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Associations of proteinuria and the estimated glomerular filtration rate with incident hypertension in young to middle-aged Japanese males ☆☆

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ABSTRACT

Objective: To investigate the independent associations of proteinuria and the estimated glomerular filtration rate (eGFR) with incident hypertension.

Methods: We investigated 29,181 Japanese males 18–59 years old without hypertension in 2000 and examined whether proteinuria and the eGFR predicted incident hypertension independently over 10 years. Incident hypertension was defined as a newly detected blood pressure of ≥140/90 mm Hg and/or the initiation of antihypertensive drugs. Proteinuria and the eGFR were categorized as dipstick negative (reference), trace or ≥1+ and ≥60 (reference), 50–59.9 or <50 ml/min/1.73 m^2, respectively. Cox proportional hazards models were used to estimate the hazard ratios (HRs) of incident hypertension.

Results: At baseline, 236 (0.8%) and 477 (1.6%) participants had trace and ≥1+ dipstick proteinuria, while 1416 (4.9%) and 129 (0.4%) participants had an eGFR of 50–59.9 and <50 ml/min/1.73 m^2, respectively. The adjusted HRs were significant for proteinuria ≥1+ (HRs 1.20, 95% CI: 1.06–1.35) and an eGFR of <50 ml/min/1.73 m^2 (1.29, 1.03–1.61). When two non-referent categories were combined (dipstick ≥ trace vs. negative and eGFR < 60 vs. ≥60 ml/min/1.73 m^2), the association was more significant for proteinuria (1.15, 1.04–1.27) than for eGFR (0.99, 0.92–1.07).

Conclusions: Proteinuria and a reduced eGFR are independently associated with future hypertension in young to middle-aged Japanese males.

Introduction

Hypertension is a highly prevalent disorder that affects more than one quarter of the population worldwide (Kearney et al., 2005) and is a major risk factor for stroke, cardiovascular disease and end-stage renal disease (Arima et al., 2003; Gueyffier, 2003; Klag et al., 1996). Hypertension is even more prevalent in Japan, with an estimated prevalence of ~40% (Kubo et al., 2008). Several factors, such as high sodium intake (1988), obesity (Fox et al., 2007) and physical inactivity (Dickinson et al., 2006), have been identified to be highly associated with hypertension. However, approximately 90% of adults with hypertension are considered to have essential hypertension, a condition without an overt primary cause (Anderson et al., 1994; Carretero and Oparil, 2000; Nishikawa et al., 2007; Rossi et al., 2006).

The kidney plays a significant role in the regulation of blood pressure (BP) by controlling blood volume, the levels of electrolytes and the sympathetic nervous system and hormonal systems, such as the renin–angiotensin–aldosterone system (Brewster and Perazella, 2004; Komukai et al., 2010). Therefore, kidney damage and dysfunction, such as proteinuria and a reduced glomerular filtration rate (GFR), have attracted attention as predictors of hypertension (Brantsma et al., 2006; Forman et al., 2008; Gerber et al., 2006; Gueyffier, 2003; Jessani et al., 2012; Kestenbaum et al., 2008; Palatini et al., 2005; Takase et al., 2012; Wang et al., 2005). However, to the best of our knowledge, only a few studies have investigated the associations of proteinuria and GFR simultaneously with the development of hypertension, and the results were not consistent (Kestenbaum et al., 2008; Takase et al., 2012), leaving uncertainty regarding the respective contributions of these factors to the development of hypertension. Asians, a racial/ethnic group with a

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high prevalence of hypertension (Kearney et al., 2005; Kubo et al., 2008), are particularly understudied regarding this issue.

Therefore, the purpose of the present study was to investigate the independent association of the presence of proteinuria and a reduced eGFR with incident hypertension in a prospective cohort study of young to middle-aged Japanese males with annual BP evaluation.

Materials & methods

Study population

The study subjects included Japanese males who underwent annual medical checkups at their workplaces, all of which were blue-chip companies in Japan (Kondo et al., 2013; Yamashita et al., 2012). Japanese males 16–59 years of age (n = 33,914) were recruited in 2000. We excluded participants with preexisting hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg or the use of antihypertensive drugs; n = 4688 at baseline examination) and excluded participants aged <18 years old (n = 45), with a final sample of 29,181 participants.

Data collection and measurements

Annual medical checkups including blood test and dipstick urine test were conducted through 2010 or until retirement at around 60 years of age. All participants were individually interviewed using a structured questionnaire in the baseline and annual follow-up surveys. The following information was recorded by trained observers: smoking status, alcohol intake, medical history and medications. The smoking status and alcohol intake were classified as current vs. former/never. Weight and height were measured while the subject was wearing light clothing without shoes. The body mass index (BMI) was computed as the weight in kilograms divided by the square of the height in meters. Urine and blood samples were obtained in the morning with overnight fasting. A urinalysis for proteinuria was conducted with Uropaper III (Eiken Chemical Co., Ltd., Tokyo, Japan), and the results were measured using a US-2100 Automated Urine Analyzer (trace (±) corresponds to proteinuria ≥15 mg/dl, 1+ to ≥30 mg/dl, 2+ to ≥100 mg/dl, 3+ to ≥300 mg/dl and 4+ to ≥1000 mg/dl). The blood analyses were conducted at a single laboratory. The GFR was estimated using the three-variable equation proposed by the Japanese Society of Nephrology (eGFR [ml/min/1.73 m^2] = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 [if female]) (Matsuo et al., 2009). In this study, the proteinuria using a dipstick and eGFR were measured at baseline (2000). Diabetes mellitus was defined as a concentration of serum fasting glucose of ≥126 mg/dl or the use of glucose-lowering medications.

