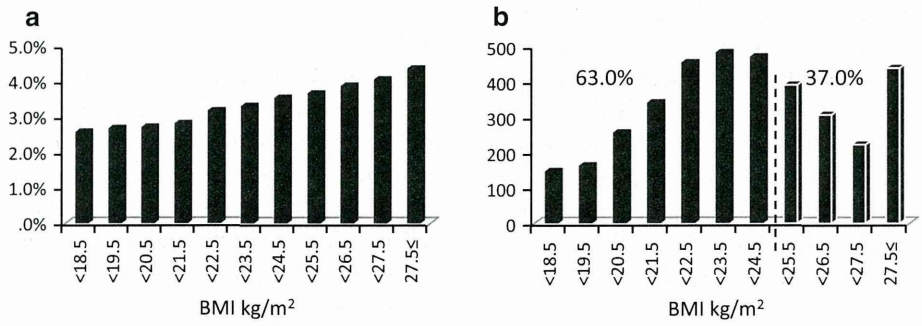

Fig. 1 Distribution of new-onset brain or heart attacks for each BMI category. **a** Prevalence or the affected number of new-onset brain or heart attacks. **b** The actual number of new-onset brain or heart attacks is higher in those with a BMI 24.5 kg/m^2 than ≥24.5 kg/m^2. The percentage of affected subjects with a BMI less than and more than 24.5 kg/m^2

Table 1 Population characteristics divided by BMI of and ≥25 kg/m^2

	BMI < 25 kg/m^2	BMI ≥ 25 kg/m^2	Total	*p* value
Number of subjects	81,013	28,336	109,349	
BMI (kg/m^2)	21.75 (2.03)	27.32 (2.27)	23.20 (3.22)	
Age (years)	63.2 (7.5)	63.2 (7.6)	63.2 (7.5)	0.260
Male, *n* (%)	29,918 (36.9 %)	13,288 (46.9 %)	43,206 (39.5 %)	<0.001
Height (cm)	156.9 (8.3)	157.1 (8.9)	157.0 (8.5)	0.003
Weight (kg)	53.8 (7.9)	67.6 (9.2)	57.4 (10.2)	<0.001
Waist circumference (cm)	80.4 (7.1)	92.9 (6.9)	83.6 (8.9)	<0.001
Serum creatinine (mg/dl)	0.71 (0.17)	0.74 (0.19)	0.71 (0.17)	<0.001
Basal eGFR, ml/min/1.73 m^2	75.1 (14.9)	73.8 (15.3)	74.8 (15.0)	<0.001
Basal dipstick proteinuria (≥1+), *n* (%)	2,859 (3.5 %)	2,064 (7.3 %)	4,923 (4.5 %)	<0.001
SBP (mmHg)	127.3 (17.4)	133.9 (16.5)	129.0 (17.4)	<0.001
DBP (mmHg)	75.4 (10.5)	79.6 (10.3)	76.5 (10.6)	<0.001
BP, SBP ≥130 or DBP ≥85 or Drug, *n* (%)	42,694 (52.7 %)	20,793 (73.4 %)	63,487 (58.1 %)	<0.001
FPG (mg/dl)	95.7 (17.1)	101.8 (21.5)	97.3 (18.6)	<0.001
HbA1C (%)	5.68 (0.55)	5.87 (0.72)	5.73 (0.61)	<0.001
FPG, ≥100 or drug, *n* (%)	21,372 (26.4 %)	11,954 (42.2 %)	33,326 (30.5 %)	<0.001
TG (mg/dl)	107.8 (68.5)	136.7 (84.6)	115.3 (74.1)	<0.001
TG, ≥150 or drug, *n* (%)	22,904 (28.3 %)	12,317 (43.5 %)	35,221 (32.2 %)	<0.001

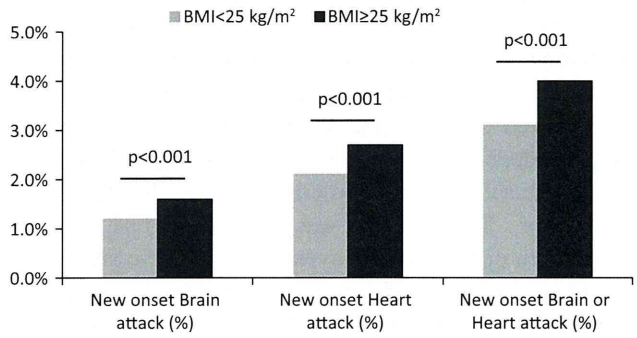

Fig. 2 Incidence of brain or heart attacks during follow-up. The rates of new-onset brain and heart attacks in non-obese and obese populations are shown. All three sets of differences were statistically significant

eGFR with BP levels. When both eGFR and BP were divided into CKD stages and BP categories, respectively, the odds ratio of each combination was calculated in a multivariate fashion adjusted by age (+5 years), sex (male vs. female), basal proteinuria (dipstick ≥1+), TG (≥150 or taking medication), and FPG (≥100 or taking medication). When the combination of 60–89 ml/min/1.73 m^2 of eGFR and normal BP was set as the reference, the odds ratios increased with decreasing eGFR and increasing BP categories, particularly in non-obese subjects. However, these relationships were not found in obese subjects. We confirmed that eGFR was still a significant risk factor and its power was strengthened when combined with BP in non-obese subjects (Fig. 4).

