Low Urine pH Is a Predictor of Chronic Kidney Disease

Naoko Nakanishi^a Michiaki Fukui^a Muhei Tanaka^a Hitoshi Toda^c Saeko Imai^d
Masahiro Yamazaki^a Goji Hasegawa^a Yohei Oda^b Naoto Nakamura^a

Departments of ^aEndocrinology and Metabolism and ^bImmunology and Inflammation, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, and ^cDepartment of Internal Medicine, Sakazaki Clinic, Kyoto, and ^dDepartment of Clinical Nutrition, Faculty of Comprehensive Rehabilitation, Osaka Prefecture University, Osaka, Japan

Key Words

Acidic urine • Low urine pH • Chronic kidney disease

Abstract

Background/Aims: A variety of risk factors for chronic kidney disease (CKD), including the metabolic syndrome, were recently reported. It has been suggested that a low urine pH is another characteristic of the metabolic syndrome. However, the relationship between urine pH and CKD remains to be elucidated. **Methods:** A cohort study was performed on 1,811 subjects who underwent a health check-up, and we examined whether low urine pH could be a predictor of CKD. The following risk factors for CKD were evaluated: age, gender, history of alcohol intake and smoking, BMI, systolic blood pressure, fasting plasma glucose, total cholesterol, uric acid, total leukocyte count, CKD stage, fasting urine pH, and protein at baseline. **Results:** We followed 1,811 subjects for a median period of 7.7 years. Three hundred and thirty-nine subjects developed stage 3 CKD defined as progression to estimated glomerular filtration rate <60 ml/min/1.73 m². Multiple Cox regression analysis revealed that the adjusted HR (95% CI) for stage 3 CKD was 1.32 (1.06–1.65; $p = 0.0129$) in subjects with fasting urine pH 5.0–5.5 compared to subjects with pH 6.5–7.0. **Conclusion:** Our study suggests that low urine pH is an independent predictor of stage 3 CKD.

Copyright © 2011 S. Karger AG, Basel

Introduction

Chronic kidney disease (CKD) is increasingly recognized as public health problem [1]. A recent study demonstrated that estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² independently predicts the risk for cardiovascular events and hospitalization [2]. It was also recently described that CKD is associated with the metabolic syndrome (MS), which is also known as the insulin resistance syndrome, characterized by a constellation of metabolic features including dyslipidemia, hyperglycemia, hypertension and obesity [3–5]. Additionally, recent reports have suggested that low urine pH is another characteristic of MS or insulin-resistant individuals [6, 7].

However, the relationship between urine pH and CKD remains to be elucidated. To determine whether low urine pH can be the predictor of CKD, we examined data of a large community-based cohort of adults.

Materials and Methods

Subjects and Study Design

The Sakazaki Health Survey is an ongoing cohort investigation of risk factors for chronic diseases, including hypertension, diabetes and CKD. The Sakazaki Clinic (Kyoto, Japan) provides regular health check-up for employees. In Japan, yearly routine examinations for employees is legally mandated, and all or most

