Evaluation of Validity of the Urine Dipstick Test for Identification of Reduced Glomerular Filtration Rate in Japanese Male Workers Aged 40 Years and Over

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Abstract: Evaluation of Validity of the Urine Dipstick Test for Identification of Reduced Glomerular Filtration Rate in Japanese Male Workers Aged 40 Years and Over: Masatoshi Kawashima, *et al.* **Department of Occupational Health, Graduate School of Medical Sciences, Kitasato University—Objectives:** We evaluated the validity of the urine dipstick test for identifying reduced glomerular filtration rate (GFR) in male workers. **Methods:** This study was conducted in male workers aged ≥ 40 yr. Reduced GFR was categorized as either estimated GFR (eGFR) < 60 ml/min/1.73 m^2 (eGFR < 60) or eGFR < 50 ml/min/1.73 m^2 (eGFR < 50). Four sets of criteria were used to evaluate the GFR on the basis of proteinuria excretion, as measured using the urine dipstick test. Receiver operating characteristic curves were created based on the sensitivity and specificity and used to calculate the area under the curve (AUC) and the 95% confidence intervals (CI). **Results:** A total of 5,799 workers were included in this study. Use of an abnormal proteinuria criterion of 1+–3+ and a reduced GFR criterion of eGFR < 60 resulted in a sensitivity and specificity of 7.8% and 97.4%, respectively, while a reduced GFR criterion of eGFR < 50 resulted in a sensitivity and specificity of 37.8% and 97.4%, respectively. The AUC was 0.52 (95% CI, 0.48–0.55) for eGFR < 60 and 0.70 (95% CI, 0.59–0.80) for eGFR < 50. **Conclusions:** In this study, 92.2% of participants with an eGFR < 60 and 62.2% of participants with an eGFR < 50 were overlooked in the urine dipstick test. These results suggest that the urine dipstick test only is not sufficient enough to identify reduced GFR and that both a urine dipstick test and other measures of GFR are required to reliably identify reduced GFR.
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Chronic kidney disease (CKD) precedes end-stage renal disease, which necessitates dialysis treatment. Appropriate treatment of CKD may delay the progression to end-stage renal disease[1]. End-stage renal disease has a poor prognosis and has been identified as a risk factor for cardiovascular disease[2, 3]. Increasing numbers of patients with end-stage renal disease represent a medical–economic issue. Early identification of CKD is crucial to prevent the potential increase in patients with end-stage renal disease.

The Kidney Diseases Outcomes Quality Initiative (K/DOQI) guidelines of the National Kidney Foundation defined CKD and also proposed diagnostic criteria and stages in 2002. These guidelines define CKD as a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 (estimated GFR [eGFR] < 60) and/or evidence of kidney damage (e.g., abnormal urinalysis results such as proteinuria, abnormal diagnostic imaging findings such as polycystic kidney disease, abnormal blood test results, pathological abnormalities) lasting for ≥3 mo[1]. In many cases, CKD is diagnosed if the patient demonstrates a reduced GFR or the presence of proteinuria. However, direct measurement of GFR is difficult, and GFR is generally estimated on the basis of serum creatinine (Cr) and the age of the patient.

Reduced GFR is an indicator of decreased renal function, which is in turn a predictor of end-stage renal disease[2–6]; the lower the renal function, the more rapid the progression to renal failure[6]. Proteinuria

is an indicator of renal damage and a documented predictor of end-stage renal disease[3, 7–10]. Moreover, although renal function can decrease in the absence of proteinuria, it has also been identified as a predictor of end-stage renal disease[3]. It is therefore necessary to evaluate not only proteinuria but also reduced GFR in order to confirm a diagnosis of CKD and prevent progression to end-stage renal disease.

Since 1972, the Industrial Safety and Health Law in Japan has required employees to undergo a medical examination at least once a year. The urine dipstick test is a mandatory test item for the identification of proteinuria, and individuals with renal damage should be identified on the basis of the check-up results. However, the recent emergence of the concept of CKD has triggered discussion about the adequacy of the urine dipstick test alone to identify workers with CKD. Indeed, the ability of the urine dipstick alone to identify reduced GFR is unknown. We therefore evaluated the validity of the urine dipstick test as a measure for identifying reduced GFR in male workers aged 40 yr or over.

Methods

Participants

Our study included all eligible male workers aged 40 yr or over who were employed at a factory manufacturing general machinery in Kanagawa Prefecture in Japan between 2003 and 2008. In the case of employees who underwent examinations with blood tests more than once a year, data from the first examination of the year were used for the analysis. Female workers were excluded from the study because they accounted for less than 10% of the number of male employees. Participants who did not undergo either a urine dipstick test or a serum Cr measurement test were excluded from the analysis on the basis of missing data.

