Relationship between a Urine Protein-to-creatinine Ratio of 150 mg/gram Creatinine and Dipstick Grade in the Health Checkup: Substantial Number of False-negative Results for Chronic Kidney Disease

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Objective: Proteinuria is a marker for cardiovascular diseases and all-cause mortality. In the Specific Health Checkups in Japan, when subjects show trace proteinuria (grade±) on dipstick assay, further examination is recommended to them. Although 150 mg/gCr is a threshold for diagnosing chronic kidney disease (CKD), little data on the relationship between dipstick grade± and the protein-creatinine ratio have been reported.
Methods: A cross-sectional study using urine specimens obtained in a single institute, JCHO Saitama Northern Medical Center, was performed from October 2014 to March 2016. The level of proteinuria was measured in fresh morning urine samples from 819 volunteer participants of the Specific Health Checkups by two methods: Eiken Uropaper III to detect and qualitatively grade proteinuria, and total protein concentration by the pyrogallol red method.
Results: Sensitivity, specificity, and the positive likelihood ratio to detect proteinuria of 30 mg/dL by 1+ were 90.3%, 97.8%, and 41.9, whereas 150 mg/gCr by ± were 45.3%, 81.4%, and 2.4, respectively. Therefore, screening for 150 mg/gCr by dipstick grade ± had a false-negative rate of 54.7% and false-negative rate was significantly higher in women (8.0%) than in men (1.7%) ($p < 0.0001$).
Conclusions: Although the dipstick assay is useful to detect clinically significant proteinuria, substantial numbers of false-negative results occur in checkups for identifying subjects with a risk of CKD.

Key words: dipstick proteinuria, protein-creatinine ratio, chronic kidney disease, Specific Health Checkup program

BACKGROUND

Proteinuria is a biomarker for cardiovascular disorders and for overall mortality in both diabetic patients and the general population [1–4], and the single most important clinical indicator for guiding the treatment of chronic kidney disease (CKD) and predicting its risk [5]. Dipstick urine examination is a non-invasive and inexpensive test, and, therefore, the most widely used method to detect clinically significant proteinuria (0.3–0.5 g/day) for the diagnosis of overt diabetic nephropathy or CKD in clinical practice.

The dipstick test provides evidence of proteinuria at a concentration of 20–30 mg/dL or greater [6], and the detection threshold for dipsticks is believed to be 10–20 mg/dL. In the Japanese standard, set by the Japanese Committee for Clinical Laboratory Standards, a grade of 1+ is equivalent to the presence of proteinuria of 30 mg/dL [7].

Dipstick grades are known to be affected by urine

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dilution and acidic agents, such as ascorbic acid, resulting in a false-negative report. Likewise, in urine with a high pH, such as with bacteriuria, the rate of false-positive results may increase [8]. The gold standard for the measurement of urinary protein excretion is the measurement of total protein or albumin excreted in 24 hours. However, this method requires both time and effort, and mistakes in urine collection can easily occur. Ginsberg and colleagues proposed a correction by calculating the protein amount excreted per gram of creatinine excretion in a single urine sample [9]. Since this method reduces individual variation [10], many guidelines recommend corrected urinary protein as the amount of urinary protein or albumin excreted per gram of creatinine [the protein-creatinine ratio (PCR) or albumin-creatinine ratio (ACR)] [11–14].

In the Specific Health Checkup program in Japan [15], when participants show trace ± proteinuria measured by dipstick, it is recommended that they visit a physician for further examinations [16] to detect chronic kidney disease (CKD). On the other hand, proteinuria of ≥150 mg/gram creatinine (gCr) is the threshold for diagnosing CKD in Japan. There is, however, little data on the relationship of dipstick grade± proteinuria and the PCR threshold of 150 mg/gCr.

In the present study, we aimed at evaluating the suitability of use of the dipstick test for detection of the subject with CKD. The precision and performance of dipstick grading were assessed according to the PCR, and the prevalence of false-negative results was investigated in the context of health checkups for the general population.

METHODS

Design and subjects

This was a cross-sectional, single-institution study of volunteers aged 40–75 years who underwent Specific Health Checkups at Japan Community Health Care Organization (JCHO) Saitama Northern Medical Center (Saitama City, Japan) between October 2014 and March 2016, undertaken as part of a study of the association between urinary salt excretion and proteinuria. The study was carried out in compliance with the Helsinki Declaration and was approved by the Saitama Northern Medical Center Ethics Committee (approval certificate no. 27-03). Written, informed consent was obtained from all participants.