Table 1. Baseline characteristics of subjects

	All	pH 5.0–5.5	pH 6.0	pH 6.5–7.0	p value
Number of subjects	1,811	795	597	419	
Age, year	45.5 ± 10.2	45.7 ± 9.8	44.5 ± 10.2	46.5 ± 10.8	0.0057
Male	1,107 (61.1)	491 (61.8)	364 (61.0)	252 (60.1)	0.8559
Smoking	323 (17.8)	176 (22.1)	106 (17.8)	41 (9.8)	<0.0001
Alcohol	661 (36.5)	304 (38.2)	219 (36.7)	138 (32.9)	0.1880
BMI	22.6 ± 3.1	22.7 ± 3.2	22.3 ± 3.1	22.7 ± 3.0	0.0189
SBP, mm Hg	117.2 ± 16.6	116.4 ± 16.0	116.5 ± 16.7	119.7 ± 17.3	0.0021
Fasting plasma glucose, mmol/l	5.2 ± 1.1	5.3 ± 1.3	5.1 ± 0.9	5.1 ± 0.7	0.0023
Total cholesterol, mmol/l	5.3 ± 0.9	5.4 ± 0.9	5.2 ± 0.9	5.3 ± 0.9	0.0152
Uric acid, μmol/l	321.0 ± 82.3	327.7 ± 85.3	318.2 ± 80.8	312.5 ± 77.8	0.0052
Total leukocyte count, × 10 ⁹ /l	5.6 ± 1.6	5.7 ± 1.7	5.5 ± 1.6	5.4 ± 1.4	0.0090
CKD stage 2	1,643 (90.7)	732 (92.1)	537 (90.0)	374 (89.3)	0.2001
Baseline GFR, ml/min/1.73 m ²	75.8 ± 11.1	75.1 ± 11.1	76.4 ± 11.1	76.3 ± 11.2	0.0711
Proteinuria	72 (4.0)	31 (3.9)	32 (5.4)	9 (2.2)	0.0355

Values are means ± SD or n (%).

of the costs for the health check-up are usually paid by their employers. Between 1998 and 2003, 2,273 Japanese subjects were enrolled in the study. We excluded 352 subjects who were stage 3–5 CKD at baseline. Subjects with urine pH >7.5 were also excluded because we considered abnormally high pH as being affected by a urinary tract infection. At the time of urine evaluation, none of the subjects were taking any medications known to alter urine pH such as potassium alkali, sodium bicarbonate or carbonic anhydrase inhibitors. We followed up 1,811 subjects and evaluated the risk factors for CKD and assessed whether low urine pH could predict CKD. Approval for all studies was obtained from the Ethical Committee of Sakazaki Clinic, and the study was conducted in accordance with Declaration of Helsinki. Written informed consent was obtained from each subject.

Data Collection and Measurements

All subjects provided details of their demographics. Smoking was defined as current tobacco usage. History of alcohol was defined as daily alcohol consumption. BMI was calculated as weight in kilograms divided by height in meters squared. After an overnight fast, venous blood was collected for the measurement of the levels of various factors, including fasting plasma glucose, total cholesterol, uric acid (UA) and total leukocyte count. GFR was estimated using the Japanese Society of Nephrology equation: $eGFR = 194 \times \text{Cre}^{-1.094} \times \text{age}^{-0.287}$ (ml/min/1.73 m²) [8]. For women, the eGFR was multiplied by a correction factor of 0.739. CKD staging was based on the level of eGFR. Stage 1, stage 2 and stage 3 CKD were defined as eGFR >90, 60–89 and <60 ml/min/1.73 m², respectively. Proteinuria was determined using dipstick testing in fasting morning urine (positive: 1+ or greater). We measured urine pH by the indicator method using a dipstick (Yurifuret-S and Aution-analyzer; Arkray, Kyoto, Japan). The available range was from pH 5.0 to pH 9.0 in 0.5 pH unit increments. The urine was not collected under oil, and we measured urine pH values immediately after the fasting morning urine sample was obtained.

Statistical Analysis

The statistical analyses were performed using the JMP version 8.0 software (SAS Institute Inc., Cary, N.C., USA). $p < 0.05$ was considered statistically significant. Continuous variables are presented as the mean value ± 1 SD and categorical variables are presented as number (%). Categorical and continuous variables were compared among the groups by a χ^2 analysis and analysis of variance (ANOVA), respectively. We evaluated the predictor for stage 3 CKD by univariate and multiple Cox regression analysis to adjust for covariates including age, gender, history of alcohol intake and smoking, BMI, systolic blood pressure (SBP), fasting plasma glucose, total cholesterol, UA, total leukocyte count, CKD stage, fasting urine protein, and pH at baseline.

