Accuracy of Urine Dipstick Test for Microalbuminuria in Type 2 Diabetes Mellitus Patients

Udom Krairittichai MD*, Somkiat Potisat MD**,
Amporn Jongsareejit MD***, Charnvate Sattaputh MD****

* Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand
** Institute of Medical Research and Technology Assessment, Department of Medical Services, MOPH, Nonthaburi, Thailand
*** Prasat Neurological Institute, Department of Medical Services, MOPH, Bangkok, Thailand
**** Lerdsin Hospital, Department of Medical Services, Ministry of Public Health, Bangkok, Thailand

Background: Testing for microalbuminuria (MA) is an important tool for detection of the earliest clinical manifestation of diabetic nephropathy. Dipstick test for MA is commonly used for screening MA but this dipstick test has not been validated in Thai patients with DM.

Objective: To evaluate the diagnostic accuracy of the dipstick test for MA in random spot urine samples of type 2 diabetic mellitus patients, using urinary albumin to creatinine ratio (UACR) as the reference standard method.

Material and Method: Type 2 diabetic mellitus patients from the out-patient department of seven public hospitals were recruited. Random spot urine samples from all patients were screened for microalbuminuria by Combi-Screen® dipstick test and UACR.

Results: A total of 6,223 urine samples from 899 diabetic patients were screened for MA. From UACR criteria, these urine samples were classified as normoalbuminuria (4,016 samples, 64.5%), MA (1,795 samples, 28.8%) and macroalbuminuria (412 samples, 6.6%). The dipstick test for MA had an overall sensitivity of 83.7%, specificity of 92.6% with a positive predictive value of 83.4% and a negative predictive value of 92.7%. The area under the receiver operating characteristics curve of the dipstick test for MA is 0.9427.

Conclusion: The dipstick test for MA may be a useful method to initially screen for MA in Thai patients with type 2 DM.

Keywords: Microalbuminuria, Urine dipstick, Diabetes mellitus

The numbers of patients with type 2 diabetes mellitus (T2DM) are increasing in Thailand. Proteinuria and hypertension are indicators of poor renal and cardiovascular outcomes in diabetic patients[1,2]. Diabetic nephropathy is characterized by persistent proteinuria, elevated blood pressure and persistent decline in the glomerular filtration rate. Increased urinary albumin excretion is the earliest clinical manifestation of diabetic nephropathy[3-5]. The normal rate of urinary albumin excretion is less than 20 mg/day. Urinary albumin excretion between 30 and 300 mg/day is called microalbuminuria (MA). Persistent MA in diabetes mellitus patients is indicative of early diabetic nephropathy. Urinary albumin excretion above 300 mg/day is considered to represent macroalbuminuria[6] that shows greater progression of diabetic nephropathy than MA. A test for MA is an important tool for detection of the earliest clinical manifestation of diabetic nephropathy.

The 24-hour or timed urine collection for urinary albumin excretion has been the initial gold standard for detection of MA[7,8]. This test is impractical because it is difficult to capture complete urinary collection. Comparing with timed urine collection for urinary albumin excretion, spot urine sampling for urinary albumin to creatinine ratio (UACR) is acceptable for detection of MA but this test has not been done in most hospitals in Thailand. Albumin-specific dipsticks are acceptable for detecting albuminuria. It has been suggested that screening could be cheaper and simply achieved by a dipstick test for MA. The sensitivity and specificity of these dipstick tests have been reported in ranges of 80-97 percent and 33-80 percent, respectively[9]. Dipstick test for MA is commonly used

Correspondence to:
Krairittichai U, Division of Nephrology, Department of Medicine, Rajavithi Hospital, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 0-2354-8059, Fax: 0-2354-8188
E-mail: krairit@yahoo.com

in general hospitals but this dipstick test has not been validated in Thai patients with DM. The purpose of this study was to evaluate the diagnostic accuracy of the dipstick test for MA in random spot urine of T2DM patients, using UACR measurement as the reference standard method.

