

Association of High Pulse Pressure With Proteinuria in Subjects With Diabetes, Prediabetes, or Normal Glucose Tolerance in a Large Japanese General Population Sample

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OBJECTIVE—To examine whether there is a difference in the association between high pulse pressure and proteinuria, independent of other blood pressure (BP) indices, such as systolic or diastolic BP, among subjects with diabetes, prediabetes, or normal glucose tolerance.

RESEARCH DESIGN AND METHODS—Using a nationwide health checkup database of 228,778 Japanese aged ≥ 20 years (mean 63.2 years; 39.3% men; none had pre-existing cardiovascular disease), we examined the association between high pulse pressure, defined as the highest quintile of pulse pressure (≥ 63 mmHg, $n = 40,511$), and proteinuria ($\geq 1+$ on dipstick, $n = 12,090$) separately in subjects with diabetes ($n = 27,913$), prediabetes ($n = 100,214$), and normal glucose tolerance ($n = 100,651$).

RESULTS—The prevalence of proteinuria was different among subjects with diabetes, prediabetes, and normal glucose tolerance (11.3 vs. 5.0 vs. 3.9%, respectively; $P < 0.001$). In subjects with diabetes, but not those with prediabetes or normal glucose tolerance, high pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (odds ratio 1.15 [95% CI 1.04–1.28]) or diastolic or mean BP (all $P < 0.01$). In patients with diabetes, a +1 SD increase of pulse pressure (+13 mmHg) was associated with proteinuria, even after adjustment for systolic BP (1.07 [1.00–1.13]) or diastolic or mean BP (all $P < 0.05$).

CONCLUSIONS—Among the Japanese general population, there was a significant difference in the association between high pulse pressure and proteinuria among subjects with diabetes, prediabetes, and normal glucose tolerance. Only in diabetes was high pulse pressure associated with proteinuria independent of systolic, diastolic, or mean BP levels.

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In the systemic circulation, the kidney has unique features: vascular resistance in the glomerular afferent arterioles is low, and the myogenic response of the glomerular arterioles is insensitive to changes in the other BP indices of systolic blood pressure (BP), including pulse pressure (1–3). These characteristics suggest that pressure pulsatility may contribute to barotrauma-induced renal microvascular injury, and in turn causes glomerular ultrastructural changes (e.g., podocyte loss and glomerular basement membrane thickness) (1–6).

In fact, several cross-sectional studies performed in general or hypertensive populations have demonstrated a significant association between pulse pressure and albuminuria (7,8), and some longitudinal studies have underscored the importance of pulse pressure as a risk factor for increased albuminuria in general or hypertensive populations (9,10); however, few studies have directly examined the impact of high pulse pressure on albuminuria with adjustment for other BP components, such as systolic BP, diastolic BP, and/or mean BP levels. Since renal autoregulation is particularly impaired in patients with diabetes (1–3,11–13), we hypothesized that the association between high pulse pressure and albuminuria would be more prominent in patients with diabetes than in subjects without diabetes (14–16); as of yet, however, there have been no studies examining this hypothesis directly in a large database. Furthermore, the association of pulse pressure with albuminuria has never been explored in prediabetics, who are classified as being at an intermediate stage between normal glucose tolerance and diabetes (17), but prediabetics have been shown to have a significantly increased risk of developing not only diabetes but also cardiovascular disease (18).

In the current study, therefore, we examined the association of high pulse pressure with proteinuria separately in each of subjects with diabetes, prediabetes, and normal glucose tolerance, using a large nationwide

database of subjects recruited from the national health checkup system in Japan.

RESEARCH DESIGN AND METHODS

Study population

This study was performed as a part of the prospective ongoing "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan" project. A new annual health check program, "The Specific Health Check and Guidance in Japan", was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprises Japanese citizens between the ages of 40 and 74 years. In Japan, there are 47 administrative divisions (prefectures), and 13 of these prefectures (Yamagata, Miyagi, Fukushima, and Niigata from the Tohoku region in northeastern Japan; Tokyo, Kanagawa, and Ibaraki from the Kanto region in central Japan; Osaka, Okayama, and Kochi from the Kansai, Tyugoku, or Shikoku region in western Japan; and Fukuoka, Miyazaki, and Okinawa from the Kyushu region in southern Japan), which were randomly distributed across Japan, agreed with the aims of this study and performed data collection prospectively from 2008 to 2009. Data were sent to an independent data center, the non-profit organization Japan Clinical Research Support Unit after anonymization in a linkable fashion, and verified by trained staff (K.I. and Y.O.). After that, the database was locked with a security password, which contained the participant's information managed by a research ID number but did not contain the participant's name, and was sent to each investigator on a recordable compact disc.