Results

A total of 1,811 subjects were followed up for a median period of 7.7 years in this study. The baseline characteristics are shown in table 1. There were 704 females and 1,107 males, aged 45.5 ± 10.2 years. All of the subjects were classified into three groups according to fasting urine pH: 5.0–5.5, 6.0 and 6.5–7.0. Each group was followed for a median period of 7.6 years with pH 5.0–5.5, 8.0 years with pH 6.0 and 7.6 years with pH 6.5–7.0, respectively. Compared with the subjects with higher urine pH, the subjects with lower urine pH had lower SBP ($p = 0.0021$), higher fasting plasma glucose ($p = 0.0023$), higher UA ($p = 0.0052$) and a higher total leukocyte count ($p = 0.0090$), and were likely to be a current smoker ($p < 0.0001$). One hundred and sixty-nine subjects (21.3%) with urine pH 5.0–5.5, 98 subjects (16.4%) with urine pH

Table 2. Predictors of stage 3 CKD by Cox regression analysis

Variables	Univariate Cox regression analysis		Multiple Cox regression analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age, per 10 years	1.87 (1.74–2.00)	<0.0001	1.81 (1.67–1.96)	<0.0001
Male, yes	1.11 (0.95–1.30)	0.1815	0.76 (0.61–0.95)	0.0151
Smoking, yes	0.74 (0.60–0.92)	0.0059	0.88 (0.68–1.12)	0.3142
Alcohol, yes	0.91 (0.77–1.06)	0.2217	0.85 (0.71–1.01)	0.0609
BMI, per 1.0 increase	1.07 (1.05–1.10)	<0.0001	1.02 (0.99–1.06)	0.1185
SBP, per 10-mm Hg increase	1.15 (1.11–1.20)	<0.0001	0.99 (0.94–1.05)	0.8289
Fasting plasma glucose, per 1.0-mmol/l increase	1.11 (1.04–1.16)	0.0017	0.94 (0.86–1.02)	0.1317
Total cholesterol, per 1.0-mmol/l increase	1.29 (1.19–1.39)	<0.0001	1.02 (0.93–1.12)	0.7011
Uric acid, per 10.0- μ mol/l increase	1.00 (1.00–1.01)	<0.0001	1.04 (1.03–1.05)	<0.0001
Total leukocyte count, $\% \times 10^6$ /l increase	1.02 (0.97–1.07)	0.4590	0.99 (0.93–1.05)	0.6981
CKD				
Stage 1 (reference)	1.0		1.0	
Stage 2	4.09 (2.89–5.26)	<0.0001	3.73 (2.62–4.91)	<0.0001
Proteinuria				
(–) or ($\pm$) (reference)	1.0		1.0	
(+)	1.31 (0.92–1.80)	0.1342	1.33 (0.89–1.90)	0.1537
Urine pH				
5.0–5.5	1.26 (1.03–1.54)	0.0221	1.32 (1.06–1.65)	0.0129
6.0	1.03 (0.84–1.29)	0.7414	1.17 (0.93–1.49)	0.1895
6.5–7.0 (reference)	1.0		1.0	

6.0 and 72 subjects with pH 6.5–7.0 (17.2%) developed stage 3 CKD during the period. Cox regression analysis was performed to assess risk factors for stage 3 CKD (table 2). Univariate Cox regression analysis demonstrated that age, history of smoking, BMI, SBP, fasting plasma glucose, total cholesterol, UA, CKD stage and urine pH were associated with progression of stage 3 CKD. Multiple Cox regression analysis revealed that the adjusted HR (95% CI) for stage 3 CKD was 1.32 (1.06–1.65; $p = 0.0129$) in subjects with fasting urine pH 5.0–5.5 compared with subjects with fasting urine pH 6.5–7.0. Age, gender, UA and CKD stage at baseline were also independent predictors of stage 3 CKD after adjustment for co-variables.

Discussion

Our study demonstrated that low urine pH was an independent predictor of stage 3 CKD. Recent studies reported that CKD was associated with increased cardiovascular disease and all-cause mortality [9, 10]. Therefore, it is important to identify a predictor of CKD. To our knowledge, this is the first report to reveal the relationship between urine pH and progression of CKD.

