ical characteristics by serum uric acid levels was performed using the Chi-square test for categorical data, and analysis of variance or the Kruskal-Wallis test for continuous variables. For multiple comparisons, Fisher's exact test with Bonferroni correction, Dunnett's parametric multiple-comparison test, or Steel's nonparametric multiple comparison test [21] was used to compare the reference category to all other categories. Prevalence of hypouricemia was stratified by age and eGFR; age categories were: 40–49, 50–59, 60–69, and 70–74 years, and eGFR categories were: ≤15, 15–29, 30–44, 45–59, 60–89, and >90 ml/min/1.73 m^2 (in accordance with the definition in Kidney Disease: Improving Global Outcomes [KDIGO]) [22].

Logistic regression was used to assess the relationship between hypouricemia and reduced eGFR after adjusting for a priori identified covariates. Four levels of multivariable adjustment were examined: (1) unadjusted; (2) Model 1, which included age (per 10-year increase), daily drinker, current smoker, hypertension, diabetes mellitus, and hypercholesterolemia; (3) Model 2, which included all covariates in Model 1 and obesity; and (4) Model 3, which included all covariates in Model 2 and history of renal failure. By using stratified analysis, we evaluated whether the relationship between hypouricemia and reduced GFR was modified by diabetic status, because serum uric acid is often low due to the effects of glycosuria on increasing uric acid excretion in diabetes [23].

All tests were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS for Windows (Version 18.0; SPSS, Chicago, Ill., USA), Stata/MP software (Version 12.1; Stata Corp., College Station, Tex., USA), and EZR (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing) [24].

Results

Of the 667,218 individuals who participated in the SHC in 2008, we excluded those for whom serum uric acid or serum creatinine levels were not measured. Although these measurements are not mandatory items of the SHC, they are included in some regions. Those with missing covariates were also excluded, resulting in a final study population of 227,645 (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000381106). There were no major differences between included and excluded individuals with respect to serum uric acid levels and BMI, but the latter group was slightly younger and more likely to have a history of stroke, heart disease, or renal failure (online suppl. table 1).

Among the 90,710 men and 136,935 women, 193 (0.2%) and 540 (0.4%) were identified as having hypouricemia, respectively. The prevalence of hypouricemia did not change significantly with age in men (p for trend = 0.24), but decreased with age in women (p for trend <0.001) (fig. 1). Next, we investigated the association between serum uric acid levels and eGFR (online suppl.
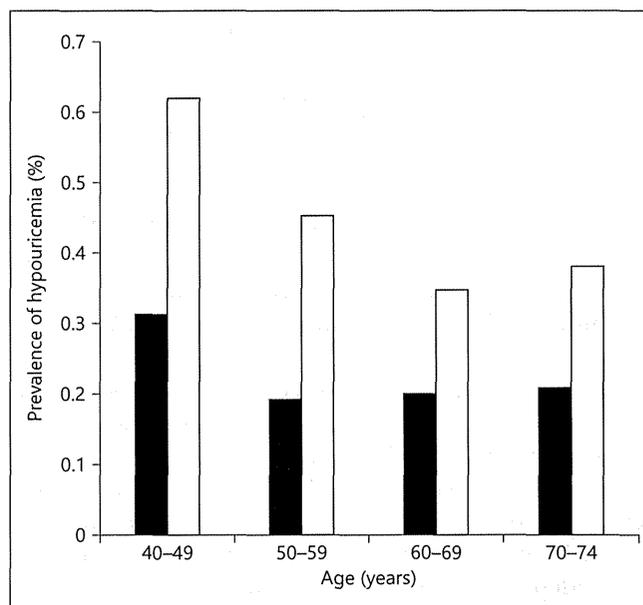

Fig. 1. Prevalence of hypouricemia by gender and age. Trends were significant for women (□; p < 0.001), but not for men (■; p = 0.24).

fig. 2). A higher proportion of men with hypouricemia had reduced eGFR (<60 ml/min/1.73 m^2), whereas a higher proportion of women with hypouricemia had an eGFR ≥90 ml/min/1.73 m^2, compared with men and women with serum uric acid levels of 4.1–5.0 mg/dl.