Measurements

Specific Health Checkups were performed in accordance with Ministry of Health, Labour and Welfare guidelines [16]. Urine samples were collected in the morning, and fresh urine samples were divided into two portions and tested by the dipstick method and total protein and creatinine quantification. The dipsticks used were Uropaper III dipsticks (Eiken Chemical Co., Ltd., Tokyo, Japan), and the results were assessed automatically using a urine chemistry analyzer (Aution MAX, Arkray, Kyoto, Japan). The results were reported as negative (–), trace ± (15 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), or 3+ (≥300 mg/dL). In the other paired portion of urine sampled, urinary protein was quantified by pyrogallol red, a dye binding assay [17] using a QUICK RUN automated analyzer (Wako Pure Chemical Industries, Ltd., Tokyo, Japan) with reagent AR_{Wako} Micro TP-AR (Wako Pure Chemical Industries, Ltd.) and reference material 2/QR (Wako Pure Chemical Industries, Ltd.), and the results were reported as concentrations (mg/dL). Creatinine concentrations (mg/dL) were also measured by enzyme assay (creatininase/HMMPS assay) using a TBA-2000FR automated biochemical analyzer (Toshiba Medical, Otawara, Japan). Urine with a urinary creatinine concentration of <50 mg/dL was defined as dilute urine [18].

Statistical analysis

Age, urinary protein concentration, urinary creatinine concentration, and the urinary PCR all have non-normal distributions, and differences in these parameters were compared using Wilcoxon's rank sum test. The χ^2 test was used to test differences of binominal variables. For two-sided tests, $p < 0.05$ was regarded as significant, and Bonferroni's correction was applied for multiple comparisons. The true-positive, false-positive, false-negative, and true-negative rates were calculated from the measured values on the basis of predetermined cut-off values, and these were used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. As performance indicators, the positive likelihood ratio (true-positive rate/false-positive rate) was defined as sensitivity/(1– specificity), and the negative likelihood ratio (true-negative rate/false-negative rate) as (1– sensitivity)/specificity. The statistical software used was STATA 14.

RESULTS

Baseline characteristics and prevalence of proteinuria in this study

A total of 819 participants (297 men, 522 women) aged 40–75 years were enrolled (Table 1). The median age was 67 years (men 68 years, women 66 years), significantly higher for men ($p < 0.001$).

The dipstick test grade was negative in 78.6% of participants, trace in 15.9%, and 1+ in 4.8%. The median urinary-protein concentration was 6 mg/dL, and the median urinary-creatinine concentration was 88 mg/dL. The median urinary PCR calculated from these values was 60 mg/gCr. The distribution of urinary protein measured by the dipstick method and the concentrations of urinary protein and creatinine were all significantly higher in men (all $p < 0.001$), but there was no significant difference in the urinary PCR ($p = 0.812$).

The prevalence of proteinuria was 21.4% when defined as dipstick test grade ≥±, 5.5% as dipstick test grade ≥1+, 10.5% as urinary PCR ≥150 mg/gCr, and 1.1% as urinary PCR ≥500 mg/gCr. There were significant differences in the rates of men and women who scored ≥± or ≥1+ (both $p < 0.001$), but not in those who scored ≥150 mg/gCr or ≥500 mg/gCr ($p = 0.219$ and $p = 0.056$, respectively).

Precision and performance of dipstick testing for urinary protein concentration ≥30 mg/dL

First, as the control, the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios when the cut-off value for true positives was set at a urinary protein concentration

≥ 30 mg/dL were investigated. When ≥ 1+ was used as the cut-off, excellent accuracy and performance were obtained (Table 2). The sensitivity was 90.3%, specificity 97.8%, accuracy 97.6%, positive predictive value 62.2%, negative predictive value 99.6%, positive likelihood ratio 41.9, and negative likelihood ratio 0.10. When ± was used as the cut-off, the sensitivity was 96.8%, specificity 81.6%, accuracy 82.2%, positive predictive value 17.1%, negative predictive value 99.8%, positive likelihood ratio 5.3, and negative likelihood ratio 0.04. Therefore, performance of the dipstick test was largely reduced because of lower positive predictive value and positive likelihood ratio when the cut-off was set at ±.

Associations between dipstick grade and dilution

Differences in urinary protein concentration stratified by dipstick test grade were evaluated (Table 2).