It was recently described that CKD was associated with MS [3, 4]. In addition, others have speculated that insulin resistance, hyperinsulinemia and inflammation resulting from lipotoxicity have a direct role in increasing excretory load and aggravating tubulointerstitial damage [11, 12]. Several reports have shown that low urine pH was associated with MS [6, 7] and obesity [13, 14]. It was also demonstrated that 24-hour urine pH is correlated to MS, and an inverse relationship was noted between urine pH and homeostasis model assessment-insulin resistance [7]. This concept is supported by a pathophysiological mechanism in which insulin influences renal production or excretion of ammonium, which is an important urinary buffer [15–18] and that insulin resistance is associated with defective renal ammoniogenesis [7]. Taking these findings together, MS and insulin resistance link to both urine pH and CKD progression, and it seems plausible that low urine pH is an independent predictor of stage 3 CKD.

We also demonstrated that hyperuricemia was associated with an increased risk for incident CKD in this study. The association between UA and CKD has gained some support from previous studies. Recent epidemiologic evidence suggested a significant and independent association between the level of serum UA and renal disease pro-

gression with beneficial effect of decreasing UA levels [19, 20]. In rats, hyperuricemia increased SBP, proteinuria, renal dysfunction, vascular disease and progressive renal scarring by a crystal-independent mechanism [21]. Recent data also suggested hyperuricemia might be the key component of the activation of the renin-angiotensin and cyclooxygenase-2 systems in progressive renal disease [22].

We obtained the results that both low urine pH and hyperuricemia were associated with progression of CKD and that subjects with low urine pH had a higher UA level. However, low urine pH was a predictor of CKD independent of UA by multiple Cox regression analysis.

This study has several strengths, which include the large community-based sample and long duration of follow-up. Nevertheless, several limitations may affect the interpretation of these results. First, we have used eGFR <60 ml/min/1.73 m² as a clinical endpoint rather than urinary protein excretion. This was supported by reports that a reduced eGFR is associated with increased risks of death, cardiovascular events and hospitalization, which was independent of the presence of documented proteinuria [2, 23]. Second, in this study, the mechanism of kidney injury caused by acidic urine was not elucidated. Lin et al. [24] demonstrated that increased intake of red meat was associated with microalbuminuria, suggesting high intake of animal protein (dietary acid) promotes renal damage. Evaluating urine components (sulfate, potassium, urine net acid excretion and ammonium) and contents of meals is valuable for identifying the causes of acidic urine. However, we believe it is noteworthy that low urine pH could be a predictor of CKD in the outpatient and routine medical check-up settings. Third, we used single, not 24-hour collected, fasting urine to measure urine pH. Although the finding of diurnal variation has

been confirmed, Capolongo et al. [25] demonstrated fasting urine pH correlates significantly with 24-hour urine pH for the entire cohort. Additionally, we measured urine pH by the indicator method using a dipstick rather than electrodes. Measurement of urine pH by the indicator method is less reliable than by electrodes; however, the indicator method might be appropriate for health check-up in terms of its convenience and cost savings. Moreover, in the previous study, the accuracy of urinary dipstick testing for pH manipulation therapy was assessed by comparing three commercial brands of dipstick paper and electrodes, revealing dipstick testing to be accurate [26].

Our study is in the line with a recent study showing daily sodium bicarbonate is an effective kidney protective adjunct to blood pressure control in hypertensive nephropathy [27]. Further investigation is warranted to elucidate the relationship between urine alkalization and the protective effect against CKD.

Conclusions

We have demonstrated that low urine pH is an independent predictor of CKD. Above all, we suggest that examination of the fasting urine pH can be a practical screening tool for CKD and that it is beneficial in recognizing the segment of the population who have acidic urine.

Acknowledgement

We thank Ms. Mayumi Kitano for collecting subject data.