Men with hypouricemia had a higher BMI compared with those in the reference category (i.e., serum uric acid levels of 4.1–5.0 mg/dl) (table 1). In contrast, women with hypouricemia had a lower BMI, a lower prevalence of hypercholesterolemia, lower low-density lipoprotein cholesterol levels, higher high-density lipoprotein cholesterol levels, lower triglyceride levels, lower alanine transaminase levels, lower gamma-glutamyl transpeptidase levels, and a higher eGFR, compared with those in the reference category (table 2). In both men and women, there were no differences between those with hypouricemia and those in the reference category with regard to past history of stroke, heart disease, or renal failure.

Men with hypouricemia had an unadjusted odds ratio (OR) of 1.71 (95% confidence interval [CI], 1.16–2.53) for reduced eGFR compared with those in the reference category (online suppl. table 2). The association did not change after adjusting for potential risk factors of reduced eGFR (i.e., age, smoking, drinking, hypertension, diabetes mellitus, and hypercholesterolemia) (OR, 1.86; 95% CI, 1.25–2.78). The association was only partially attenuated after additionally adjusting for obesity (OR, 1.85;

Wakasugi et al.

Table 1. Characteristics of male participants in the Japanese Specific Health Checkups and Guidance System (n = 90,710)

	Serum uric acid category, mg/dl						
	≤2 (n = 193 [0.2%])	2.1–3.0 (n = 774 [0.9%])	3.1–4.0 (n = 4,565 [5.0%])	4.1–5.0 (n = 14,310 [15.8%])	5.1–6.0 (n = 27,252 [30.0%])	6.1–7.0 (n = 25,192 [27.8%])	>7.0 (n = 18,424 [20.3%])
Serum uric acid, mg/dl	1.1 (0.5)[a]	2.7 (0.2)[a]	3.7 (0.3)[a]	4.6 (0.3)	5.6 (0.3)[a]	6.5 (0.3)[a]	7.9 (0.8)[a]
Age, years	63.3 (9.3)	64.9 (7.9)	65.1 (7.8)[a]	64.6 (8.0)	64.1 (8.4)[a]	63.5 (8.7)[a]	62.7 (9.1)[a]
BMI, kg/m²	23.7 (2.9)[a]	22.5 (3.0)[a]	22.9 (3.0)	22.9 (2.9)	23.4 (2.9)[a]	24.0 (2.9)[a]	24.6 (3.1)[a]
History of stroke, %	4.1	6.3	5.2	4.7	4.4	5.0	5.0
History of heart disease, %	7.8	10.1	7.7	7.7	7.6	8.1	8.3
History of renal failure, %	1.0	0.3	0.6	0.4	0.6	0.7[a]	1.0[a]
Current smoker, %	20.7	25.8	26.1	26.3	25.6	25.5	26.1
Daily drinker, %	34.7	35.0	38.6	38.7	41.4[a]	45.7[a]	50.4[a]
Hypertension, %	47.7	41.6	44.8	44.2	47.3[a]	53.0[a]	57.5[a]
Diabetes, %	14.0	20.5	19.8*	17.0	13.6[a]	12.2[a]	11.4[a]
Hypercholesterolemia, %	30.1	28.0	31.1	30.6	33.6[a]	35.6[a]	37.0[a]
Systolic BP, mm Hg	129 (17)	128 (17)	129 (17)	129 (17)	130 (17)[a]	132 (17)[a]	133 (17)[a]
Diastolic BP, mm Hg	77 (10)	76 (10)	77 (10)	77 (11)	78 (10)[a]	79 (11)[a]	80 (11)[a]
LDL-cholesterol, mg/dl	116 (30)	115 (29)[a]	118 (29)	118 (29)	121 (29)[a]	122 (30)[a]	123 (32)[a]
HDL-cholesterol, mg/dl	59 (16)	60 (16)	59 (16)	59 (15)	58 (15)[a]	57 (15)[a]	55 (15)[a]
Triglycerides, mg/dl	96 [75, 134]	87 [65, 122][a]	91 [67, 130]	93 [68, 131]	101 [73, 141][a]	112 [80, 158][a]	129 [90, 189][a]
Glucose, mg/dl	100 (24)	103 (26)[a]	103 (24)[a]	101 (21)	100 (19)[a]	100 (18)[a]	100 (17)[a]
Hemoglobin A₁c, %	5.7 (1.0)	5.9 (0.9)	5.9 (0.8)[a]	5.8 (0.7)	5.7 (0.7)[a]	5.7 (0.6)[a]	5.7 (0.5)[a]
AST, IU/l	22 [19, 28]	22 [19, 26][a]	22 [19, 26]	22 [19, 26]	22 [19, 27][a]	23 [20, 28][a]	24 [20, 30][a]
ALT, IU/l	21 [15, 29]	18 [14, 24][a]	19 [15, 25]	19 [15, 25]	20 [16, 27][a]	21 [16, 29][a]	23 [17, 32][a]
γ-GTP, IU/l	31 [21, 52]	27 [19, 43]	28 [20, 44]	28 [20, 44]	30 [21, 47][a]	35 [23, 56][a]	42 [27, 74][a]
sCr, mg/dl	0.81 (0.20)	0.76 (0.14)[a]	0.78 (0.21)[a]	0.80 (0.16)	0.83 (0.20)[a]	0.87 (0.19)[a]	0.94 (0.29)[a]
Proteinuria, %	5.2	5.9	6.5	6.6	6.6	7.7[a]	10.4[a]
eGFR, ml/min/1.73 m²	79.7 (22.9)	82.2 (17.3)[a]	79.7 (16.4)[a]	77.7 (15.1)	74.9 (14.6)[a]	71.5 (14.7)[a]	67.5 (15.4)[a]
Reduced kidney function, %	16.1	7.0[a]	9.0	10.0	14.3[a]	21.5[a]	33.1[a]