The median urinary protein concentration was 4 mg/dL for dipstick test grade–, 12 mg/dL for ±, 34 mg/dL for 1+, and 105 mg/dL for ≥ 2+. Comparisons between those graded– and ±, ± and 1+, and 1+ and ≥ 2+ showed different distributions. This indicates that stratification by urinary protein concentration was feasible.

Of the 31 samples with urinary protein concentration ≥ 30 mg/dL, 1 sample was graded– and 2 were ±, resulting in 3/31 (9.7%) false negatives. This could be due to acidic samples containing ascorbic acid or intra-assay variance.

When urinary creatinine concentrations stratified by dipstick test grade were compared, the median urinary creatinine concentration was 73 mg/dL for grade –, 183 mg/dL for ±, 187 mg/dL for 1+, and 343 mg/dL for ≥ 2+. The comparison of urinary creatinine concentrations in samples graded– and ≥± showed that the concentration was significantly higher in the samples graded ≥± ($p < 0.001$). In comparisons between samples graded ± and 1+ and between 1+ and ≥ 2+, neither of these differences was significant ($p = 0.297$ and $p = 0.171$, respectively). However, the rates of diluted urine (if defined by creatinine level < 50 mg/dL) were 29.4% of the group graded–, 1.5% of grade ±, 2.6% of 1+, and 0.0% of ≥ 2+, showing a biased distribution (χ^2 test, $p < 0.001$). These results suggested that diluted samples were included in the group graded–.

Relationship between dipstick grade and PCR

Next, PCR distribution stratified by dipstick grade was evaluated (Table 2). The median PCR was 57 mg/gCr for those graded–, 62 mg/gCr for those graded ±, and 191 mg/gCr for those graded 1+. Distributions of urine PCR were significantly different between samples graded– and graded± ($p = 0.005$) and between samples graded ± and 1+ ($p < 0.001$), whereas the difference did not reach statistical significance between samples graded 1+ and ≥ 2+ ($p = 0.425$).

Of the 86 samples with PCR ≥ 150 mg/gCr, 47 (54.7%) were false-negative for the group grade–. Of the 47 samples, 46 had urine creatinine < 30 mg/dL. The main cause of the false negatives with the dipstick test was likely urine dilution. Of the 733 with PCR < 150 mg/gCr graded ≥± by the dipstick test, 136 (18.6%) were false positive. Of them, 118 (86.8%)

Table 1 Baseline characteristics and prevalence of proteinuria

Participants	n	Age* (years)	Dipstick grade*					Urine protein concentration* (mg/dL)	Urine creatinine concentration* (mg/dL)	PCR (mg/g creatinine)	Prevalence of proteinuria			
			-	±	1+	2+	3+				Dipstick ≥ ±*	Dipstick ≥ 1+*	PCR ≥ 150 mg/gCr	PCR ≥ 500 mg/gCr
Total	819	67 (63, 70)	644 (78.6)	130 (15.9)	39 (4.8)	5 (0.6)	1 (0.1)	6 (3, 9)	88 (52, 136)	60 (38, 97)	175 (21.4)	45 (5.5)	86 (10.5)	9 (1.1)
Male	297	68 (64, 71)	204 (68.7)	66 (22.2)	22 (7.4)	4 (1.4)	1 (0.3)	8 (5, 11.5)	119 (79, 176)	57 (39, 93)	93 (31.3)	27 (9.1)	26 (8.8)	6 (2.0)
Female	522	66 (62, 70)	440 (84.3)	64 (12.3)	17 (3.3)	1 (0.2)	0 (0.0)	5 (2, 7)	73 (43, 109)	62 (36, 98)	82 (15.7)	18 (3.5)	60 (11.5)	3 (0.6)

Expressed as median (25th percentile, 75th percentile) for continuous variables and as n (%) for binominal variables.
For comparison between male and female subjects, Wilcoxon's rank sum test was used for continuous variables, and the $\chi 2$ test was used for binominal variables. *$p < 0.05$
Abbreviations: PCR, protein-creatinine ratio; gCr, gram creatinine

Table 2 Urine concentrations of protein and creatinine and the PCR according to dipstick grade