Measures

Estimated GFR and proteinuria were used for the analysis. The eGFR was based on the serum Cr level (enzymatic method) and age at the time of the medical examination and calculated using the following equation, which is based on the 3-variable Japanese equation of the Japanese Society of Nephrology[11]: $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$. Freshly voided urine samples were used for the urine dipstick test (Roche Diagnostics K.K., Tokyo, Japan), and proteinuria assessments were performed by trained clinical laboratory technicians. Proteinuria excretion was assessed on a 5-point scale using the following criteria: negative, <15 mg/dl; trace, ≥15 mg/dl; 1+, ≥30 mg/dl; 2+, ≥100 mg/dl; and 3+, ≥300 mg/dl. Participants with reduced GFR were categorized as eGFR < 60, which

is a diagnostic criterion for CKD according to the K/DOQI guidelines[1], or eGFR < 50, which requires referral to a nephrologist according to the Japanese CKD treatment guidelines[12].

Statistical analysis

Statistical analysis was performed to evaluate the association between reduced GFR and proteinuria excretion. Four sets of criteria were used to evaluate reduced GFR according to the measurements of proteinuria excretion. Normal/abnormal assessments were based on proteinuria values of: negative/trace –3+; negative–trace/1+–3+; negative–1+/2+–3+ and negative–2+/3+. The sensitivities, specificities and positive predictive values of the urine dipstick test for identifying reduced GFR were calculated based on each of the above criteria. A receiver operating characteristic (ROC) curve was constructed based on the sensitivity and specificity calculated for each set of criteria[13]. The area under the curve (AUC) and the 95% confidence intervals (CI) were calculated based on the ROC curve. AUCs range from 0.5 to 1.0; an AUC closer to 1 indicates a higher predictive and diagnostic power. The validity of the urine dipstick test for identifying reduced GFR was evaluated based on the calculated AUCs. Data were analyzed using SPSS 17.0J for Windows (SPSS, Tokyo, Japan)[14].

Ethical approval

This study was conducted with the approval of the ethics committee of Kitasato University School of Medicine.

Results

A total of 5,799 workers were included in the study between 2003 and 2008. The numbers of participants from each year were 880 (2003), 913 (2004), 945 (2005), 953 (2006), 1,059 (2007) and 1,049 (2008). The characteristics of the participants and associations among age, reduced eGFR and proteinuria are presented in Table 1. The mean age (± standard deviation) was 50.6 (± 6.2) yr. A total of 294 participants (5.1%) had an eGFR < 60, while 37 participants (0.6%) had an eGFR < 50. A total of 165 participants (2.8%) tested positive for proteinuria at a level of (+) or higher. The association between reduced GFR and proteinuria excretion according to participant age is presented in Table 1. Among participants aged 40–49 yr, 2.6% had an eGFR < 60 compared with 6.0% of participants aged 50–59 yr and 11.5% of participants aged 60 yr or over. Among participants aged 40–49 yr, 0.5% had an eGFR < 50 compared with 0.6% of participants aged 50–59 yr and 2.0% of participants aged 60 yr or over.

Table 2 shows the distribution of reduced eGFR and

Table 1. Characteristics of participants and associations among age, reduced eGFR and proteinuria (N=5,799)

Age (yr)	%	eGFR					Proteinuria (%)				
		Mean	Max	Min	Less than 60 (%)	Less than 50 (%)	Negative	Trace	1+	2+	3+
40–49	38.8	81.3	134.8	19.4	2.6	0.5	89.9	6.9	2.3	0.5	0.4
50–59	54.4	78.8	135.7	3.4	6.0	0.6	90.5	6.6	2.1	0.6	0.2
≥60	6.8	73.5	130.7	44.2	11.5	2.0	95.4	3.8	0.5	0.0	0.3
Total	100.0	79.4	135.7	3.4	5.1	0.6	90.6	6.6	2.1	0.5	0.3

eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2).

Table 2. Distribution of reduced eGFR and proteinuria excretion levels

Proteinuria excretion level	eGFR %	
	Less than 60 (N=294)	Less than 50 (N=37)
Negative	87.8	54.1
Trace	4.4	8.1
1+	3.7	13.5
2+	1.7	13.5
3+	2.4	10.8

eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2).

Table 3. Sensitivities, specificities and PPVs of urine dipstick tests for identifying reduced eGFR

Abnormal proteinuria		eGFR less than 60			eGFR less than 50		
		Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Trace–3+	(N=545)	12.2	90.8	6.6	45.9	90.8	3.1
1+ –3+	(N=165)	7.8	97.4	13.9	37.8	97.4	8.5
2+ –3+	(N=45)	4.1	99.4	26.7	24.3	99.4	20.0
3+	(N=15)	2.4	99.9	46.7	10.8	99.8	26.7

eGFR: estimated glomerular filtration rate (ml/min/1.73 m^2). PPV: positive predictive value.

proteinuria excretion levels. Of the participants with an eGFR < 60, 87.8% tested negative for proteinuria, and 7.8% tested positive for proteinuria (1+ or higher). Of the participants with an eGFR < 50 , 54.1% tested negative for proteinuria, and 37.8% positive tested proteinuria (1+ or higher).