Material and Method

      This is a cross-sectional study measuring of urinary albumin excretion in Thai T2DM patients. The Ethics Review Committee for Research in Human Subjects, Ministry of Public Health approved this study and all patients gave written informed consent after reviewing a written summary of the study plan. The authors recruited type 2 diabetic mellitus patients diagnosed with the American Diabetes Association's criteria[10] from the out-patient department of seven public hospitals, including Rajavithi Hospital (Bangkok), Lerdsin Hospital (Bangkok), Nopparatrajathanee Hospital (Bangkok), Mettaphacharak Hospital (Nakhonpathom), Pathumthani Hospital (Pathumthani), Lardlumkaew Hospital (Pathumthani) and Nongsau Hospital (Pathumthani). The study period was from January 2007 to September 2009. Exclusion criteria were UACR more than 300 mg/gm, pregnancy, breast feeding and acute systemic diseases (for example: active infection, malignancy or heart failure). Their clinical status was assessed. Random spot urine samples from all patients were collected and divided into two half. One urine sample was immediately tested by Combi-Screen® test strip for MA (Analyticon® Biotechnologies AG, Germany). The interpretation of this test strip was visually compared by means of color to the color blocks on a chart attached to the vial. A color presentation between 20 mg/l and 100 mg/l albumin was classified as MA[11] and normoalbumin (NA) if less than 20 mg/l. The second urine sample was measured by UACR in one hour. The quantity of urinary albumin concentration was determined by immunoturbidimetric assay and urine creatinine concentration by Jaffe reaction using COBAS INTEGRA 400® analyzer. UACR was classified into three groups, NA (UACR less than 30 mg/gm), MA (UACR 30-300 mg/gm) and macroalbuminuria (UACR more than 300 mg/gm).

      Statistical mean $\pm$ standard deviation (SD) was the determining factor in urinary albumin classification. Data were analyzed using statistical methods to determine the diagnostic accuracy of the dipstick test including sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence interval (95% CI) and the receiver operating characteristic (ROC) curve. Analysis was made with the software program SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

      A total of 6,223 urine samples from 899 diabetic patients were recruited for the present study. Baseline characteristics of all patients are shown in Table 1. Based on UACR criteria, these urine samples were classified as NA (4,016 samples, 64.5%), MA (1,795 samples, 28.8%) and macroalbuminuria (412 samples, 6.6%). Results of dipstick tests for MA were analyzed and compared to the reference standard method (UACR) performed in urine samples of classified NA and MA (total 5,811 samples).

      Table 2 shows the results of the dipstick test compared to UACR. The dipstick test for MA gave a sensitivity of 83.7% (95% CI 82.7-84.6%), specificity of 92.6% (95% CI 91.9-93.3%), positive predictive value of 83.4% (95% CI 82.5-84.4%) and negative predictive value of 92.7% (95% CI 92.0-93.4%). Fig. 1 shows the diagnostic accuracy of the dipstick test as determined by the ROC curve. The area under the ROC curve is 0.9427.

Discussion

      Diabetic nephropathy is the leading cause of end-stage renal disease that requires renal replacement therapy[12]. MA is the earliest clinical manifestation of diabetic nephropathy and indicates an increased cardiovascular risk and the presence of kidney disease. MA should be measured in all T2DM patients because diabetic nephropathy and cardiovascular disease can be treated as soon as this risk factor appears. Reports of cost effectiveness suggest that a screening program

Table 1. Baseline characteristics of all patients.

Factors	n = 899
Male (%)	257 (28.6)
Age (year)	59.64 $\pm$ 9.90
Duration of DM (year)	8.12 $\pm$ 6.12
Body weight (kg)	66.80 $\pm$ 13.17
Systolic BP (mmHg)	130.20 $\pm$ 18.58
Diastolic BP (mmHg)	71.52 $\pm$ 10.88
HbA1c (%)	8.80 $\pm$ 1.9
Serum creatinine (mg/dl)	0.95 $\pm$ 0.56

Values are represented as n (%), Means $\pm$ SD

Table 2. Diagnostic accuracy of dipstick test for the detection of MA (n = 899)

