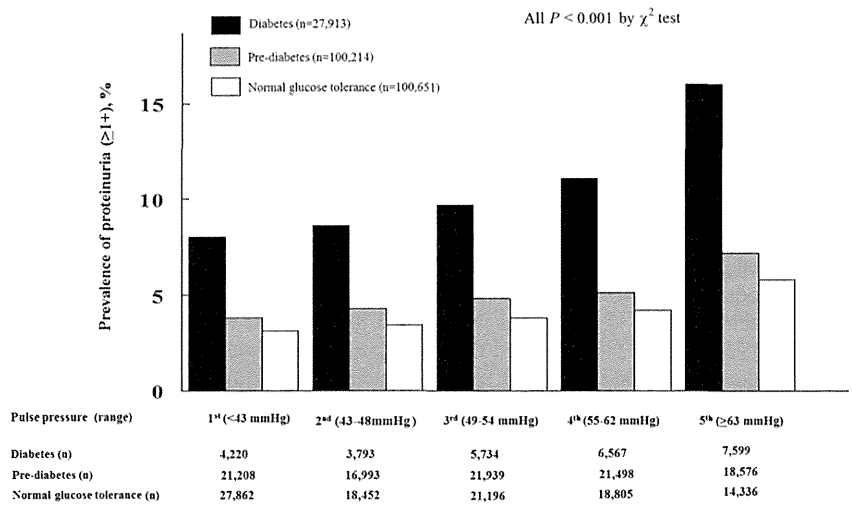

Figure 1—*Prevalence of proteinuria according to the quintile of pulse pressure in subjects with diabetes, prediabetes, or normal glucose tolerance. The prevalence of proteinuria (≥1+) was calculated among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, 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 antihyperlipidemic 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)		
Overall (n = 228,778)		Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)
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 (≥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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No potential conflicts of interest relevant to this article were reported.

Y.Y. and Y.S. analyzed the data. S.F. designed the study, collected data, and wrote the paper. 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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Glycohemoglobin not as predictive as fasting glucose as a measure of prediabetes in predicting proteinuria

Yuji Sato[1], Yuichiro Yano[2], Shouichi Fujimoto[3], Tsuneo Konta[4], Kunitoshi Iseki[5], Toshiki Moriyama[5], Kunihiro Yamagata[5], Kazuhiko Tsuruya[5], Hideaki Yoshida[5], Koichi Asahi[5], Issei Kurahashi[6], Yasuo Ohashi[7] and Tsuyoshi Watanabe[5]

[1]Circulatory and Body Fluid Regulation, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan, [2]Division of Community and Family Medicine, University of Miyazaki, Miyazaki, Japan, [3]Division of Dialysis, University of Miyazaki Hospital, Miyazaki, Japan, [4]Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine, Yamagata, Japan, [5]Steering Committee for the 'Examination of the Positioning of CKD in Specific Health Check and Guidance', Tokyo, Japan, [6]Department of Planning, Information, and Management, University of Tokyo Hospital, Tokyo, Japan and [7]Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan

Correspondence and offprint requests to: Yuji Sato; E-mail: ysato@fc.miyazaki-u.ac.jp

Abstract

Background. There is little data on the assessment of prediabetes with proteinuria.

Methods. This is a cross-sectional cohort study assessing prediabetes with proteinuria in a large Japanese population. Using a nationwide health checkup database of 228 778 Japanese aged ≥20 years (median 66 years; 39.3% were men; none had pre-existing cardiovascular disease), we examined the association between prediabetes and proteinuria (≥1+ on dipstick) separately in prediabetes subjects diagnosed with the new hemoglobin A1c (HbA1c) criterion only (PD-A1c), the impaired fasting plasma glucose only (PD-IFG) and fulfilling both criteria (PD-Both).

Results. According to the American Diabetes Association's (ADA's) criterion of 5.7–6.4% HbA1c and/or 100–125 mg/dL fasting plasma glucose, 43.8% of the subjects were judged as having prediabetes. Prediabetes subjects were divided into subclasses of PD-A1c (53.7%), PD-IFG (21.7%) and PD-Both (24.5%), respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1c criterion only. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) [95% confidence interval (95% CI)] for the increased risk of proteinuria (≥1+) in diabetes itself was 2.191 (2.081–2.307) and in whole prediabetes was 1.093 (1.046–1.142); when prediabetes was subdivided, the OR for proteinuria in PD-IFG was 1.217 (1.140–1.300) and that in PD-Both was 1.249 (1.174–1.329), but that in PD-A1c was not significant, even after adjustment for significant covariates, such as age, sex, body mass index, systolic blood pressure, antihypertensive medication, eGFR, lifestyle and lipid profile.