References

- 1 Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: approaches and initiatives – a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007;72: 247–259.
- 2 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351: 1296–1305.
- 3 Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J: The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004; 140:167–174.
- 4 Kurella M, Lo JC, Chertow GM: Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005;16:2134–2140.
- 5 Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. *Lancet* 2005;365:1415–1428.
- 6 Takahashi S, Inokuchi T, Kobayashi T, Ka T, Tsutsumi Z, Moriawaki Y, Yamamoto T: Relationship between insulin resistance and low urinary pH in patients with gout, and effects of PPAR alpha agonists on urine pH. *Horm Metab Res* 2007;39:511–514.

- 7 Maalouf NM, Cameron MA, Moe OW, Adams-Huet B, Sakhaee K: Low urine pH: a novel feature of the metabolic syndrome. *Clin J Am Soc Nephrol* 2007;2:883–888.
- 8 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–992.
- 9 Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, Sarnak MJ: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 2003;63:1121–1129.
- 10 Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, Saitoh S, Sakata K, Okayama A, Ueshima H, NIPPON DATA90 Research Group: Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. *Circ J* 2006;70:954–999.
- 11 Cusumano AM, Bodkin NL, Hansen BC, Iotti R, Owens J, Klotman PE, Kopp JB: Glomerular hypertrophy is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. *Am J Kidney Dis* 2002;40:1075–1085.
- 12 Kamijo A, Kimura K, Sugaya T, Yamanouchi M, Hase H, Kaneko T, Hirata Y, Goto A, Fujita T, Omata M: Urinary free fatty acids bound to albumin aggravate tubulointerstitial damage. *Kidney Int* 2002;62:1628–1637.
- 13 Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY: Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004;65:1422–1425.
- 14 Taylor EN, Curhan GC: Body size and 24-hour urine composition. *Am J Kidney Dis* 2006;48:905–915.
- 15 DuBose TD Jr, Good DW, Hamm LL, Wall SM: Ammonium transport in the kidney: New physiological concepts and their clinical implications. *J Am Soc Nephrol* 1991;1:1193–1203.
- 16 Agarwal BN, Cabebe FG: Renal acidification in elderly subjects. *Nephron* 1980;26:291–295.
- 17 Nissim I, States B, Nissim I, Lin ZP, Yudkoff M: Hormonal regulation of glutamine metabolism by OK cells. *Kidney Int* 1975;47:96–105.
- 18 Klisic J, Hu MC, Nief V, Reyes L, Fuster D, Moe OW, Ambühl PM: Insulin activates Na⁺/H⁺ exchanger 3: biphasic response and glucocorticoid dependence. *Am J Physiol Renal Physiol* 2002;283:532–539.
- 19 Tomita M, Mizuno S, Yamanaka H, Hosoda Y, Sakuma K, Matuoka Y, Odaka M, Yamaguchi M, Yosida H, Morisawa H, Murayama T: Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 2000;10:403–409.
- 20 Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S: Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004;44:642–650.
- 21 Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang D-H, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001;38:1101–1106.
- 22 Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ: A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002;13:2888–2897.
- 23 Kiyosue A, Hirata Y, Ando J, Fujita H, Morita T, Takahashi M, Nagata D, Kohro T, Imai Y, Nagai R: Relationship between renal dysfunction and severity of coronary artery disease in Japanese patients. *Circ J* 2010;74:786–791.
- 24 Lin J, Fung TT, Hu FB, Curhan GC: Association of dietary patterns with albuminuria and kidney function decline in older white women: a subgroup analysis from the Nurses' Health Study. *Am J Kidney Dis* 2011;57:245–254.
- 25 Capolongo G, Sakhaee K, Pak CY, Maalouf NM: Fasting versus 24-hour urine pH in the evaluation of nephrolithiasis. *Urol Res* 2011, E-pub ahead of print.
- 26 Desai RA, Assimos DG: Accuracy of urinary dipstick testing for pH manipulation therapy. *J Endourol* 2008;22:1367–1370.
- 27 Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE: Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010;78:303–309.