There were a total of 346,942 subjects (mean age, 63.4 years; 41% [$n = 141,938$] men) for whom information on age, sex, BP, BMI, habitual smoking or drinking, use of antihypertensive drugs, and previous history of cardiovascular diseases (i.e., stroke and cardiac diseases such as angina and myocardial infarction) were available, as well as data on the serum creatinine level and dipstick urine test for proteinuria (19). Some of the regions participating in our project (i.e., Okinawa and Osaka) concomitantly performed regular health checkups for employees as legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years ($n = 2,025$). Among the 346,942 subjects, 29,820 subjects with a previous

history of cardiovascular disease, 243 subjects with chronic kidney disease stage 5 (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73m²), and 47 subjects with both were excluded from the present analysis. Moreover, 88,101 subjects with insufficient blood sampling data of glucose and lipid parameters were excluded. Supplementary Table 1 shows the differences in clinical characteristics between subjects who were included in the present analysis ($n = 228,778$) and those who had missing data ($n = 88,101$).

The study was conducted according to the guidelines of the Declaration of Helsinki and Ethical Guidelines for Epidemiological Research (1 November 2007, Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor, and Welfare of Japan). Ethical approval from the respective institutional review boards was also granted.

Baseline measurement

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habits (current smoker or not), and alcohol intake (daily drinker or not). The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m²). BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical checkup. According to the recommendations of the Japanese Ministry of Health, Labor, and Welfare (<http://www.mhlw.go.jp/bunya/shakaihoshou/iryouseido01/info03a.html>), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after the subject had rested for 5 min in a seated position with the legs not crossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement. Pulse pressure was calculated as systolic BP – diastolic BP, and mean BP was calculated as diastolic BP + (pulse pressure/3).

Blood samples were collected after an overnight fast and were assayed within 24 h with an automatic clinical chemical analyzer. All measurements were conducted locally rather than at a central laboratory without calibration among different laboratories, despite the fact that beginning several years ago, standardized methods to measure laboratory data were recommended

and widely adopted by the activity of the Japan Society of Clinical Chemistry.

The value for hemoglobin A_{1c} (HbA_{1c}) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following equation (20): HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%.

Diabetes was defined in accordance with American Diabetes Association guidelines (17) as a fasting glucose concentration of 126 mg/dL or higher, HbA_{1c} 6.5% or higher, or self-reported use of antihyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) or HbA_{1c} 5.7–6.4%, or both (17).

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early morning after overnight fasting. Urine dipstick results are interpreted by the medical staff in each local medical institution and recorded as –, ±, 1+, 2+, and 3+. In Japan, it is recommended and widely adopted by the activity of the Japanese Committee for Clinical Laboratory Standards (<http://jccs.org/>) that all urine dipstick tests be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dL. In the current study, proteinuria was defined as 1+ or more. eGFR was derived using the following equation (21): eGFR (mL/min/1.73 m²) = 194 × age (years)^{-0.287} × serum creatinine (mg/dL)^{-1.094} (if women × 0.739).

Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Data were expressed as the means ± SD (age, BMI, eGFR, and BP values) or median and interquartile range (glucose and lipid parameters). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using ANOVA, and categorical parameters were compared with the χ^2 test. We subdivided the study population according to the quintiles of pulse pressure, and the prevalence of proteinuria ($\geq 1+$) was compared by χ^2 test among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The highest quintile of pulse pressure (≥ 63 mmHg, $n = 40,511$) was defined as the high pulse pressure group in the present analysis.