Conclusions. Prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and subjects with prediabetes defined using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Keywords: odds ratio; prediabetes; proteinuria

Introduction

Chronic kidney disease (CKD) is now recognized as a major global public health issue [1, 2]. Persistent proteinuria is one of the major criteria of CKD [3]. The prevalence of proteinuria among subjects with diabetes was reported to be high. For example, Ballard *et al.* [4] reported the incidence of proteinuria at initial diagnosis of type 2 diabetes and followed up ~20 years later as 8.2 and 24.6%, respectively, in 30-year-old and older US citizens. Parving *et al.* reported the prevalence of albuminuria among cases of type 2 diabetes as 13.8% in 66-year-old and older Danish individuals [5]. We also reported a rate of dipstick proteinuria of 11.3% among diabetes in a large Japanese cohort study [6].

In 1997 and 2009, the American Diabetes Association proposed the criterion for prediabetes of 100–125 mg/dL fasting plasma glucose (impaired fasting glucose, IFG) or 140–199 mg/dL OGT 2-h plasma glucose (impaired glucose tolerance, IGT) [7, 8]; subsequently, in 2011, an HbA1c level of 5.7–6.4% corresponding to the IFG was proposed [9]. There is a little data concerning the prevalence of proteinuria in prediabetes except our reported value of 5% for the same Japanese cohort [6].

Subjects with prediabetes were reported to have higher incidence of hypertension and obesity, and to be older than subjects with normal glucose tolerance [10, 11]. These variables are also independent risk factors for proteinuria [12]. After all, basic pathophysiology of prediabetes is thought to be insulin resistance [13]. Therefore, prediabetes is expected to be a risk factor for proteinuria; however, little data have been reported on this issue.

In a large national Japanese cohort, we examined the independent association of proteinuria with prediabetes, and further compared the association of prediabetes with proteinuria when it was defined by the recently proposed HbA1c criterion versus the standard impaired fasting glucose criterion.

Methods

Study design and population

This is a cross-sectional cohort study assessing the prediabetes with proteinuria in a large Japanese 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. Local governments called for the citizen to attend this annual health check under their own volition. Other details such as the participants' area were reported previously [6].

There was a total of 346 942 subjects [mean age, 63.4 years, 41% (n = 141 938) were men] for whom information on age, gender, BP, body mass index (BMI), habitual smoking or drinking, use of anti-hypertensive drugs and previous history of cardiovascular diseases (i.e. stroke and cardiac diseases such as angina and myocardial infarction) was available, as well as data on the serum creatinine level and dipstick urine test for proteinuria [14]. Individuals in certain regions participating in our project concomitantly underwent a regular health checkup for employees, which is legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years (n = 2025).

Among the 346 942 subjects, 29 820 subjects with a previous history of cardiovascular disease, 243 subjects with CKD stage 5 (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2) 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. There was no clinical difference 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 was granted ethical approval by the respective institutional review boards.

Baseline measurement

Blood samples were collected after an overnight fasting 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 starting several years ago, standardized methods to measure laboratory data have been recommended by the Japan Society of Clinical Chemistry and widely adopted.

The value for hemoglobin A1c (HbA1c) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following formula [15]:

$$\text{HbAlc}\,(\%) = \text{HbAlc}\,(\text{Japan Diabetes Society})\,(\%) + 0.4\%$$

Diabetes was defined in accordance with American Diabetes Association guidelines [9] as a fasting glucose concentration of 126 mg/dL or higher, HbA1c 6.5% or higher or self-reported use of anti-hyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL), HbA1c 5.7–6.4% or both [9].