Dipstick grade	n (%)	Urine protein concentration (mg/dL)		Urine creatinine concentration (mg/dL)		Urine PCR (mg/gCr)			
		Distribution†	≥ 30	Distribution‡	< 50	Distribution§	< 150	150- < 500	≥ 500
-	644 (78.6)	4 (2, 7)	1 (0.2)	73 (45, 105)	189 (29.4)	57 (33, 90)	597 (92.7)	45 (7.0)	2 (0.3)
±	130 (15.9)	12 (9, 16)	2 (1.5)	183 (135, 217)	2 (1.5)	62 (47, 98)	118 (90.8)	11 (8.5)	1 (0.8)
1+	39 (4.8)	34 (21, 47)	22 (56.4)	187 (132, 253)	1 (2.6)	191 (114, 341)	17 (43.6)	19 (48.7)	3 (7.7)
≥ 2+	6 (0.7)	105 (84, 225)	6 (100.0)	344 (115, 604)	0 (0.0)	618 (145, 1417)	1 (16.7)	2 (33.3)	3 (50.0)

Expressed as medians (25th percentile, 75th percentile) for continuous variables and n (%) for binominal variables.
† Wilcoxon's rank sum test with Bonferroni correction: - vs ±, $p < 0.001$; ± vs 1+, $p < 0.001$; 1+ vs ≥ 2+, $p < 0.001$
‡ Wilcoxon's rank sum test with Bonferroni correction: - vs ±, $p < 0.001$; ± vs 1+, $p = 0.891$; 1+ vs ≥ 2+, $p = 0.513$
§ Wilcoxon's rank sum test with Bonferroni correction: - vs ±, $p = 0.005$; ± vs 1+, $p < 0.001$; 1+ vs ≥ 2+, $p = 0.425$
Abbreviations: PCR, protein-creatinine ratio; gCr, gram creatinine

Table 3 Diagnostic accuracy and performance of the dipstick test according to cut-off levels

Standard reference (mg/gCr)	Cut-off	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
PCR ≥ 150	±	45.3 [34.6-56.5]	81.4 [78.4-84.2]	22.3 [16.4-29.2]	92.7 [90.4-94.6]	2.4 [1.9-3.2]	0.67 [0.55-0.82]
	1+	31.4 [21.8-42.3]	97.5 [96.1-98.5]	60.0 [44.3-74.3]	92.4 [90.3-94.1]	12.8 [7.4-22.2]	0.70 [0.61-0.81]
PCR ≥ 200	±	55.1 [40.2-69.3]	80.8 [77.8-83.5]	15.4 [10.4-21.6]	96.6 [94.9-97.8]	2.9 [2.1-3.8]	0.56 [0.41-0.76]
	1+	42.9 [28.8-57.8]	96.9 [95.4-98.0]	46.7 [31.7-62.1]	96.4 [94.8-97.6]	13.8 [8.3-22.9]	0.59 [0.46-0.75]
PCR ≥ 300	±	85.7 [63.7-97.0]	80.3 [77.4-83.0]	10.3 [6.2-15.8]	99.5 [98.6-99.9]	4.4 [3.5-5.5]	0.18 [0.06-0.51]
	1+	71.4 [47.8-88,7]	96.2 [94.7-97.4]	33.3 [20.0-49.0]	99.2 [98.3-99.7]	19.0 [12.2-29.6]	0.30 [0.15-0.58]
PCR ≥ 400	±	76.9 [46.2-95.0]	79.5 [76.6-82.3]	5.7 [2.8-10.3]	99.5 [98.6-99.9]	3.8 [2.7-5.2]	0.29 [0.11-0.78]
	1+	69.2 [38.6-90.9]	95.5 [93.9-96.9]	20.0 [9.6-34.6]	99.5 [98.6-99.9]	15.5 [9.6-25.1]	0.32 [0.14-0.73]
PCR ≥ 500	±	77.8 [40.0-97.2]	79.3 [76.3-82.0]	4.0 [1.6-8.1]	99.7 [98.9-100.0]	3.8 [2.6-5.5]	0.28 [0.08-0.95]
	1+	66.7 [29.9-92.5]	95.2 [93.5-96.6]	13.3 [5.1-26.8]	99.6 [98.9-99.9]	13.8 [8.0-24.1]	0.35 [0.14-0.88]

Expressed as each value [95% confidence interval]
Abbreviations: PCR, protein-creatinine ratio; gCr, gram creatinine

were graded ±.

Precision analysis for the dipstick test

Finally, precision and performance indicators were calculated to determine the usefulness of the dipstick test for health checkups (Table 3). The highest positive likelihood ratio was determined when the standard reference was set at PCR ≥ 300 mg/gCr, and the cut-off was set at dipstick grade ≥ 1+. Sensitivity, specificity, and the positive likelihood ratio were 71.4%, 96.2%, and 19.0, respectively. When the standard reference was set at PCR ≥ 150 mg/gCr and the cut-off was set at dipstick grade ≥±, the positive likelihood ratio was the lowest. Sensitivity, specificity, and the positive likelihood ratio under this condition were 45.3%, 81.4%, and 2.4, respectively. These results suggest that the best performance of this dipstick was obtained at a standard reference of PCR ≥ 300 mg/gCr, which is sufficient when screening for clinically significant proteinuria.