Data are shown as % for categorical variables, and mean (standard deviation) or median [interquartile range] for continuous variables. BMI = Body mass index; BP = blood pressure; sCr = serum creatinine; LDL = low-density lipoprotein; HDL = high-density lipoprotein; AST = aspartate transaminase; ALT = alanine transaminase; γ-GTP = gamma glutamyl transpeptidase; eGFR = estimated glomerular filtration rate. [a] Indicates statistical significance (p < 0.05) compared to the reference category (i.e., serum uric acid levels of 4.1–5.0 mg/dl).

95% CI, 1.24–2.76) and history of renal failure (OR, 1.83; 95% CI, 1.23–2.74).

Women with hypouricemia had an unadjusted OR of 0.60 (95% CI, 0.42–0.85) for reduced eGFR compared with those in the reference category. The direction and magnitude of the association did not change after adjusting for potential risk factors of reduced eGFR (OR, 0.61; 95% CI, 0.43–0.88). Moreover, the association did not change after additionally adjusting for obesity (OR, 0.61; 95% CI, 0.43–0.87) and history of renal failure (OR, 0.61; 95% CI, 0.43–0.86).

Subgroup analyses stratified by diabetic status were performed, because diabetes mellitus is reportedly associated with both hypouricemia and hyperuricemia [23]. Point estimates of the OR of hypouricemia were similar in those with and without diabetes compared with the entire study population (men without diabetes; 1.81, 95% CI, 1.17–2.80; men with diabetes; 1.88, 95% CI, 0.68–5.20; women without diabetes; 0.62, 95% CI, 0.43–0.89; women with diabetes; 0.49, 95% CI, 0.12–2.05), although the association was not significant in participants with diabetes due to the small sample size (fig. 2).

Discussion

In this study, the prevalence of hypouricemia and its association with reduced eGFR was examined using nationwide data in Japan, leading to two new insights. First, the prevalence of hypouricemia decreased with age in women, but not in men. Second, hypouricemia was associated with reduced eGFR in men, but not in women. These findings suggest the possibility that men with hypouricemia are at a higher risk of reduced kidney function.