Urinalysis by the dipstick method was performed manually by trained staff on a single spot urine specimen collected early in the morning after overnight fasting. Urine dipstick results were interpreted by the medical staff in each local medical institution and recorded as (−), (+), (1+), (2+) and (3+). In Japan, it has been recommended by the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dL. Proteinuria was defined as 1+ or more. Because dipstick +/− sometimes indicates microalbuminuria in the Japanese general population [16], taking changeable urine concentration or protein other than albumin contained in urine into consideration, we adopted dipstick 1+ or more as reflecting positive urine protein.

eGFR was derived using the following equation [17]:

$$\text{eGFR}\,(\text{mL/min/1.73 m}^2) = 194 \times \text{age}\,(\text{years})^{-0.287} \times \text{serum creatinine}\,(\text{mg/dL})^{-1.094}\ (\text{if female} \times 0.739)$$

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/shakaihosho/iryouseido01/info03a.html), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after resting for 5 min in a seated position with the legs uncrossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement.

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habit (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/m^2).

Statistical analysis

All statistical analyses were performed with SPSS version 20.0J software (SPSS, Chicago, IL). Data are expressed as median (25th to 75th percentile). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using analysis of variance (ANOVA), and categorical parameters were compared with the chi-

squared test. We divided the study population into three groups (normal glucose tolerance, prediabetes and diabetes), and then the prediabetes population was subdivided into three subgroups [PD-A1c, fulfilled HbA1c criterion but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria] [9], according to the fasting glucose level or HbA1c level.

Next, we used multivariable logistic regression analysis to examine the independent association of prediabetes with proteinuria (≥1+) separately in subjects with normal glucose tolerance, prediabetes or diabetes. In the initial model (Model 1), these associations were assessed with adjustment for age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol. An extended model (Model 2) was used to assess whether there was an association of subtype of prediabetes with proteinuria (≥1+). Statistical significance was defined as $P < 0.05$.

Results

Clinical characteristics of the study population

The median age (interquartile range) of the 228 778 subjects was 66 (59–70) years, and 89 877 of the subjects (39.3%) were men. There were 27 913 subjects (12.2%) with diabetes and 100 214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes compared with those of subjects with normal glucose are shown in Table 1. Age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria, eGFR, chemistry data and blood pressure levels were significantly different between the groups. Subjects among prediabetes, 53.7, 21.7 and 24.5% subjects were divided into subclasses of PD-A1C, PD-IFG and PD-Both, respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1C criterion only. Clinical and laboratory data of subjects with subdivided prediabetes were shown in Table 2. Similar to Table 1, age, gender, BMI, use of antihypertensive or antihyperlipidemic medications, smoking habit, drinking habit, proteinuria, eGFR, chemistry data and blood pressure levels were significantly different between the groups. Especially, the prevalence of proteinuria in subjects with PD-IFG or PD-Both was higher than in subjects with PD-A1C.

Prediabetes and proteinuria

Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) (95% CI) for the increased risk of proteinuria (≥1+) in diabetes itself was 2.191 (2.081–2.307), and that in prediabetes was 1.093 (1.046–1.142), even after adjustment for significant covariates, such as age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol (both $P < 0.001$) (Table 3, Model 1).