Next, we used a multivariable logistic regression analysis to examine the independent

association of high pulse pressure with proteinuria ($\geq 1+$) separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. In the initial model (Model 1), these associations were assessed with adjustment for age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and eGFR. Extended models were used to assess whether the association of high pulse pressure with proteinuria ($\geq 1+$) was attenuated by the potential confounding effects of glucose and lipid parameters (Model 2) and systolic BP (Model 3). In addition, to minimize the influence of systolic BP in the association between pulse pressure and proteinuria, we examined the association only in patients with diabetes whose systolic BP was within the normal BP range (i.e., <130 mmHg) (22). Finally, we examined the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes by a multivariable logistic regression analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics of the study population

The mean age \pm SD of the 228,778 subjects was 63.2 ± 8.9 years, and 89,877 of

the subjects (39.3%) were men. There were 27,913 subjects (12.2% of the total subject population) with diabetes, of whom 10,980 subjects (39.1%) were taking antihyperglycemic medications. There were 100,214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes are shown in Table 1. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) for the increased risk of proteinuria ($\geq 1+$) in diabetes itself was 2.14 (95% CI 2.03–2.25), and that in prediabetes was 1.10 (1.05–1.14), even after adjustment for significant covariates, such as age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and systolic BP level (both $P < 0.001$).

Pulse pressure and proteinuria

Clinical characteristics and metabolic or BP parameters according to the quintile of pulse pressure are shown in Supplementary Table 2. The increasing prevalence of proteinuria ($\geq 1+$) in accordance with the increasing pulse pressure was more prominent in subjects with diabetes than those without diabetes (Fig. 1). Supplementary Table 3 shows the prevalence of proteinuria subdivided by the dipstick positive scale according to the quintile of pulse pressure with or without diabetes.

Next, a multivariable logistic regression analysis was performed to examine the independent association between the highest quintile of pulse pressure and proteinuria, separately in subjects with diabetes, prediabetes, and normal glucose tolerance. In patients with diabetes, the highest quintile of pulse pressure (≥ 63 mmHg) was positively associated with proteinuria, independently of significant covariates, including systolic BP (Models 1–3 in Table 2). When we examined the association between pulse pressure and proteinuria only in patients with diabetes whose systolic BP was within the normal range (i.e., <130 mmHg, $n = 11,074$ [39.7%]), the highest quintile of pulse pressure still remained significantly associated with proteinuria (OR 1.46 [95% CI 1.03–2.08]; $P = 0.04$, respectively), even after adjustment for significant covariates, as shown in Model 2 in Table 2. When diastolic BP or mean BP was entered into Model 3 in Table 3 in place of systolic BP, the association between the highest quintile of pulse pressure and proteinuria still remained significant (1.61 [1.49–1.75] and 1.42 [1.31–1.55]; both $P < 0.001$, respectively). In contrast, the highest quintile of pulse pressure in subjects with prediabetes or normal glucose tolerance was not associated with proteinuria independently of systolic BP (Model 3 in Table 2). When

Table 1—Characteristics of the study population according to the presence of diabetes or prediabetes

	Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)	P value
Age (years)	65.2 \pm 7.3	64.2 \pm 7.9	61.6 \pm 9.8	<0.001
Men, n (%)	14,626 (52.4)	40,077 (40.0)	35,174 (34.9)	<0.001
BMI (kg/m ²)	24.1 \pm 3.7	23.3 \pm 3.3	22.5 \pm 3.1	<0.001
Current smoker, n (%)	4,846 (17.4)	12,960 (12.9)	13,971 (13.9)	<0.001
Daily drinker, n (%)	7,162 (25.7)	22,825 (22.8)	21,521 (21.4)	<0.001
eGFR (mL/min/1.73 m ²)	76.2 \pm 17.8	74.7 \pm 15.6	76.1 \pm 15.9	<0.001
Proteinuria ($\geq 1+$), n (%)	3,164 (11.3)	5,013 (5.0)	3,913 (3.9)	<0.001
Glucose and lipid parameters				
Fasting glucose (mg/dL)*	125.0 (100.0–143.0)	98.0 (90.0–105.0)	89.0 (84.0–93.0)	<0.001
HbA _{1c} (%)*	6.2 (5.6–6.9)	5.4 (5.3–5.6)	5.0 (4.8–5.1)	<0.001
Triglycerides (mg/dL)*	112.0 (79.0–162.0)	101.0 (74.0–142.0)	91.0 (67.0–127.0)	<0.001
LDL (mg/dL)*	123.0 (104.0–145.0)	127.0 (108.0–148.0)	124.0 (105.0–144.0)	<0.001
HDL (mg/dL)*	57.0 (48.0–68.0)	60.0 (51.0–72.0)	63.0 (53.0–75.0)	<0.001
Antihypertensive drugs, n (%)	11,101 (39.8)	29,157 (29.1)	21,410 (21.3)	<0.001
Antihyperlipidemic drugs, n (%)	6,823 (24.4)	17,440 (17.4)	12,233 (12.2)	<0.001
Antihyperglycemic drugs, n (%)	10,980 (39.1)	0 (0)	0 (0)	<0.001
BP parameters				
Systolic BP (mmHg)	133.4 \pm 17.5	129.7 \pm 17.0	125.7 \pm 17.2	<0.001
Diastolic BP (mmHg)	77.1 \pm 10.8	76.8 \pm 10.5	75.1 \pm 10.7	<0.001
Pulse pressure (mmHg)	56.2 \pm 13.4	52.9 \pm 12.4	50.6 \pm 12.2	<0.001