Table 2. Characteristics of female participants in the Japanese Specific Health Checkups and Guidance System (n = 136,935)

	Serum uric acid category, mg/dl						
	≤2 (n = 540 [0.4%])	2.1–3.0 (n = 6,331 [4.6%])	3.1–4.0 (n = 32,223 [23.5%])	4.1–5.0 (n = 52,579 [38.4%])	5.1–6.0 (n = 31,892 [23.3%])	6.1–7.0 (n = 10,339 [7.6%])	>7.0 (n = 3,031 [2.2%])
Serum uric acid, mg/dl	1.5 (0.6)[a]	2.7 (0.2)[a]	3.6 (0.3)[a]	4.5 (0.3)	5.5 (0.3)[a]	6.4 (0.3)[a]	7.7 (0.7)[a]
Age, years	62.5 (9.0)[a]	62.4 (9.0)[a]	62.7 (8.7)[a]	63.6 (7.9)	64.5 (7.3)[a]	65.1 (7.0)[a]	65.3 (7.0)[a]
BMI, kg/m^2	21.7 (3.3)[a]	21.5 (3.0)[a]	21.8 (3.0)[a]	22.5 (3.2)	23.6 (3.5)[a]	24.7 (3.8)[a]	25.4 (4.2)[a]
History of stroke, %	1.7	2.1	2.2	2.3	2.9[a]	3.4[a]	4.8[a]
History of heart disease, %	4.4	4.5	4.3	4.6	5.5[a]	6.8[a]	8.9[a]
History of renal failure, %	0.6	0.5	0.4	0.4	0.6[a]	0.9[a]	2.3[a]
Current smoker, %	7.2	6.3	6.3	6.0	6.8[a]	8.1[a]	9.7[a]
Daily drinker, %	4.8	5.3[a]	5.6[a]	7.0	8.7[a]	10.3[a]	12.5[a]
Hypertension, %	38.1	31.8[a]	33.5[a]	39.4	49.4[a]	59.0[a]	70.0[a]
Diabetes, %	7.4	7.0	6.4	6.7	8.6[a]	11.8[a]	17.0[a]
Hypercholesterolemia, %	41.1[a]	40.9[a]	44.0[a]	50.8	55.5[a]	59.9[a]	60.8[a]
Systolic BP, mm Hg	127 (18)	125 (18)[a]	126 (18)[a]	128 (18)	131 (18)[a]	133 (17)[a]	135 (18)[a]
Diastolic BP, mm Hg	74 (10)	73 (11)[a]	74 (10)[a]	75 (10)	76 (10)[a]	78 (10)[a]	78 (11)[a]
LDL-cholesterol, mg/dl	122 (30)[a]	124 (29)[a]	127 (29)[a]	130 (30)	133 (31)[a]	135 (32)[a]	133 (33)[a]
HDL-cholesterol, mg/dl	69 (17)[a]	69 (16)[a]	68 (16)[a]	66 (16)	64 (16)[a]	61 (15)[a]	59 (16)[a]
Triglycerides, mg/dl	83 [61, 111][a]	78 [59, 104][a]	82 [62, 111][a]	90 [68, 123]	102 [75, 140][a]	115 [84, 158][a]	128 [95, 180][a]
Glucose, mg/dl	91 (20)	94 (18)	93 (16)[a]	94 (15)	96 (15)[a]	98 (16)[a]	101 (19)[a]
Hemoglobin A$_{1c}$, %	5.6 (0.7)	5.7 (0.6)[a]	5.6 (0.6)[a]	5.7 (0.5)	5.7 (0.5)[a]	5.8 (0.6)[a]	5.9 (0.6)[a]
AST, IU/l	21 [18, 25]	21 [18, 24][a]	21 [18, 25][a]	21 [19, 25]	22 [19, 26][a]	23 [20, 27][a]	24 [20, 29][a]
ALT, IU/l	16 [13, 20][a]	15 [13, 20][a]	16 [13, 20][a]	17 [14, 22]	18 [14, 24][a]	20 [15, 27][a]	21 [16, 29][a]
γ-GTP, IU/l	18 [13, 26][a]	17 [13, 23][a]	18 [14, 24][a]	19 [15, 27]	21 [16, 31][a]	24 [18, 37][a]	28 [20, 44][a]
sCr, mg/dl	0.58 (0.17)[a]	0.58 (0.10)[a]	0.60 (0.11)[a]	0.63 (0.11)	0.66 (0.14)[a]	0.70 (0.22)[a]	0.80 (0.41)[a]
Proteinuria, %	3.9	2.8	2.9	3.0	4.7[a]	7.4[a]	13.8[a]
eGFR, ml/min/1.73 m^2	83.5 (19.6)[a]	83.3 (16.7)[a]	79.9 (15.4)[a]	75.3 (14.4)	71.2 (14.4)[a]	67.2 (14.7)[a]	61.6 (17.0)[a]
Reduced kidney function, %	6.1[a]	3.8[a]	5.4[a]	9.8	17.9[a]	28.6[a]	43.7[a]