Table 1. Characteristics of the study population overall

	Normal glucose tolerance (*n* = 100 651, 44.0%)	Prediabetes (*n* = 100 214, 43.8%)	Diabetes (*n* = 27 913, 12.2%)	Total (*n* = 228 778)	P-value
Age (years)	64 (56–69)	66 (60–70)	67 (61–71)	66 (59–70)	<0.01
Men, *n* (%)	35 174 (34.9%)	40 077 (40.0%)	14 626 (52.4%)	89 877 (39.3%)	<0.01
BMI (kg/m^2)	22.2 (20.3–24.3)	23.1 (21.1–25.3)	23.8 (21.7–26.2)	22.8 (20.8–25.0)	<0.01
Current smoker, *n* (%)	13 971 (13.9%)	12 960 (12.9%)	4 846 (17.4%)	31 777 (13.9%)	<0.01
Daily drinker, *n* (%)	21 521 (21.4%)	22 825 (22.8%)	7 162 (25.7%)	51 508 (22.5%)	<0.01
Proteinuria (≥1+), *n* (%)	3 913 (3.9)	5 013 (5.0)	3 164 (11.3)		<0.01
eGFR (mL/min/1.73 m^2)	74.4 (64.5–85.4)	74.1 (63.8–84.3)	74.4 (63.9–86.9)	74.4 (64.1–85.2)	<0.01
eGFR stage					<0.01
≥60 without proteinuria, *n* (%)	85 560 (85.0)	82 518 (82.3)	21 458 (76.9)	189 536 (82.8)	
≥60 with proteinuria, *n* (%)	3 052 (3.0)	3 634 (3.6)	2 320 (8.3)	9 006 (3.9)	
45–59, *n* (%)	11 035 (11.0)	12 832 (12.8)	3 531 (12.7)	27 398 (12.0)	
30–44, *n* (%)	912 (0.9)	1 095 (1.1)	510 (1.8)	2 517 (1.1)	
15–29, *n* (%)	92 (0.1)	135 (0.1)	94 (0.3)	321 (0.1)	
Antihypertensive drug, *n* (%)	21 410 (21.3%)	29 157 (29.1%)	11 101 (39.8%)	61 688 (27.0%)	<0.01
Antihyperlipidemic drug, *n* (%)	12 233 (12.2%)	17 440 (17.4%)	6 823 (24.4%)	36 496 (16.0%)	<0.01
Antihyperglycemic drug, *n* (%)	0 (%)	0 (%)	10 908 (39.1%)		
Chemistry data					
FPG (mg/dL)	89 (84–93)	98 (90–105)	125 (100–143)	93 (87–102)	<0.01
HbA1c (%)	5.4 (5.2–5.5)	5.8 (5.7–6.0)	6.6 (6.0–7.3)	5.6 (5.4–5.9)	<0.01
TG (mg/dL)	91 (67–127)	101 (74–142)	112 (79–162)	97 (71–138)	<0.01
LDL (mg/dL)	124 (105–144)	127 (108–148)	123 (104–145)	125 (106–146)	<0.01
HDL (mg/dL)	63 (53–75)	60 (51–72)	57 (48–68)	61 (51–73)	<0.01
BP parameters					
SBP (mmHg)	126 (114–136)	130 (120–140)	132 (122–144)	128 (118–140)	<0.01
DBP (mmHg)	75 (69–82)	78 (70–83)	78 (70–84)	76 (70–82)	<0.01

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square test as appropriate.
BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Characteristics of the subjects with prediabetes

	PD-A1c (n = 53 838, 53.7%)	PD-IFG (n = 21 794, 21.7%)	PD-Both (n = 24 582, 24.5%)	P-value
Age (years)	66 (60–70)	66 (59–70)	67 (61–71)	<0.01
Men, n (%)	16 620 (30.9%)	11 589 (53.2%)	11 868 (48.3%)	<0.01
BMI (kg/m^2)	22.6 (20.7–24.8)	23.3 (21.4–25.4)	23.9 (21.9–26.1)	<0.01
Current smoker, n (%)	6 402 (11.9%)	3 216 (14.8%)	3 342 (13.6%)	<0.01
Daily drinker, n (%)	9 145 (17.0%)	7 113 (32.6%)	6 567 (26.7%)	<0.01
Proteinuria (≥1+), n (%)	2 102 (3.9%)	1 329 (6.1%)	1 582 (6.4%)	<0.01
eGFR (mL/min/1.73 m^2)	74.1 (63.6–83.7)	74.1 (64.1–84.7)	73.8 (63.8–84.7)	<0.01
Antihypertensive drug, n (%)	13 800 (25.6%)	6 690 (30.7%)	8 667 (35.3%)	<0.01
Antihyperlipidemic drug, n (%)	10 159 (18.9%)	2 682 (12.3%)	4 559 (18.7%)	<0.01
Antihyperglycemic drug, n (%)	0 (%)	0 (%)	0 (%)	
Chemistry data				
FPG (mg/dL)	91 (86–95)	105 (102–110)	106 (102–112)	<0.01
HbA1C (%)	5.8 (5.7–6.0)	5.4 (5.3–5.5)	5.9 (5.8–6.1)	<0.01
TG (mg/dL)	97 (71–135)	104 (75–148)	110 (80–155)	<0.01
LDL (mg/dL)	128 (109–148)	124 (105–145)	129 (109–144)	<0.01
HDL (mg/dL)	61 (52–73)	60 (50–72)	58 (49–69)	<0.01
BP parameters				
SBP (mmHg)	128 (116–138)	130 (120–142)	132 (121–142)	<0.01
DBP (mmHg)	76 (70–82)	80 (70–85)	79 (70–84)	<0.01