Discussion

The main conclusion from this study is that the health nurse intervention criteria of the 'Specific Counseling Guidance' generally seem to be appropriate. However, as the ultimate aim of the 'Specific Health Checkup' is to prevent cardiovascular events, eGFR measurement, particularly in non-obese subjects, as well as proteinuria should be included in the criteria.

The primary purpose of the 2008 Specific Health Checkup was to identify the high-risk cardiovascular subjects, and then to intervene via the Specific Counseling Guidance, also called 'Metabolic Syndrome Checkup', to reduce future cardiovascular events. Measurement of urine protein is also listed as being necessary, but is not included in the Specific Counseling Guidance criteria. However, CKD has recently become well known as a strong risk factor for the future development of cardiovascular events [10], but the measurement of eGFR is not recommended in this health checkup system as its value is not readily understood.

Table 2 Adjusted odds ratios of basal eGFR stratification (chronic kidney disease stages) for new-onset brain or heart attacks in the 2008–2010 longitudinal study

	Total population			BMI <25 kg/m^2			BMI ≥25 kg/m^2		
	OR	95 % CI		OR	95 % CI		OR	95 % CI	
Basal eGFR stratification (ml/min/1.73 m^2)									
eGFR ≥ 90 (stage G1)	1.040	0.943	1.148	0.981	0.872	1.104	**1.197**	1.003	1.429
60≤ eGFR <90 (stage G2)	1			1			1		
45≤ eGFR <60 (stage G3a)	**1.174**	1.072	1.286	**1.191**	1.065	1.332	1.147	0.979	1.344
eGFR < 45 (stage G3b or worse)	**1.751**	1.398	2.193	**1.515**	1.109	2.069	**2.105**	1.516	2.922
2-year eGFR change, −10 ml/ml/1.73 m^2	**1.105**	1.043	1.170	**1.126**	1.050	1.207	1.061	0.959	1.175
Male vs. female	**1.434**	1.339	1.536	**1.431**	1.317	1.551	**1.451**	1.282	1.642
Age, +5 years	**1.300**	1.264	1.337	**1.300**	1.256	1.345	**1.303**	1.240	1.369
Basal proteinuria	**1.356**	1.190	1.546	**1.446**	1.218	1.718	**1.245**	1.018	1.522
BMI, ≥25 vs.<25 kg/m^2	**1.129**	1.048	1.215						
BP, SBP ≥130 or DBP ≥85 or Drug	**1.513**	1.401	1.633	**1.527**	1.400	1.667	**1.468**	1.251	1.722
TG, ≥50 or drug	**1.080**	1.007	1.159	1.074	0.985	1.171	1.093	0.969	1.233
FPG, ≥100 or drug	1.026	0.955	1.102	0.994	0.909	1.086	1.089	0.965	1.229