DISCUSSION

The present report demonstrated that a substantial number of samples were false-negative on dipstick screening in the health checkup setting when dipstick grade ± was chosen for the detection of proteinuria of 150 mg/gCr.

A recent study found that dipstick proteinuria is a predictor of long-term mortality after myocardial infarction [19] and of all-cause mortality among the general population [20]. In the Takahata Study, urinary albumin ≥ 30 mg/gCr was an independent predictor of overall mortality in the general population [21]. In the present study, when the standard reference was set at a unified standard, urinary protein of 30 mg/dL, and the cut-off value of the dipstick was set at 1+, the dipstick test was an excellent method, with sensitivity of 90.3%, specificity 97.8%, positive likelihood ratio 41.9, and 3 of 819 false negatives (0.37%). One study found that, when the standard reference was set at urinary protein of 300 mg/24 h, dipstick tests had

sensitivity of 67–100% and specificity of 36–97% [6], and their precision may also have been similar to that of the dipstick test used in the present study.

Since the sensitivity and specificity of a test varies depending on the assignment of cut-off values, their positive predictive value is dependent on the prevalence in the subject population (prior probability), and the value of the test is determined by performance measures such as the positive or negative likelihood ratio [22, 23]. In the present study, both precision and performance indicators were calculated in different pairs of values for true positives and cut-off levels. From the best performance, the sensitivity was reduced from 85.7% to 45.3% and the positive likelihood ratio was reduced from 19.0 to 2.4 when the value for true positive was 150 mg/gCr and the cut-off level was ±. This means that over half of true-positive participants were missed by the dipstick test and may have missed a chance for early intervention. In the present cohort, false-negative results were obtained in 47 (54.7%) of 86 participants, which was 5.7% of all participants. Given that the prevalence of proteinuria is the same as that of the present cohort in the general population, 5,700 per 100,000 participants were false-negative. Therefore, further improved screening methods for proteinuria is an important issue.

We found that in 47 false-negatives, those of male and female were 5 (1.7%) and 42 (8.0%), respectively, of which difference was significant ($p < 0.001$). Since there were 18 true-positives in women, false-negative was found to be 2.3 times that of true-positives. The false-negative odds ratio for women to men was 5.1. It is unclear why the false-negative rate is more in women. Further analyses are awaited if the mechanistic cause is related to not simply gender-specific but pathophysiological relevance.

In the group with high risk factors including CKD, cardiovascular disease, diabetes, hypertension, dyslipidemia, obesity, or old age, measurement of urinary protein and creatinine concentrations might be helpful to detect early proteinuria even if the dipstick test grade in a health checkup is categorized as grade –.

With the dipstick test, a large proportion of false-negative occur with a cutoff grade of ±. It has been reported that cost performance would be better if dipstick tests were used for high-risk groups, such as those with hypertension and diabetes [24, 25]. Although a cost analysis has not been done in Japan, to the best of our knowledge, screening for proteinuria with PCR, especially in high-risk groups and women, might be better. Likewise, to make the false-negative by the cut-off grade of ± as small as possible it might be recommended to participants to have health check-up examination without excess water intake. Standardized amount of water intake before the examination, especially in women, may reduce the occurrence of urine dilution and consequently the false-negatives. Because in over 60% of the urine samples protein concentration was under 20mg/dL, precise maneuver of dipstick examination with sufficient reaction time according to instruction manual is also important to correctly detect ± proteinuria in real-world setting.

The study limitations need to be considered. First, a relatively small cohort was evaluated. Because of the small numbers with proteinuria, dipstick grade could not be precisely stratified according to PCR, especially in cases with advanced proteinuria. Second, the samples came from volunteers in a single institution. Since the Specific Health Checkups are carried out in many institutions, biases in the population compared to the general population could not be ruled out. Third, in this cohort, the men were significantly older than the women. Such variations may be acting as confounding factors.

In conclusion, although the dipstick test is an excellent screening method for predicting clinically significant proteinuria, a substantial number of false-negative results were obtained. It is inappropriate to set the cut-off point at ± for detection of PCR ≥ 150 mg/gCr, which is the level at which detailed assessments for CKD should be initiated.

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