Data are expressed as median (interquartile range) or percentage.
Differences were evaluated using ANOVA test or chi-square test as appropriate.
PD-A1c, fulfilled HbA1c criterion (5.7–6.4%) but not FPG; PD-IFG, fulfilled impaired fasting glucose criterion (100–125 mg/dL) but not HbA1c criterion; PD-Both, fulfilled both HbA1c and IFG criteria.
BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Prediabetes subclass and proteinuria

According to univariable logistic regression analysis, not PD-A1C but PD-IFG and PD-Both were significant risk factors for proteinuria as well as diabetes. Next, multivariable logistic regression analysis was performed to examine the independent association with proteinuria, separately in subjects in prediabetes subclasses PD-A1c, PD-IFG and PD-Both, in addition to normal glucose tolerance or diabetes mellitus. Compared with subjects with normal glucose tolerance (as a reference), the OR (95% CI) for the increased risk of proteinuria (≥1+) in PD-IFG was 1.217 (1.140–1.300) and that in PD-Both was 1.249 (1.174–1.329) (both $P < 0.001$), but that in PD-A1c was not significant, even after adjustment for significant covariates, such as age, gender, BMI, systolic blood pressure, antihypertensive medication, current smoking, daily drinking, eGFR level, triglyceride and LDL-cholesterol (Table 3, Model 2 and Figure 1).

Discussion

The messages of this article are that prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and that subjects with prediabetes defined by using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Prediabetes and proteinuria

We showed that prediabetes was a significant risk factor associated with proteinuria independent of age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking) and lipid profile. Prediabetes is a risk factor not only for the development of diabetes but also for CVD occurrence [9, 18, 19]. Persistent proteinuria is one of the major criteria of CKD and promotes CVD [20–23]. Subjects having prediabetes with proteinuria are expected to be particularly susceptible to the development of CKD and/or CVD; therefore, these individuals should undergo medical intervention, such as lifestyle guidance and, if needed, medication.

We investigated 228 778 subjects who received a Japanese Tokutei Kenshin health checkup. Prediabetes was defined using the criterion of impaired fasting glucose level ($100 \leq \text{FPG} < 126$ mg/dL) or HbA1c level ($5.7 \leq \text{HbA1c} \leq 6.4\%$). According to these criteria, 100 214 (43.8%) subjects were judged as having prediabetes in our cohort. Clinical and laboratory data were significantly different among the groups of normal glucose tolerance, prediabetes and diabetes; however, because of the large number of participants, their clinical means, especially eGFRs, are unclear, and seem almost to be equal among groups (Table 1).

Why does this cohort exhibit so much prediabetes? A cohort study in the USA, the '1999 through 2006 National Health and Nutrition Examination Survey', (NHANES) revealed that 27.7% of participants had prediabetes, according to the ADA's IFG criterion [11]. Japanese data from a single facility revealed a rate of prediabetes of 33.5% among those undergoing an annual health checkup, according to the ADA criterion of IFG and/or IGT [24]. Possible reasons for the high level of prediabetes in our cohort are discussed. First, we can point out the age difference; mean age in the '1999 through 2006 NHANES was around 47 years of age, on the other hand, median age of our cohort was 66 years of age. Second, there are some possible biases toward the

Table 3. Results of the univariable and multivariable logistic regression analyses for proteinuria