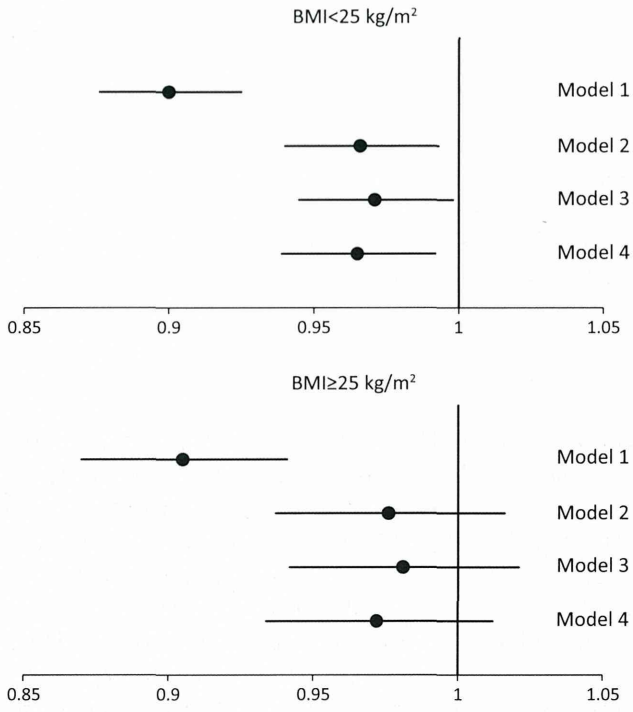

Fig. 3 Odds ratios of basal eGFR (+10 ml/min/1.73 m^2) for new-onset brain or heart attacks in non-obese (BMI <25 kg/m^2) and obese subjects (BMI ≥25 kg/m^2). Odds ratios of basal increment of eGFR (+10 ml/min/1.73 m^2) for new-onset brain or heart attack events were analyzed in a step-by-step manner. In non-obese subjects (*upper panel*), eGFR was a significant factor with not only unadjusted but also multivariate adjustment. In obese subjects (*lower panel*), eGFR was not significant when multivariate analysis was applied. Model 1, unadjusted, Model 2, model 1+ age, sex, Model 3, model 2+ basal proteinuria, Model 4, model 3+ systolic BP, TG, low-density lipoprotein, and FPG

Therefore, the aim of this study was to check the adequacy of these criteria using a large Japanese nationwide database. According to our data, the criteria for BMI, BP, and TG were verified as significant predictors of brain or heart attacks. The criterion of higher FPG was not significant, but had a tendency of predicting future brain or heart attack events. Proteinuria was shown to be an independent and strong significant risk factor for brain or heart attacks, and therefore, it should be added to the criteria.

Estimated GFR, calculated from serum creatinine, was also an independent risk factor in the total population. We divided the subjects into two groups using a BMI threshold of 25 kg/m^2. Though eGFR was a significant risk factor for future brain or heart attack events in non-obese subjects, it was not significant in obese ones. From these observations, assessing eGFR in obese subjects appears to be unnecessary. However, since the aim of the Specific Health Checkup is to prevent future brain or heart attack events, the measuring of eGFR should be recommended, particularly in the non-obese population.

Our study evaluated the usability of eGFR for predicting brain or heart attacks compared with using CKD stage G2. In a step-by-step manner, this CKD stage showed a worse odds ratio for brain or heart attack events in non-obese subjects. In obese subjects, however, CKD stage G3a compared with G2 was not significant, but stage G3b or worse was significant. It is unclear why stage G3a was not a risk factor in obese subjects, but possible explanations are (1) in obese subjects, there are some unknown but strong risk factors related to brain or heart attacks, such as adiponectin [12], resistin [12], and tumor necrosis factor

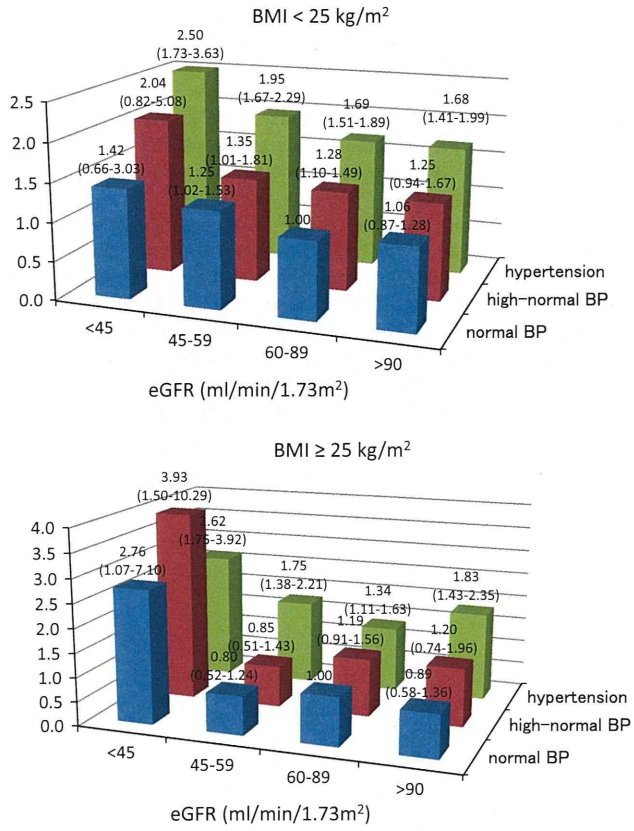

Fig. 4 Odds ratios for new-onset brain or heart attacks at combined levels of eGFR and BP in non-obese (BMI <25 kg/m^2) and obese populations (BMI ≥25 kg/m^2). When both eGFR and BP were divided in the chronic kidney disease (CKD) stages and BP categories, respectively, the odds ratios of each combination were calculated in a multivariate fashion adjusted by age, sex, basal proteinuria, TG abnormality, and glucose abnormality. The combination of 60–89 ml/min/1.73 m^2 of eGFR and normal BP was set as the reference. The odds ratios increased with decreasing eGFR and increasing BP categories in subjects with a BMI less than 25 kg/m^2 (*upper panel*). In subjects with a BMI of 25 kg/m^2 or more (*lower panel*), this relationship is unclear. Given numbers were odds ratio and 95 % confidence intervals

[13], and (2) subjects with higher BMI tend to have larger muscle mass, resulting in higher serum creatinine and lower calculated eGFR. This is because the eGFR equation does not include body weight [9], and therefore, some higher BMI subjects were included in CKD stage G3a even though their kidney function was in the normal range. Furthermore, stage G1 was also significant compared with stage G2 in obese subjects. In obese subjects, stage G1 refers to a hyperfiltration state, which has been reported as a risk factor for developing proteinuria [14] [15]. Therefore, the subsequent development of brain or heart attacks can be easily understood.