Data are expressed as the means \pm SD or percentage. P values were obtained by ANOVA or χ^2 test. *Variables with skewed distribution are expressed as median (interquartile range).

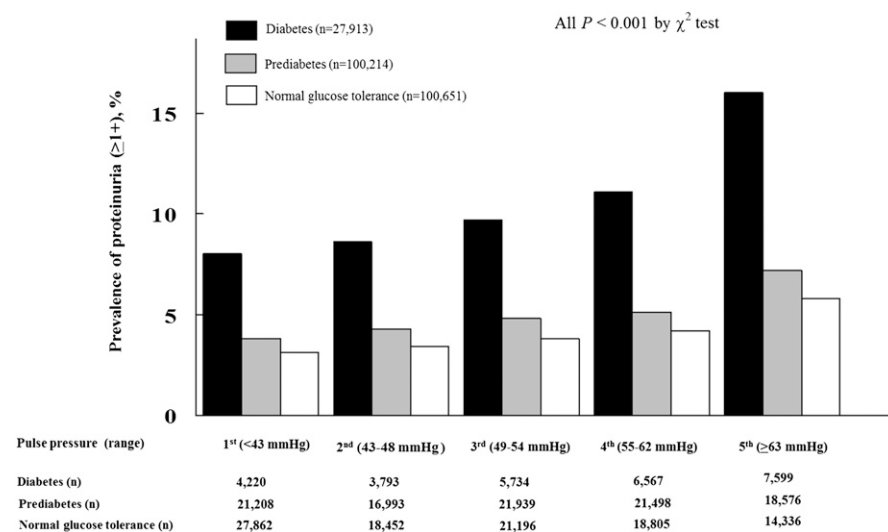


Figure 1—Prevalence of proteinuria according to the quintile of pulse pressure in subjects with diabetes, prediabetes, or normal glucose tolerance. The prevalence of proteinuria (≥1+) was calculated among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The P value was obtained by a χ^2 test among each group of the quintiles of pulse pressure.

we examined the risk of the highest quintile of pulse pressure on proteinuria among subjects without antihypertensive medications ($n = 167,110$), the conclusion remained unchanged (Model 4 in Table 2). Use of antihyperglycemic or anti-hyperlipidemic drugs did not influence any of the above results (data not shown). In contrast, systolic BP, used as an adjusted factor in Model 3 in Table 2, showed significant associations with proteinuria in subjects with diabetes, prediabetes, and normal glucose tolerance (data not shown).

Finally, we analyzed the association of a +1 SD increase of pulse pressure (+13

mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes. We found that a +1 SD increase of pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (Table 3), diastolic BP, or mean BP (data not shown).

CONCLUSIONS—In this nationwide study of 228,778 Japanese people (mean age 63.2 years) who had no known cardiovascular disease, we demonstrated for the first time that there was a significant difference in the association between the highest

quintile of pulse pressure (≥63 mmHg) and proteinuria (≥1+ on dipstick) among subjects with diabetes, prediabetes, and normal glucose tolerance. The cross-sectional design of the current study did not allow us to elucidate the pathophysiological pathway linking high pulse pressure and proteinuria (≥1+). However, there are some possible explanations for the observed association.