Blood pressure assessment and incident hypertension

BP was measured annually with the participant in the sitting position after 5 min of rest using an automated sphygmomanometer (BP-203IIIB; Colin Corporation, Tokyo, Japan). The BP was measured two times at intervals of 1 min on the right arm, and the average value was calculated as the baseline BP. When a subject had frequent premature contractions or atrial fibrillation, trained nurses confirmed the BP using a conventional mercury sphygmomanometer. Incident hypertension was defined as a newly detected BP of ≥140/90 mm Hg and/or the initiation of antihypertensive drugs during follow-up.

Statistical analysis

All analyses were performed using the STATA software program version 11 (Stata Corp. College Station, TX, USA). Continuous variables were presented as the medians (interquartile ranges), and differences between the two/three groups were evaluated using the Wilcoxon test/Kruskal–Wallis analysis because not all continuous variables were normally distributed. Categorical variables were presented as numbers (percentages), and comparisons across the groups were made using the chi-square test. Survival curves were calculated according to the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to estimate the hazard ratios (HRs) of incident hypertension according to the level of proteinuria and eGFR adjusted for age (continuous), BMI (continuous), serum total cholesterol (continuous), serum uric acid (continuous), diabetes mellitus (category), current smoking (category), current alcohol intake (category) and proteinuria (category) or eGFR (continuous), as appropriate. We used time from baseline as time variable in the Cox models.

We assessed the independent associations of proteinuria and eGFR with incident hypertension after dividing both kidney measures into three categories (dipstick proteinuria: negative, trace and ≥1+; and eGFR: <50, 50–59.9 and ≥60 ml/min/1.73 m^2). A dipstick negative status and eGFR of ≥60 ml/min/1.73 m^2 were used as reference groups. Due to the limited number of individuals with an eGFR of <50 ml/min/1.73 m^2 and dipstick proteinuria ≥1+, we also tested dichotomized proteinuria (positive [trace, and ≥1+] vs. negative)

Table 1
Baseline characteristics (dipstick negative, ±, ≥+ and eGFR ≥ 60, 50–59.9, <50 ml/min/1.73 m^2): Aichi, Japan, 2000.

	Total (n = 29,181)	Proteinuria			p Value	eGFR (ml/min/1.73 m^2)			p Value
		Negative (n = 28,468)	Trace (±) (n = 236)	(≥+) (n = 477)		≥60 (n = 27,636)	50–59.9 (n = 1416)	<50 (n = 129)	
Age (years old)	35 (30–40)	36 (31–43)	39 (31–50)	41 (33–51)	<0.001	36 (30–42)	46 (42–51)	52 (48–57)	<0.001
Body mass index (kg/m^2)	22.3 (20.6–24.3)	22.4 (20.6–24.3)	22.7 (20.8–25.1)	23.3 (21.0–25.7)	<0.001	22.3 (20.6–24.3)	23.6 (22.0–25.3)	23.6 (21.8–25.0)	<0.001
Systolic blood pressure (mm Hg)	114 (106–121)	114 (106–122)	117 (108–126)	118 (110–128)	<0.001	114 (106–122)	116 (108–124)	120 (110–129)	<0.001
Diastolic blood pressure (mm Hg)	68 (62–76)	69 (63–77)	72 (65–80)	74 (66–81)	<0.001	69 (63–76)	74 (66–81)	77 (69–84)	<0.001
Total cholesterol (mg/dl)	190 (169–214)	190 (169–214)	194 (168–219)	199 (173–225)	<0.001	189 (168–213)	206 (185–230)	210 (184–231)	<0.001
HDL cholesterol (mg/dl)	55 (47–64)	55 (47–65)	54 (45–63)	52 (45–62)	<0.001	55 (47–65)	54 (45–63)	52 (44–62)	<0.001
Triglyceride (mg/dl)	101 (70–148)	100 (70–148)	109 (78–175)	113 (77–179)	<0.001	100 (69–147)	115 (81–169)	121 (92–169)	<0.001
Uric acid (mg/dl)	5.8 (5.1–6.6)	5.8 (5.1–6.6)	6.0 (5.0–6.9)	6.1 (5.3–7.0)	<0.001	5.8 (5.1–6.5)	6.4 (5.6–7.3)	6.9 (6.1–7.7)	<0.001
eGFR (ml/min/1.73 m^2)	75.5 (69.4–82.8)	75.0 (68.3–82.0)	73.1 (64.7–80.5)	70.8 (63.0–78.8)	<0.001	75.5 (69.4–82.8)	56.9 (55.1–58.3)	47.1 (43.2–49.3)	<0.001
Fasting blood glucose (mg/dl)	89 (83–96)	90 (84–96)	94 (86–103)	93 (86–105)	<0.001	89 (83–96)	93 (87–101)	94 (88–102)	<0.001
Diabetes (%)	2	2	9	13	<0.001	2	4	9	<0.001
Current smoker (%)	55	55	55	52	0.524	56	42	36	<0.001
Current alcohol intake (%)	72	72	70	66	0.027	72	75	60	0.001

The data are presented as medians (interquartile ranges) for continuous variables and percentages for categorical variables.
HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.