Among the criteria used in the Specific Counseling Guidance, higher BP had the strongest risk. To check the effect of combined eGFR and higher BP, we found a synergistic and stepwise effect between the two in non-obese subjects, but not in obese ones. Again, this finding supports the importance of eGFR in predicting brain or heart attacks.

The limitations in this study include possible biases toward recruiting participants who were particularly motivated to undergo a health examination, and also in the many subjects who were excluded because of missing data. Another limitation was the urine dipstick analyses which were performed manually. In addition, the BMI threshold was set at 25 kg/m^2, even though this variable shows some gender difference [5].

In conclusion, the criteria used for the health nurse intervention as specified in the 'Specific Counseling Guidance' seem appropriate in an obese population (BMI ≥ 25 kg/m^2). However, as the ultimate aim of the 'Specific Health Checkup' (Japanese name: Tokutei Kenshin) is to prevent cardiovascular events, eGFR should be evaluated in non-obese subjects with a BMI < 25 kg/m^2.

Acknowledgments This work was supported by Health and Labour Sciences Research Grants for "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan" (20230601) from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest All the authors declare no competing interests.

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Clin Exp Nephrol (2015) 19:152–153
DOI 10.1007/s10157-014-1034-6

LETTER TO THE EDITOR

Quantitative evaluation of proteinuria for health checkups is more efficient than the dipstick method

Kei Nagai · Kunihiro Yamagata

Received: 31 July 2014 / Accepted: 18 September 2014 / Published online: 24 September 2014

Keywords Proteinuria · Albuminuria · Dipstick · Creatinine · Epidemiology

To the Editor,

Albuminuria and dipstick-determined proteinuria are markers for detecting high-risk populations with end-stage renal disease and cardiovascular diseases [1, 2]. Recently, the CGA classification of chronic kidney diseases (CKD) by cause, glomerular filtration rate and level of albuminuria was recommended and recognized in the Kidney Disease Improving Global Outcomes (KDIGO) 2012 CKD guideline as the gold standard for managing patients with CKD [3]. However, the quantitative examination of albuminuria is expensive, and Japanese health insurance covers it only for diagnosing diabetic nephropathy. Therefore, Japanese physicians have used dipstick-determined proteinuria instead of albuminuria to classify CKD. Whereas urinary albumin can be corrected by the level of urinary creatinine to avoid the effect of urinary density, dipstick-determined proteinuria is only qualitative, and the results are sometimes confounded by urinary density [4]. In contrast, the quantitative examination of proteinuria is broadly accepted in clinical practice, and Japanese health insurance covers it for diagnosing any kidney disease. Moreover, the quantitative examination of proteinuria is much less expensive than that of albuminuria.

We demonstrated the distribution of dipstick proteinuria and quantitative proteinuria among the general population and evaluated the data to identify any correlation between quantitative proteinuria and albuminuria. Data were from health checkups of 1,584 subjects (821 men, 763 women) from Ibaraki, Japan. Their age was 59.8 ± 9.4 (mean ± SD) years old. We categorized dipstick-determined levels of proteinuria as follows: − or ±, D1; +, D2; and ≥2+, D3. Similarly, the level of albuminuria was categorized as <30 mg/g creatinine (cre), A1; 30–300 mg/g cre, A2; and >300 mg/g cre, A3. Quantitative proteinuria was categorized as <150 mg/g cre, P1; 150–500 mg/g cre, P2; and >500 mg/g cre, P3. These categories agree with the recommendations of the Japanese Society of Nephrology.

The urine from 1,318 subjects had concentrations of urinary protein below the sensitivity in the quantitative method and was therefore classed as P1. Using the urine from the remaining 266 subjects, whose urinary protein level was over the method's sensitivity, we tested for any correlation between urinary protein and urinary albumin.