Data are shown as % for categorical variables, and mean (standard deviation) or median [interquartile range] for continuous variables. BMI = Body mass index; BP = blood pressure; sCr = serum creatinine; LDL = low-density lipoprotein; HDL = high-density lipoprotein; AST = aspartate transaminase; ALT = alanine transaminase; γ-GTP = gamma glutamyl transpeptidase; eGFR = estimated glomerular filtration rate. [a] Indicates statistical significance (p < 0.05) compared to the reference category (i.e., serum uric acid levels of 4.1–5.0 mg/dl).

The present study found that the prevalence of hypouricemia in the general population was 0.2% in men and 0.4% in women, respectively. This prevalence is consistent with that reported in previous reports, that is, 0.15% (5/3,258) in outpatients [25], 0.34% in 586 normal subjects [2], and 0.23% (4/1,730) in Japanese children aged 9–15 [26]. Our study, however, is the first to report a gender difference, demonstrating that the prevalence remains constant at any age in men, whereas it decreases with age in women. Although the reason for this is unclear, a possible role of estrogen has been suggested, given that serum uric acid levels increase after menopause [27–29]. Because 80% of Japanese women undergo menopause between the ages 45 and 54 [30], menopausal status may explain the decrease in prevalence of hypouricemia with age in women. Unfortunately, information regarding menopausal status was not available in this study.

Another important and interesting finding was the association of hypouricemia with reduced eGFR in men, but not in women. To our knowledge, this study is the first to show a moderately J-shaped association between serum uric acid levels and the prevalence of reduced eGFR in men. That is, both hypouricemia and hyperuricemia are associated with an increased risk of reduced eGFR in men.