	Unadjusted OR		Adjusted OR			
			Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
NGT (0 = no, 1 = yes)	1 (Reference)		1 (Reference)			
PD (0 = no, 1 = yes)	1.302 (1.247:1.359)	<0.001	1.093 (1.046:1.142)	<0.001		
DM (0 = no, 1 = yes)	3.161 (3.010:3.319)	<0.001	2.191 (2.081:2.307)	<0.001		
NGT (0 = no, 1 = yes)					1 (Reference)	
PD-A1c (0 = no, 1 = yes)	1.004 (0.952:1.060)	0.872			0.951 (0.900:1.005)	0.074
PD-IFG (0 = no, 1 = yes)	1.605 (1.506:1.712)	<0.001			1.217 (1.140:1.300)	<0.001
PD-Both (0 = no, 1 = yes)	1.7 (1.601:1.806)	<0.001			1.249 (1.174:1.329)	<0.001
DM (0 = no, 1 = yes)					2.207 (2.096:2.324)	<0.001
Age, +10 years	1.133 (1.111:157)	<0.001	0.910 (0.889:0.932)	<0.001	0.910 (0.889:0.932)	<0.001
Male, gender	2.061 (1.987:2.139)	<0.001	1.645 (1.576 :1.717)	<0.001	1.618 (1.550:1.689)	<0.001
BMI, +3 kg/m^2	1.134 (1.325:1.363)	<0.001	1.145 (1.127:1.164)	<0.001	1.141 (1.123:1.160)	<0.001
SBP, +10 mmHg	1.264 (1.252:1.277)	<0.001	1.173 (1.161:1.186)	<0.001	1.170 (1.157:1.183)	<0.001
Antihypertensives (0 = no, 1 = yes)	2.380 (2.295:2.472)	<0.001	1.709 (1.641:1.781)	<0.001	1.703 (1.634:1.774)	<0.001
Current smoker (0 = no, 1 = yes)	1.584 (1.512:1.659)	<0.001	1.420 (1.349:1.494)	<0.001	1.428 (1.356:1.503)	<0.001
Daily drinker (0 = no, 1 = yes)	1.325 (1.271:1.381)	<0.001	0.900 (0.859:0.943)	<0.001	0.892 (0.851:0.935)	<0.001
eGFR, +10 mL/min/1.73 m^2	0.829 (0.819:0.839)	<0.001	0.845 (0.834:0.855)	<0.001	0.844 (0.833:0.854)	<0.001
TG, +50 mg/dL	1.123 (1.114:1.132)	<0.001	1.043 (1.033:1.053)	<0.001	1.042 (1.032:1.052)	<0.001
LDL, +10 mg/dL	0.99 (0.984:0.996)	<0.001	0.998 (0.982:1.004)	0.545	0.998 (0.992:1.004)	0.508

NGT, normal glucose tolerance; PD, prediabetes; DM, diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low-density lipoprotein; SBP, systolic blood pressure.

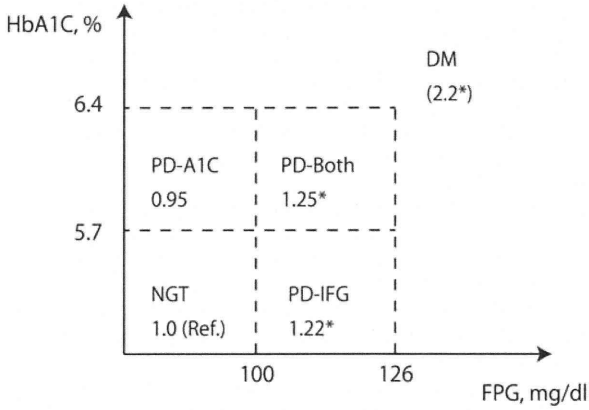

Fig. 1. OR for proteinuria according to subclass of prediabetes. The ORs of proteinuria in subjects with NGT, PD-A1c, PD-IFG, PD-Both or DM are shown. The analysis was adjusted for age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking), TG and LDL-C. *P < 0.001 versus NGT. NGT, normal glucose tolerance; PD, prediabetes; DM, diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL, low-density lipoprotein; SBP, systolic blood pressure.

participants who are particularly concerned about their physical condition or might be worried about their health status, such as the fact that many prediabetes subjects enrolled in this study under their own volition. Third, the actual number of subjects with prediabetes is increasing worldwide, especially in Asia. Increasing numbers of cases of prediabetes or diabetes itself have been reported not only in Japan, but also in India and China [25–27]. Dietary habits have also changed from the traditional style to a Western style, involving an increase in total calories, meat and fatty meals [28, 29]. Asians also exercise less now, associated with the spread of motorization [30]. A recent report stated that Asians tend to have much visceral fat tissue, in spite of a relatively low BMI score, compared with Caucasians [31–34]. Furthermore, genetically, Asians have a low insulin secretory ability [35–37]. These mechanisms of why Asians may be susceptible to diabetes are well summarized elsewhere [25].

Our study showed prediabetes was an independent risk factor for proteinuria, to diagnose prediabetes in a positive manner is meaningful for the measure to CKD in terms of prophylaxis transition to overt diabetes, renal function decrement or cardiovasucular disease.

In this study, the use of antihypertensive medication is one of the major risk factors associated with proteinuria (Table 3); however, the kind of antihypertensive drugs that patients used was unknown. The prevalence of ACE inhibitor or angiotensin II receptor antagonist users among cases of prediabetes, undiagnosed diabetes and diagnosed diabetes was reported in the USA to be lower than expected, at 8, 11 and 21%, respectively, in spite of these drugs being reported to have antiproteinuric effects or to delay CKD progression [11]. There are no data on the prevalence of the use of these drugs in patients with prediabetes in Japan. Longitudinal study is needed to clarify whether intervention using these drugs applied to prediabetes with proteinuria could prevent progression to CKD or to cardiovascular diseases.