In the A2 subpopulation, more subjects had D1 than P1 ($P < 0.001$, Chi square test; Fig. 1a, b). Similarly, in the A3 subpopulation, more subjects had D1 or D2 than P1 or P2 ($P < 0.01$; Fig. 1a, b). These results suggest that dipstick proteinuria misses more cases (negative result) of positive urinary albumin than does quantitative proteinuria. Because the correlation between the amount of urinary albumin and that of urinary protein was excellent (Fig. 1c), quantitatively determined proteinuria seems to be a better tool for CKD classification and albuminuria detection than dipstick proteinuria. Nevertheless, because the majority of the A2 subpopulation was missed by quantitative examination of a low concentration of proteinuria (i.e., P1; Fig. 1a, b), we consider it difficult to substitute quantitative

On behalf of the Steering Committee for "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by specific health checkups".

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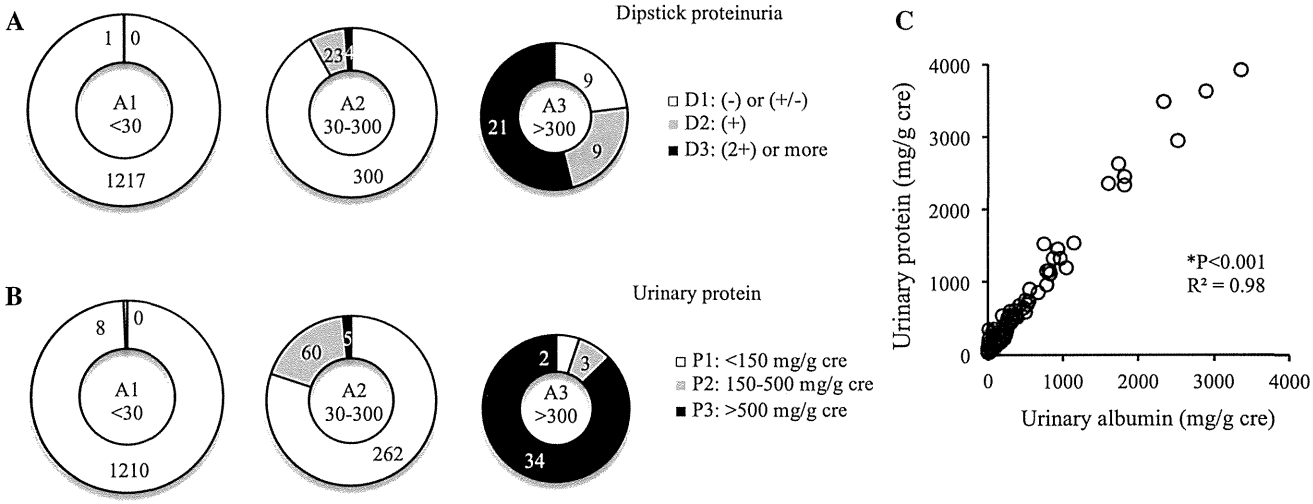

Fig. 1 Distribution and correlation of levels of albuminuria and proteinuria in the general population. The subpopulation size and levels of dipstick proteinuria (**a**) and that of urinary protein (**b**) are shown with categorization based on the results of albuminuria [A1, A2 or A3 indicated in the circles, with the amount of urinary albumin in mg/g creatinine (cre)]. **c.** The correlation between the amount of urinary protein and urinary albumin was examined using urine samples from 266 subjects with proteinuria over the dipstick's lower limit of sensitivity

proteinuria for quantitative albuminuria, which is the gold standard.

Sincerely yours,
Kei Nagai, MD, PhD, and Kunihiro Yamagata, MD, PhD

Acknowledgments This study was performed as part of the prospective ongoing project, "Research on the positioning of chronic kidney disease in specific health check and guidance in Japan." The Steering Committee for "Design of the comprehensive health care system for chronic kidney disease (CKD) Based on the individual risk assessment by specific health checkups" comprises the following members: Koichi Asahi, MD, PhD; Kunitoshi Iseki, MD, PhD; Kenjiro Kimura, MD, PhD; Toshiki Moriyama, MD, PhD; Ichiei Narita, MD, PhD; Shouichi Fujimoto, MD, PhD; Kazuhiko Tsuruya, MD, PhD; Tsuneo Konta, MD, PhD; Masahide Kondo, MD, PhD; and Tsuyoshi Watanabe, MD, PhD. This study was supported by Health and Labor Sciences Research Grants for "Study on the Appropriate States of Specific Health Checkups and Specific Health Guidance for Prevention of CKD Progression" and "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by specific health checkups" from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest The authors have declared that no conflict of interest exists.

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American Journal of Hypertension Advance Access published February 11, 2015

ORIGINAL ARTICLE

Blood Pressure, Proteinuria, and Renal Function Decline: Associations in a Large Community-Based Population

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BACKGROUND
Hypertension and proteinuria are risk factors for adverse renal outcomes in patients with chronic kidney disease. This study investigated the associations of blood pressure and proteinuria on renal function in a community-based population.