Pulse pressure, proteinuria, and patients with diabetes

Since the glomerular afferent arterioles provide relatively low resistance, the glomerulus is susceptible to barotrauma if the pulse pressure is elevated (1–6). In fact, prior studies have demonstrated an association of high pulse pressure with microalbuminuria even in subjects without diabetes (7,8). In the current study, we examined the possible association of high pulse pressure and proteinuria (≥1+), i.e., macroalbuminuria, and found that this association was not significant independently of systolic BP in subjects without diabetes. In contrast, systolic BP was significantly associated with proteinuria in these subjects. Although the usefulness of the urine dipstick test for risk stratification of renal and cardiovascular disease has been recognized, this method is a less sensitive measure of albuminuria compared with the measurement of urinary albumin excretion (23–26). Accordingly, we cannot deny the possibility of an association between high pulse pressure and microalbuminuria in subjects without diabetes.

Table 2—OR for the highest quintile of pulse pressure in the association of proteinuria (≥1+) according to the presence of diabetes or prediabetes

Model	Adjusted covariates	OR (95% CI)		
		Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)
Overall (n = 228,778)				
Model 1	Age + sex + BMI + current smoking + daily drinking + antihypertensive medications + eGFR	1.72 (1.59–1.87)‡	1.45 (1.35–1.55)‡	1.48 (1.37–1.61)‡
Model 2	Model 1 + fasting glucose + triglycerides + HDL + LDL	1.63 (1.50–1.77)‡	1.41 (1.31–1.50)‡	1.48 (1.36–1.60)‡
Model 3	Model 2 + systolic BP	1.16 (1.05–1.29)†	0.97 (0.89–1.05)	1.08 (0.98–1.20)
Subjects without antihypertensive medications (n = 167,110)		Diabetes (n = 16,812)	Prediabetes (n = 71,057)	Normal glucose tolerance (n = 79,241)
Model 4	Age + sex + BMI + current smoking + daily drinking + eGFR + fasting glucose + triglycerides + HDL + LDL + systolic BP	1.21 (1.03–1.43)*	1.09 (0.97–1.23)	1.13 (0.98–1.29)

OR (95% CI) of proteinuria (≥1+) was calculated for highest quintile of pulse pressure (≥63 mmHg, n = 40,511) vs. lower quintiles of pulse pressure (<63 mmHg) in each model. Statistical significance was defined as $P < 0.05$. * $P < 0.05$. † $P < 0.01$. ‡ $P < 0.001$.

Table 3—OR (95% CI) for proteinuria in diabetes (n = 27,913)

Model	OR (95% CI)	P value
Age (+9 years)*	0.94 (0.89–1.00)	0.04
Sex (0, men; 1, women)	0.55 (0.50–0.60)	<0.001
BMI (+3 kg/m ²)*	1.18 (1.14–1.22)	<0.001
Current smoking (0, no; 1, yes)	1.49 (1.35–1.65)	<0.001
Daily drinking (0, no; 1, yes)	0.90 (0.82–0.99)	0.04
Antihypertensive medications (0, no; 1, yes)	0.59 (0.54–0.64)	<0.001
eGFR (+16 mL/min/1.73 m ²)*	0.76 (0.73–0.79)	<0.001
Fasting glucose (+21 mg/dL)*	1.20 (1.18–1.22)	<0.001
Triglycerides (+78 mg/dL)*	1.06 (1.03–1.09)	<0.001
LDL (+30 mg/dL)*	1.07 (1.03–1.11)	<0.001
HDL (+16 mg/dL)*	1.02 (0.98–1.07)	0.39
Systolic BP (+17 mmHg)*	1.27 (1.20–1.36)	<0.001
Pulse pressure (+13 mmHg)*	1.08 (1.01–1.14)	0.02

Statistical significance was defined as $P < 0.05$. *The OR (95% CI) of proteinuria ($\geq 1+$) was calculated for a +1 SD increase of each indicated variable as well as dichromatic variables.