Many observational studies have reported that increased serum uric acid levels independently predict the development of reduced eGFR in the general population [31–36]. However, very few studies have assessed the association between hypouricemia and the risk of reduced eGFR. One possible reason for this is that the lower cutoff level for serum uric acid was higher than 2.0 mg/dl. In the present study, hypouricemia was associated with reduced eGFR in men, but not among participants with serum
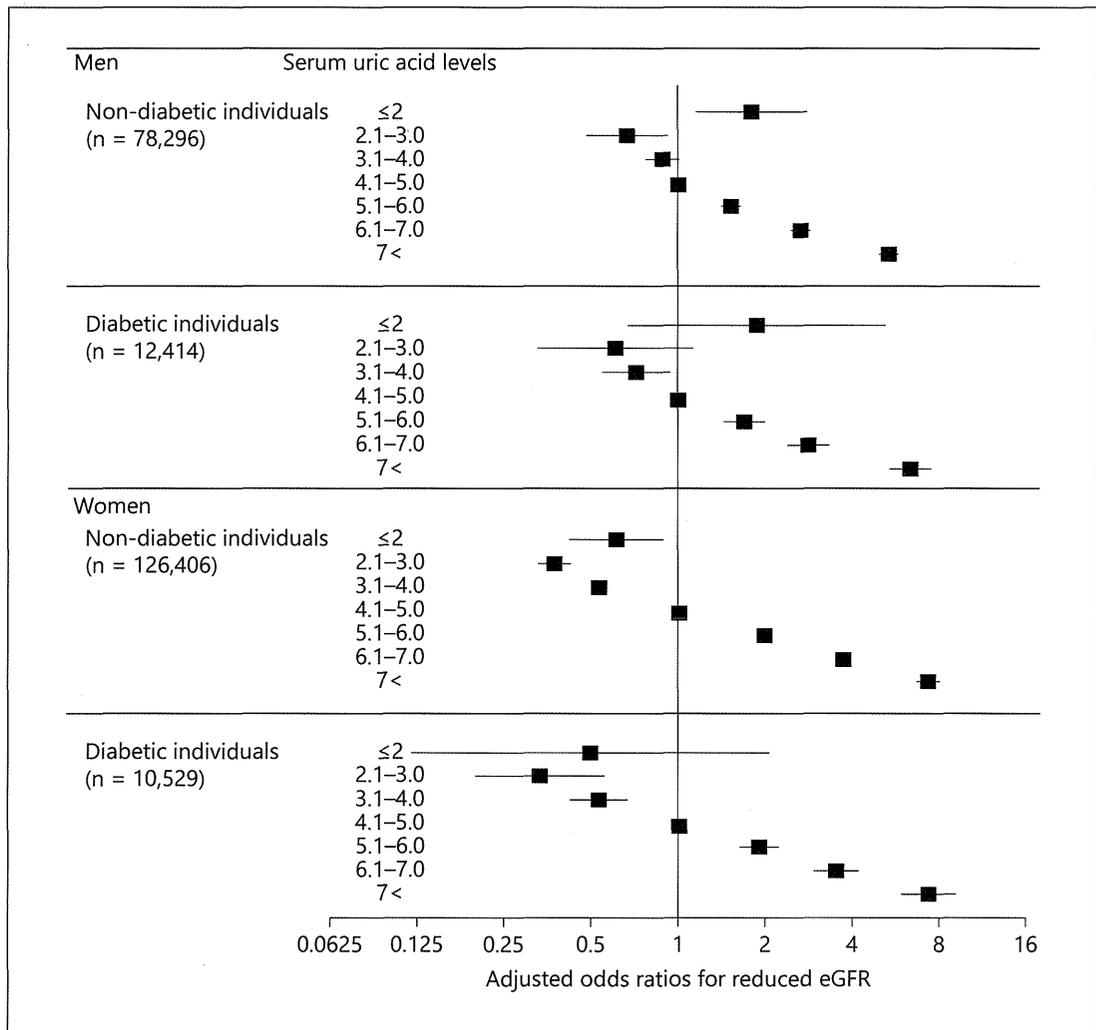
Wakasugi et al.

Fig. 2. Forest plot showing odds ratios with 95% confidence intervals for the relationship between serum uric acid levels and reduced kidney function. All analyses were adjusted for the following covariates: age (per 10-year increase), daily drinker, current smoker, hypertension, hypercholesterolemia, obesity, and history of renal failure.

uric acid levels of 2.1–3.0 mg/dl or 3.1–4.0 mg/dl, compared with those in the reference category. Thus, categorization with higher cutoff levels may cancel out the effects on reduced eGFR. Another reason might be related to the small sample size, that is, the statistical power of previous studies was insufficient to detect the influence of hypouricemia. A retrospective cohort study conducted in Taiwan showed a moderately J-shaped effect of serum uric acid on the incidence of chronic kidney disease, which was defined as a decrease of GFR to less than 60 ml/min/1.73 m^2 at a follow-up examination. Moreover, that study showed significantly increased hazard ratios in participants with hyperuricemia and moderately increased

hazard ratios in participants with hypouricemia, although the latter estimates were not significant [37].

Given that uric acid is considered one of the most important antioxidants in human plasma [3–5], it is tempting to speculate that hypouricemia, through decreased antioxidant potential, increases the risk of reduced kidney function. Low uric acid levels have been linked to several inflammatory and degenerative diseases, such as acute graft-versus-host disease [38] and neurological diseases, such as Alzheimer's disease, Huntington's disease, Parkinson's disease, and multiple sclerosis [39]. These associations have been attributed to the reduced antioxidative capacity associated with hypourisemia [38, 39].