METHODS
We analyzed data from a nationwide database of 141,514 subjects who participated in the annual "Specific Health Check and Guidance in Japan" checkup in 2008 and 2010. The study subjects were aged between 29 and 74 years, and the cohort comprised 40% men. We examined relationships between blood pressure levels, proteinuria at baseline, and the 2-year change in the estimated glomerular filtration rate (eGFR), which was determined using the Japanese equation.

RESULTS
After adjusting for possible confounders, the change in the eGFR was inversely correlated with systolic blood pressure (SBP), but not diastolic blood pressure (DBP), at baseline, irrespective of the presence of proteinuria. Compared with the lowest SBP sixtile (≤118 mm Hg), eGFRs declined significantly at SBPs ≥ 134 mm Hg in subjects with proteinuria, while eGFRs declined significantly at SBPs ≥ 141 mm Hg in those without proteinuria. At the same SBPs, renal function decline was faster and the risk for incident renal insufficiency was higher in subjects with proteinuria compared with those without proteinuria.

CONCLUSIONS
This study showed that a difference in SBP, but not DBP, is independently associated with a rapid eGFR decline in the general Japanese population, and that the association of SBP on the decline of renal function was greater in subjects with proteinuria compared with those without proteinuria.

Keywords: blood pressure; cohort study; hypertension; renal function.

doi:10.1093/ajh/hpv003

INTRODUCTION

Hypertension is one of the most prevalent lifestyle-related diseases and it is strongly associated with the risk of cardiovascular and renal events, and death.[1] Similarly, proteinuria or albuminuria, which is a component of chronic kidney disease (CKD), is a risk factor for cardiovascular events, end-stage kidney disease (ESKD), and mortality.[2–4] The mutual interactions between blood pressure and kidney disease are well established,[5] and increases in blood pressure are thought to increase the risk of incident CKD and ESKD in specific subjects.[6–9] However, the associations have not been elucidated within the general population.

In the recently published guidelines for the management of high blood pressure in adults, which were produced by the Eighth Joint National Committee (JNC 8), the expert panel recommends treating the population that is aged ≥18 years and has CKD to achieve a goal systolic blood pressure (SBP) of <140 mm Hg and a goal diastolic blood pressure (DBP) of <90 mm Hg, irrespective of the presence of proteinuria.[1] However, this recommendation is largely derived from the findings of several randomized controlled trials involving hypertensive patients, namely, the African American Study of Kidney Disease and Hypertension trial, Modification of Diet in Renal Disease study, and Ramipril Efficacy In Nephropathy 2 trial,[10–12] as opposed to the general population, and from studies conducted within populations from westernized countries as opposed to populations from Asian countries, which have different backgrounds and lifestyles. Furthermore, the analysis in the populations that had and did not have proteinuria were performed as *post hoc* analyses that involved a limited number of subjects. Therefore, it is unclear whether the recommendations from the JNC 8 are applicable to proteinuric and nonproteinuric Asian people within the general population.

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Initially submitted October 30, 2014; date of first revision November 19, 2014; accepted for publication December 24, 2014.

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To address this issue, we accessed a nationwide database and examined the associations between blood pressure, proteinuria, and changes in renal function within a community-based Japanese population.

SUBJECTS AND METHODS

Study population

This study was part of the ongoing "Research on Design of the Comprehensive Health Care System for CKD Based on the Individual Risk Assessment by Specific Health Checkup" study. The Specific Health Check and Guidance program provides an annual health checkup for all inhabitants aged between 40 and 74 years, and Japanese national health insurance pays for them. Data from 16 of the prefectures (administrative regions), namely, Hokkaido, Tochigi, Saitama, Chiba, Nagano, Niigata, Ishikawa, Fukui, Gifu, Hyogo, Tokushima, Fukuoka, Saga, Nagasaki, Kumamoto, and Okinawa, that were held in a nationwide database were included in the analysis. We collected data from 219,235 people (87,750 men and 131,485 women) who took part in the health checkup program in 2008 and 2010. The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the relevant institutional ethics committees. The details of this study have been described elsewhere.[13]

We excluded 53,388 participants from this study because essential data, including blood pressure, proteinuria, and serum creatinine, were missing, and 24,333 subjects who showed renal insufficiency at baseline. Therefore, our statistical analyses comprised the data from 141,514 individuals (54,152 men and 87,362 women, an age range of between 40 and 74 years). There were 5,514 subjects with proteinuria and the proportion of the subjects in CKD stage 1 (eGFR ≥ 90 and proteinuria) and stage 2 (eGFR 60–89 and proteinuria) was 4,500 subjects (3.2%) and 1,014 subjects (0.7%), respectively, in total population.

We examined the associations between blood pressure levels and proteinuria at baseline, and the change in renal function, which was assessed using the estimated glomerular filtration rate (eGFR). We defined the change of eGFR as the difference in eGFR between baseline and 2-year value.