In spite of the strict collinearity between systolic BP and pulse pressure, the OR of high pulse pressure to proteinuria was reduced but remained significant even after adjustment for systolic BP in patients with diabetes (Table 2). Table 3 also shows that a +1 SD increase of systolic BP and a +1 SD increase of pulse pressure were associated with proteinuria independently of each other, with the OR of the systolic BP increase on proteinuria being higher than that of the pulse pressure increase. These findings indicate that high systolic BP showed a confirmed association with proteinuria and is an important confounder explaining the association between high pulse pressure and proteinuria; however, even after adjustment for systolic BP, the pulsatile component of BP itself was still significantly associated with proteinuria in patients with diabetes. Intriguingly, even in the patients with diabetes who were within the normal range of systolic BP values, high pulse pressure was associated with proteinuria. Some possible explanations for these findings exist. First, since renal autoregulation is impaired in diabetes (1–3,11–13), it may be possible that when pulse pressure is elevated, more barotrauma-induced glomerular ultrastructural changes leading to albuminuria occur in subjects with diabetes than in those without diabetes (1–5). Second, much as in the previous reports (27,28), higher pulse pressure was observed in diabetes than nondiabetes (Table 1), suggesting the possibility that diabetes accelerates aortic and large arterial stiffness (29). Aortic stiffness itself has a potential etiologic role in the causation and progression of renal dysfunction (30–32), because loss of the

damping of ventricular ejection in the stiffened aortae could lead to an increase in the transmission of these pressure changes to the renal microcirculation. In the current study, however, we did not use any measure of vascular stiffness more direct than pulse pressure, such as pulse wave velocity, and thus the potential efficacy of such measures will need to be investigated in the future. Third, overt proteinuria in patients with diabetes, which is observed in long-standing diabetes, together with hypertension and increased arterial stiffness, is a surrogate marker not only for renal structural damages but also generalized vascular damages (3,6,24,25). Therefore, we speculate that patients with diabetes with proteinuria are likely to have systemic vasculopathy, and as a consequence, they have high pulse pressure. Lastly, since the current study is a cross-sectional analysis, we have to pay attention to another possibility that diabetic renal disease indicated by greater proteinuria raises systolic BP as well as pulse pressure rather than the reverse in patients with diabetes.

Pulse pressure, proteinuria, and prediabetes

The current study provided the first examination of the association of pulse pressure with proteinuria in prediabetes using a large sample size. Understanding such risk estimates is important, given the increases in the prevalence of prediabetes that have occurred in many populations in conjunction with the increasing prevalence of obesity, particularly in Asian populations (33,34). In the current study, the prevalence of prediabetes was substantially high (44%). Another Japanese study performed in healthy Japanese

people ($n = 6,636$, mean age 50 years) demonstrated that the prevalence of prediabetes was 32% (35). This survey was performed between 1997 and 2003, and since the prevalence of diabetes in Asian populations has increased rapidly in recent years (33,34), the high prevalence of prediabetes in the current study was not entirely unexpected.

Several limitations of our study should be mentioned. First, single-measurement readings of BP, fasting glucose or HbA_{1c}, and proteinuria cannot be considered fully accurate. In particular, some of the dipstick-positive proteinuria could have been transient, and thus could not be taken as definitive evidence of the presence of persisting proteinuria. These factors may introduce a source of variability that could have led to a tendency to underestimate the true association between pulse pressure and proteinuria. Second, we could not separate diabetes into type 1 or type 2 diabetes. However, the incidence of type 1 diabetes is extremely low (approximately two cases/year/100,000 individuals), and Japan has one of the lowest incidence rates of type 1 diabetes in the world (36). Third, we could not assess the diabetes- and atherosclerosis-related information, such as the duration of diabetes and the presence of diabetes complications (e.g., neuropathy), which would be informative and extend the knowledge achieved in the current study. Lastly, we could not assess what kinds of antihypertensive drugs had been prescribed in treated hypertensive subjects. Some antihypertensive drugs (e.g., angiotensin receptor blockers or angiotensin enzyme-converting inhibitors) have more favorable effects on vascular and renal protection (37). Therefore, their use was potentially confounding, although our conclusions remained unchanged when we analyzed our data while excluding the subjects with antihypertensive medications.

In conclusion, among the Japanese general population, high pulse pressure, particularly in individuals with diabetes, was associated with proteinuria, and this information has the potential to supplement other BP indices. To confirm our findings, a prospective study as well as interventions that examine whether or not reduction of pulse pressure can enhance nephron-protective benefits in diabetes will be required.

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Y.Y. and Y.S. analyzed data. S.F. designed the study, collected data, and wrote the manuscript. T.K. and K.I. designed the study and collected data. T.M., K.Y., K.T., H.Y., K.A., I.K., Y.O., and T.W. designed the study, collected data, supervised the study, and revised the manuscript. S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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