Another possibility is that the control of renal uric acid, rather than serum uric acid levels *per se*, is associated with reduced kidney function. A previous study using two community-based general population samples found that subjects having the common nonsense mutation, W258X, which is responsible for renal hypouricemia, showed significantly reduced renal function independent of age, sex, BMI, hypertension, and serum uric acid levels [8]. Furthermore, a recent study using the statistical genetics approach of Mendelian randomization demonstrated that increased genetic risk score, which was strongly associated with serum uric acid levels, was associated with significantly improved renal function in men, but not in women [40]. Analysis of individual genetic variants demonstrated that the effect size associated with serum urate did not correlate with that associated with renal function in the Mendelian randomization model [40]. This is consistent with the possibility that the physiological action of these genetic variants in raising serum urate correlates directly with improved renal function [40]. Taken together, genetic variants, which reduce or increase serum uric acid levels, rather than serum uric acid *per se*, may be associated with kidney function.

A recent study using the statistical genetics approach of Mendelian randomization has provided new insights regarding uric acid. In contrast to previous observational findings, there is no strong evidence for causal associations between uric acid and ischemic heart disease or blood pressure [41]. The approach has also demonstrated that elevated serum uric acid is a consequence, rather than a cause, of adiposity [42, 43], and is not a cause of type 2 diabetes [44] or metabolic syndrome [45]. Although we could not rely on Mendelian randomization due to the lack of genetic data, these reports and our results suggest that the association between uric acid levels and reduced kidney function is far more complex than what was previously thought.

From a clinical perspective, our results suggest that the presence of hypouricemia should prompt clinicians to look for the presence of reduced kidney function in men. Although direct evidence is lacking, reduced eGFR may be associated with AKI or nephrolithiasis, given that they are both risk factors for reduced eGFR [12, 13] and are well-known complications in patients with renal hypouricemia [9–11]. The gender specificity of the association between hypouricemia and reduced eGFR in men might be explained by the fact that the majority of patients with exercise-induced AKI associated with renal hypouricemia are men, with a male:female ratio of 8:1

[10]. Although the short-term prognosis of exercise-induced AKI associated with renal hypouricemia is generally good [10], further clinical studies are needed to determine the long-term prognosis of patients with hypouricemia.

Study Limitations and Strengths

The present study has several limitations. First, there may have been selection bias in the study population, because all participants underwent annual health checkups and may thus be generally healthier than those who did not. However, the prevalence of hypouricemia in our study was in line with previous studies that targeted the general population. Second, we cannot rule out the possibility of a confounding effect by other factors which cause hypouricemia, such as malignancies, severe liver disease, and medication use, and dietary factors. Hypouricemia can be caused not only by enhanced uric acid excretion, but also by decreased uric acid production or uric acid oxidation due to treatment with uricase. Moreover, hypouricemia in some participants might not be attributed to renal hypouricemia, as information on the primary cause of hypouricemia was not available. However, levels of aspartate transaminase, alanine transaminase, and gamma-glutamyl transpeptidase in this study were not indicative of severe liver diseases. Unfortunately, detailed information on medication use was not available. However, medication treatment for hyperuricemia rarely results in a serum uric acid level ≤2 mg/dl. This study was conducted using data collected in 2008, when febuxostat, a non-purine selective xanthine oxidase inhibitor, was unavailable in Japan. Dietary information was also unavailable. While dietary factors can affect serum uric acid levels, even vegetarians and individuals who eat fish but not meat rarely had serum uric acid levels ≤2 mg/dl [46]. Thus, it is unlikely that this would have affected our main results. Third, despite adjusting for potential confounding factors, residual confounding remains possible. Finally, given the cross-sectional design of this study, causality could not be determined. However, it is unlikely that reduced eGFR causes hypouricemia.

A major strength of this study was its large sample population. This study was a large-scale cross-sectional study with participants from all over Japan, and included more than 700 individuals with hypouricemia. To the best of our knowledge, this is the first study to demonstrate the prevalence of hypouricemia stratified by age and gender and assess the association between hypouricemia and reduced eGFR.

In conclusion, we found that hypouricemia is associated with reduced eGFR in men. Further studies will be needed to clarify the true biological and clinical significance of hypouricemia.

Support

Disclosure Statement

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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.

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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.

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/m² 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 m². 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/1.73m² and found that the association between SBP and incident renal insufficiency was similar to that in subjects with eGFR ≥ 60 ml/min/1.73m² (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