Measurements

Subjects used a self-reporting questionnaire to document their medical histories, current medications, smoking habits (smokers or nonsmokers), and whether they consumed alcohol or not. SBP and DBP were measured by trained staff using a standard sphygmomanometer or an automated device, after subjects had been seated for at least 5 minutes. Hypertension was defined as a SBP ≥ 140 mm Hg, a DBP ≥ 90 mm Hg, or the use of antihypertensive medications. The body mass index (BMI) was calculated by dividing the weight in kg by the square of the height in m, and obesity was defined as a BMI ≥ 25.0 kg/m^2 for both men and women.[14] Subjects were identified as having diabetes if they had fasting plasma glucose concentrations ≥126 mg/dl, glycated hemoglobin (HbA1c) values ≥6.5%, or if they were on antidiabetic medications. Triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations were measured using enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) concentrations were measured directly. Dyslipidemia was defined as a triglyceride concentration ≥150 mg/dl, an HDL-C level <40 mg/dl, an LDL-C level ≥140 mg/dl, or being on lipid-lowering medications. Hyperuricemia was defined as a serum uric acid concentration ≥7 mg/dl.

Urinalysis was performed using a single, spot urine specimen collected in the early morning after an overnight fast and a dipstick that measured protein levels. The results of the urinalysis were recorded as negative (−), trace, 1+, 2+, and 3+. Positive proteinuria was defined as ≥1+. Serum creatinine was measured using an enzymatic method, and the eGFR was calculated using the Japanese equation.[15] CKD was defined as the presence of proteinuria and/or renal insufficiency with an eGFR <60 ml/min/1.73 m^2. Incident renal insufficiency was defined as the recent development of renal insufficiency at the 2-year follow-up assessment by subjects who did not have renal insufficiency at baseline.

Statistical analysis

We grouped the subjects based on the presence or absence of proteinuria and we further divided the subjects with proteinuria into sixtiles according to their SBP at baseline, where S1 = ≤118, S2 = 119–127, S3 = 128–133, S4 = 134–140, S5 = 141–150, and S6 = ≥151 mm Hg. The subjects without proteinuria were divided into 6 groups using the same cutoff values used for the subjects with proteinuria. The distributions of every continuous value were tested by Shapiro–Wilk's test. The changes of eGFR did not show Gaussian distribution (Shapiro–Wilk's test, $P = 0.01$). However, the previous community-based studies successfully evaluated the factors for the change of eGFR using the linear regression analyses[16,17] and we assumed that the range of error in the results could be minimized by our very large sample size. Accordingly, we used the similar statistical methods in this study. The chi-squared test was used to evaluate differences in proportions. To compare the mean values in the unadjusted model and the regression coefficients in the adjusted model among the sixtiles groups, we used a one-factor analysis of variance test and least squares analyses, respectively.

We adjusted for possible confounders that showed significant correlations across the SBP sixtiles, including age, sex, BMI, DBP, eGFR, uric acid, HbA1c, triglyceride, LDL-C, HDL-C, smoking habits, alcohol consumption, and the use of antihypertensive medications. We confirmed that there is no significant collinearity among these variables. In addition, we performed *post hoc* analyses using the Dunnett–Hsu test and the lowest sixtile (S1) as a reference. To examine the factors associated with the 2-year changes in eGFR, we performed multivariate linear regression analyses, adjusted for the above mentioned confounding factors. To examine the factors associated with incident renal insufficiency, we performed multivariate logistic regression analyses adjusted for possible confounding factors that included age, sex, obesity, diabetes, dyslipidemia, hyperuricemia, smoking, alcohol consumption, eGFR, DBP, and the use of antihypertensive medications, and we calculated the odds ratios

(OR) and 95% confidence intervals (CI). Continuous data are expressed as the means and standard deviations (SD). All statistical analyses were performed using JMP®, version 10 (SAS Institute Inc., Cary, NC, USA). A P value < 0.05 was considered statistically significant.

RESULTS

Compared with those without proteinuria, the subjects with proteinuria had a higher prevalence of men, smokers, individuals who consumed alcohol, obesity, hypertension, diabetes, dyslipidemia, hyperuricemia, and individuals who used antihypertensive medications, and they had higher BMIs, SBPs, DBPs, triglyceride, HbA1c, and uric acid, and lower HDL-C. The baseline characteristics of the subjects with proteinuria divided into sixtiles according to their baseline SBP levels are described in Table 1. High SBP was accompanied by a significantly high prevalence of men, alcohol consumption, obesity, dyslipidemia, hyperuricemia, and the use of antihypertensive medications, and the mean ages, BMIs, DBPs, triglyceride levels, HbA1c levels, and uric acid levels. The mean eGFRs did not differ significantly among the SBP sixtiles. The subjects without proteinuria were divided into 6 groups using the same cutoff values as those used for the subjects with proteinuria. The distribution of the subjects' baseline characteristics across the 6 groups was similar to that of the subjects with proteinuria (Supplementary Table 1).