Table 3 shows the sensitivities, specificities and positive predictive values of the urine dipstick test for identifying reduced GFR. Using the criteria of eGFR < 60 for reduced GFR, negative and trace proteinuria for normal and 1+–3+ proteinuria for abnormal, the sensitivities, specificities and positive predictive values were 7.8, 97.4 and 13.9%, respectively. Using the criteria of eGFR < 50 for reduced GFR, negative and trace proteinuria for normal and 1+–3+ proteinuria for abnormal, the sensitivities, specificities and positive predictive values were 37.8, 97.4 and 8.5%, respectively.

ROC curves were constructed based on the sensitivities and specificities of each set of criteria for identifying reduced GFR according to the proteinuria excretion level to determine the AUCs. Figure 1(A) presents the ROC curve based on the criterion of eGFR < 60 for reduced GFR; the AUC was 0.52, with a 95% CI of 0.48–0.55. Figure 1(B) presents the ROC curve constructed based on the criterion of eGFR < 50 for reduced GFR; the AUC was 0.70, with a 95% CI of 0.59–0.80.

Discussion

We evaluated the validity of the urine dipstick test for identifying reduced GFR. Using a criterion of eGFR < 60 for reduced GFR, 92.2% of the participants with reduced GFR were overlooked (negative and trace proteinuria: 87.8 and 4.4%, respectively), while 62.2% of the participants with reduced GFR were overlooked using a criterion of eGFR < 50 (negative and trace proteinuria: 54.1 and 8.1%, respectively).

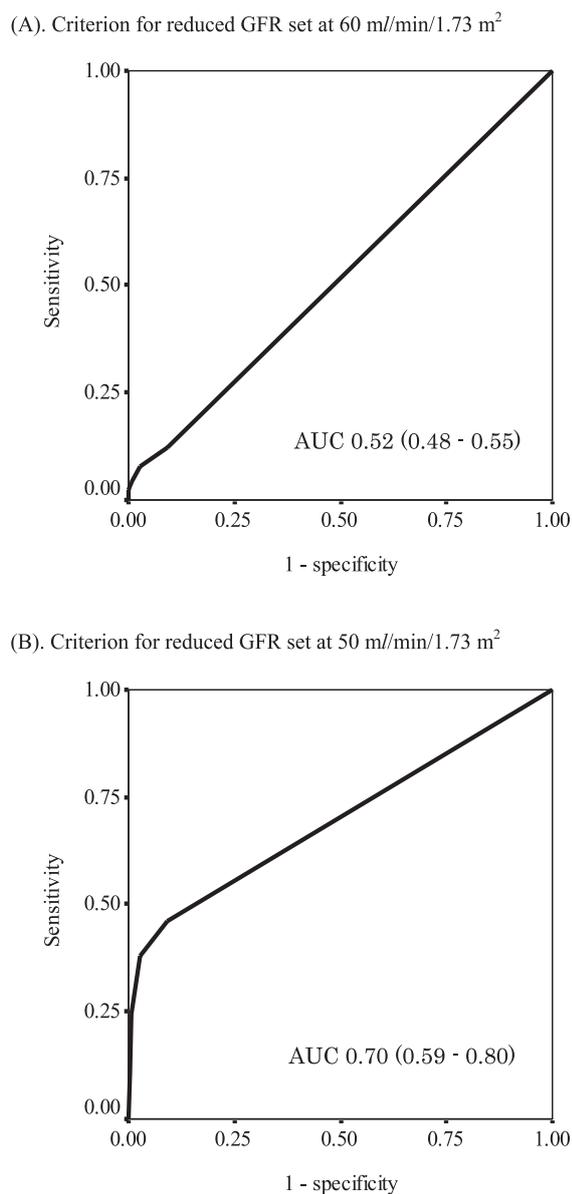Proteinuria of 1+ or higher is considered an abnor-

(A). Criterion for reduced GFR set at 60 ml/min/1.73 m²

AUC 0.52 (0.48 - 0.55)

(B). Criterion for reduced GFR set at 50 ml/min/1.73 m²

AUC 0.70 (0.59 - 0.80)

Fig. 1. ROC curves for the urine dipstick test to identify reduced GFR defined as 60 ml/min/1.73 m² (A) or 50 ml/min/1.73 m² (B).