Subclass of prediabetes and proteinuria

Subjects with prediabetes were classified into three groups: PD-A1c, PD-IFG and PD-Both, as defined above. The OR for proteinuria was significantly higher in subjects in the groups of PD-IFG and PD-Both than in PD-A1c, independent of age, sex, BMI, SBP, antihypertensive medication, eGFR, lifestyle (smoking, drinking)

and lipid profile. Our data clearly revealed that the different groups, defined by different criteria, have different risks for proteinuria in the same category of prediabetes.

Insulin resistance is a principal pathophysiology of prediabetes as well as overt diabetes; however, two types of prediabetes, impaired fasting glucose or impaired glucose tolerance, are reported to be quite different in their causality of impaired glucose metabolism, such as hepatic insulin resistance or muscle insulin resistance [13]. There is a possibility that population of PD-A1c or PD-IFG has different bases of insulin resistance pathophysiology. However, we do not have sufficient data to support this idea yet.

A recent ADA statement indicated that HbA1c is a good marker to detect those at increased risk for diabetes (prediabetes) [9]; however, our data showed that HbA1c was not sufficient to identify subjects with prediabetes defined by impaired fasting glucose.

Limitations

This study is cross-sectional, so we were unable to infer causality for proteinuria. There might be some bias toward the participants who were particularly motivated to undergo a health examination. Many people were excluded because of missing data. Urine dipstick analyses were performed manually. This visual judgment is limitation. In particular, some of the dipstick-positive proteinuria could have been transient, and the presence of persisting proteinuria was not confirmed. Physiological proteinuria could not be ruled out because the dipstick test for detecting proteinuria was only carried out once. Urine-specific gravity and pH were not recorded; therefore, the effect of urine concentration on test performance was not assessed. Furthermore, a relatively high false-positive rate for proteinuria by judging isolated dipstick test results was reported [38]. Possible HbA1c value variability has also been mentioned. However, the effect of this should be minimal in this study because Japanese HbA1c assay CV has been reported to be low [39].

We could not rule out the presence of subjects who had not fasted and had plasma glucose levels above 100 mg/dL; therefore, these could have been counted among those actually having prediabetes. However, because participants were strictly instructed to attend a health checkup in a fasting state, we speculate that there were only a minimal number of nonfasting subjects.

Summary

We examined the association of prediabetes with proteinuria, and compared the risk of proteinuria among those classified prediabetes by two ADA prediabetes criteria, fasting plasma glucose and newer HbA1c, in a large (>200 000) Japanese database of health checkup data of adults with no pre-existing cardiovascular diseases. We found that prediabetes was a significant risk factor for proteinuria compared with completely normal glucose level, and subjects with prediabetes defined by using impaired fasting glucose were at significantly higher risk for proteinuria than those defined by HbA1c, only.

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Predicting outcomes after myocardial infarction by using the Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease study equation: results from the Korea Acute Myocardial Infarction Registry

Joon Seok Choi[1], Chang Seong Kim[1], Eun Hui Bae[1], Seong Kwon Ma[1], Young-Keun Ahn[1,2], Myung Ho Jeong[1,2], Young Jo Kim[3], Myeong Chan Cho[4], Chong Jin Kim[5], Soo Wan Kim[1] and Korea Acute Myocardial Infarction Registry Investigators*

[1]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, Korea, [2]Cardiovascular Research Institute of Chonnam National University, Gwangju, Korea, [3]Department of Internal Medicine, Yeungnam University, Daegu, Korea, [4]Department of Internal Medicine, Chungbuk National University, Cheongju, Korea and [5]Department of Internal Medicine, Kyunghee University, Seoul, Korea

Correspondence and offprint requests to: Soo Wan Kim; E-mail: skimw@chonnam.ac.kr
*See the appendix.

Abstract

Background. The presence of chronic kidney disease is an independent prognostic factor in patients with myocardial infarction (MI). We compared the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) study equation with regard to prognostic value in patients with MI.

Methods. This study analyzed a retrospective cohort of 11 050 consecutive patients who had MI and were