We evaluated the independent association of every +10 mm Hg difference in SBP and DBP on changes in renal function. In the unadjusted linear regression model, the SBP and DBP at baseline were inversely correlated with changes in the eGFR in subjects with and without proteinuria. In the multivariate linear regression model that was adjusted for possible confounders, the regression coefficients for +10 mm Hg differences in SBP and DBP were −0.592 (standard error (SE) 0.116, P < 0.001) and 0.331 (SE 0.182, P = 0.070), respectively, in subjects with proteinuria, and −0.151 (SE 0.023, P < 0.001) and 0.071 (SE 0.036, P = 0.047), respectively, in subjects without proteinuria (Table 2). These results indicated that changes in the eGFR were more significantly associated with the SBP, than the DBP. Therefore, we investigated the association between renal function and SBP. In addition, a significant interaction between the SBP and proteinuria on the changes in the eGFR (P for interaction = 0.002) was evident in synergistic manner, with higher SBP having a greater impact on the eGFR of individuals who had higher grades of proteinuria. The regression coefficients were as follows: − 0.142 (SE 0.024, P < 0.001) for negative proteinuria, − 0.249 (SE 0.085, P = 0.003) for trace proteinuria, − 0.467 (SE 0.132, P < 0.001) for proteinuria 1+, and − 0.758 (SE 0.238, P = 0.002) for proteinuria >2+ (Supplementary Figure 1).

To investigate the association between the changes in the eGFR and the SBP category, we performed a least squares analysis with adjustments for confounding factors. The adjusted analysis showed that changes in the eGFR at the 2-year follow-up assessment were inversely correlated with the SBP levels at baseline in subjects with proteinuria and nonproteinuric subjects (P < 0.001), and that compared with the lowest SBP sixtile (S1: ≤118 mm Hg), the eGFR declined rapidly and significantly at SBPs ≥134 mm Hg (S4–S6) in subjects with proteinuria, while the eGFR declined significantly at SBPs ≥141 mm Hg (S5–S6) in those without proteinuria (Figure 1). We further divided the subjects into 4 group according to the presence of proteinuria and the use of antihypertensives and found that the association between SBP and the decline of eGFR was seemed to be stronger in subject with proteinuria and antihypertensive medication (Supplementary Figure 2).

We examined the association between SBP and the renal prognosis using incident renal insufficiency as the endpoint. At the 2-year follow-up assessment, there were 534 cases (9.7%) and 8,635 cases (6.3%) of incident renal insufficiency in subjects with and without proteinuria, respectively. Multivariate logistic regression analysis adjusted for confounding factors showed that the OR increased significantly in high SBP levels in subjects with and without proteinuria (P = 0.018 and P < 0.001, respectively) (Figure 2), and that for incident renal insufficiency, the ORs for the same SBP categories were higher in subjects with proteinuria compared with those without proteinuria. The ORs for a +10-mm Hg difference in SBP in incident renal insufficiency were 1.131 (95% CI, 1.056–1.210) for subjects with proteinuria and 1.082 (95% CI, 1.063–1.103) for subjects without proteinuria, after adjustment for the previously mentioned confounders. To avoid that physiologic age-dependent decline of renal function be assimilated to true renal progression, we performed an additional analysis in subjects with baseline eGFR ≥ 65 ml/min/1.73m^2 and found that the association between SBP and incident renal insufficiency was similar to that in subjects with eGFR ≥ 60 ml/min/1.73m^2 (Supplementary Figure 3).

To investigate the association between SBP and eGFR changes in subjects without proteinuria further, we extracted the clinical parameter-matched data of 7,027 subjects who did not have proteinuria and had backgrounds that were similar to those of the subjects who had proteinuria (Supplementary Table 2) and we performed an additional analysis. In the subjects without proteinuria a weak inverse association was identified between the SBP levels and changes in the eGFRs (P = 0.014) (Supplementary Figure 4) and there was no statistically significant association between the SBP and incident renal sufficiency (P = 0.203) (Supplementary Figure 5).

DISCUSSION

The results of this longitudinal nationwide cohort study show that a difference in SBP, but not DBP, is independently associated with a rapid decline in the eGFR in the general Japanese population. The association between blood pressure and the decline of renal function was greater in subjects with proteinuria than in those without proteinuria.

The very large sample size available to us in this study enabled analyses to be undertaken with sufficient statistical power, different classifications of blood pressure to be used, namely, sixtiles and 10 mm Hg difference in blood pressures, and the inclusion of different correction factors and endpoints, namely, the eGFR decline and incident renal