ROC curves were constructed based on the sensitivity and specificity of the urine dipstick test results for identifying reduced GFR defined as <60 ml/min/1.73 m² (A) or <50 ml/min/1.73 m² (B). The AUCs (95% CI) were calculated based on the ROC curves. AUCs range from 0.5 to 1.0. An AUC closer to 1 indicates a higher predictive and diagnostic power. GFR: glomerular filtration rate, AUC: area under the curve, ROC: receiver operating characteristic, CI: confidence interval.

mal finding in routine proteinuria examinations. Although 165 participants (2.8%) had proteinuria assessed as 1+ to 3+, these included only 23 of the 294 participants (7.8%) with an eGFR < 60. When eGFR < 60 was used as a criterion for reduced eGFR,

urine dipstick tests in which proteinuria 1+ to 3+ was evaluated as abnormal had a sensitivity of 7.8% and a specificity of 97.4% for detecting reduced GFR. Using evaluation criteria for abnormality of proteinuria trace to 3+, 2+ to 3+ and 3+, urine dipstick tests showed sensitivities of 12.2, 4.1 and 2.4%, and specificities of 90.8, 99.4 and 99.9%, respectively. Although the urine dipstick test showed high specificities, the low sensitivities indicated that it would fail to identify the majority of participants with reduced GFR. The urine dipstick test was therefore considered to lack validity for the detection of reduced GFR.

Similarly, the 165 participants with proteinuria assessed as 1+ to 3+ included only 14 of the 37 participants with an eGFR < 50 (37.8%). When eGFR < 50 was used as a criterion for reduced eGFR, urine dipstick tests in which proteinuria 1+ to 3+ was evaluated as abnormal had a sensitivity of 37.8% and a specificity of 97.4% for detecting reduced GFR. Using evaluation criteria for abnormality of proteinuria trace to 3+, 2+ to 3+ and 3+, urine dipstick tests showed sensitivities of 45.9, 24.3 and 10.8%, and specificities of 90.8, 99.4 and 99.8%, respectively. Although the urine dipstick test detected about a third of the participants who had reduced GFR based on considering proteinuria of 1+ or higher as abnormal (the abnormality criterion used in routine proteinuria examinations), higher sensitivity is required because eGFR < 50 represents a criterion for referral to a nephrologist[12]. Thus, the fact that the urine dipstick test overlooked about two thirds of participants with reduced GFR indicates its unsuitability as a means of assessing reduced GFR.

When eGFR < 60 was used as a criterion for reduced GFR, the urine dipstick test had a prevalence rate (pretest probability) of 5.1%, and a positive predictive value (posttest probability) of 13.9% when proteinuria 1+ to 3+ was evaluated as abnormal. When the evaluation criteria for abnormality were trace to 3+, 2+ to 3+ and 3+, the urine dipstick test had positive predictive values of 6.6, 26.7 and 46.7%, respectively. When eGFR < 50 was used as a criterion for reduced GFR, the test had a prevalence rate (pretest probability) of 0.6% and a positive predictive value (posttest probability) of 8.5%. With evaluation criteria for abnormality of trace to 3+, 2+ to 3+ and 3+, the urine dipstick test had positive predictive values of 3.1, 20.0 and 26.7%, respectively. These results suggest that the reduction in GFR may decrease as proteinuria increases, irrespective of whether eGFR < 60 or eGFR < 50 is used as the criterion for reduced GFR.

The AUC for the GFR criterion of eGFR < 60 was 0.52 (95% CI, 0.48–0.55), which is close to 0.5. Because an AUC closer to 1 indicates higher predic-

tive and diagnostic powers, this result suggests that the urine dipstick test may not be a useful method for identifying an eGFR < 60. The AUC when the criterion was set at eGFR < 50 was 0.70 (95% CI, 0.59–0.80), indicating that the dipstick urine test may have higher predictive and diagnostic power for identifying an eGFR < 50 than when the criterion is set at eGFR < 60. However, higher sensitivity is required because eGFR < 50 represents a criterion for referral to a nephrologist[12]. Thus, although the urine dipstick test may be more effective for identifying an eGFR < 50 than an eGFR < 60, its performance remains inadequate.

A potential limitation of this study was the fact that the participants were factory workers and might therefore not be representative of the general population because of the so-called "healthy worker effect"[15]. However, this effect was unlikely to have influenced the study results, which clearly demonstrated that detecting reduced GFR by the urine dipstick test lacks validity.

Early identification of CKD is crucial for preventing the potential increase in the number of patients with end-stage renal disease. Identification of reduced GFR and proteinuria is important for the diagnosis of CKD for prevention of progression to end-stage renal disease. However, the results of this study indicate that the ability of the urine dipstick test to identify an eGFR < 60 is low because 92.2% of participants with reduced GFR may be overlooked. Although its ability to identify individuals with an eGFR < 50 is better, 62.2% of patients with reduced GFR may still be overlooked. In conclusion, the urine dipstick test only is not sufficient enough to identify reduced GFR, and both a urine dipstick test and other measures of GFR are required to reliably identify reduced GFR.

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