	MA diagnosed by UACR criteria	
	< 30 mg/gm	30-300 mg/gm
Dipstick test: Negative	3,718	293
Dipstick test: Positive	298	1,502
Sensitivity	83.7%	(95% CI 82.7-84.6%)
Specificity	92.6%	(95% CI 91.9-93.3%)
Positive predictive value	83.4%	(95% CI 82.5-84.4%)
Negative predictive value	92.7%	(95% CI 92.0-93.4%)
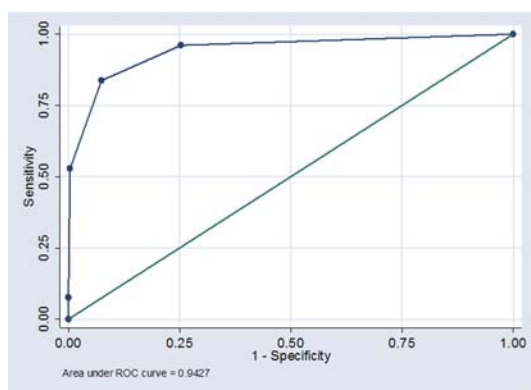
Fig. 1 Diagnostic accuracy of dipstick test for MA as determined by the ROC curve.

for MA and intervention with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers can reduce the cost of treatment[13,14]. In addition, the screening program could reduce the likelihood of progression from NA to MA[15-17] or MA to macroalbuminuria in T2DM patients as well[18-20]. Annual screening for MA in diabetic patients is currently recommended. In contrast to macroalbuminuria which may be detected by conventional dipstick urinalysis for protein, MA is usually detected using sensitive laboratory techniques. Measurement of UACR in spot urinary sample is the preferred screening strategy for MA in all T2DM patients[3] but this test is expensive and cannot be done in most hospitals in Thailand. The dipstick test for MA in spot urine is an accepted tool for the initial screening of T2DM patient.

Analysis shows that the dipstick test for MA gave a sensitivity of 83.7% and specificity of 92.6%. This result is agreeable with previous studies of other dipstick tests for MA. The Clinitek Microalbumin

Reagent Strip® (Bayer Corporation, Tarrytown, NY) gave a sensitivity of 79.0-95.4% and specificity of 73.0-81.0%[21-23]. The Micral-Test II test strip for MA® (Boehringer Mannheim, Indianapolis, IN), gave a sensitivity of 93.0-97.0% and specificity of 33.0-93.0%[11,13,24]. The American Diabetes Association has recommended that dipstick testing may be used if it shows acceptable sensitivity (95.0%) and specificity (95.0%)[25]. The National Academy of Clinical Biochemistry has recommended that the sensitivity of dipstick testing should exceed 95.0%[26]. The result of dipstick test for MA in this present study, however, does not meet these requirements for detecting MA. One reason for this lack of accuracy may account for the fact that the concentration of urine albumin depends on urine volume as well as the amount of albuminuria[27]. The diagnosis of MA is prone to error due to changes in urinary flow and concentration. Changes in urine volume will respectively lower or raise the urine albumin concentration, which could eventually affect visual interpretation of the test strip. The confounding effect of the urine volume can be minimized by repeated measurements of early morning specimens[7]. Although this dipstick test does not give more than 95.0% sensitivity, the large area under the ROC curve suggests that this dipstick test may still be suitable to detect MA. Dipstick test of MA can be used for initial screening for MA if urine albumin excretion cannot be directly measured. In addition, it is easier and cheaper in diagnosis for MA. A positive result of this dipstick test should be followed by measurement of UACR to confirm the presence for MA. Rapid dipstick test of MA enables the physician to regularly check the urine albumin and prescribe the appropriate treatment for positive-test patients. We suggested that dipstick test for MA may be an appropriate screening tool for hospitals in Thailand.

Conclusion

When comparing with UACR, the diagnostic accuracy of dipstick test for MA in T2DM patients is good. In addition to cost, the convenience in testing by urinary dipstick may be an important consideration for general practice. The recommendation for the initial screening of T2DM patients is to use a spot urine dipstick test for MA. If positive, spot urine for UACR should be completed to confirm the finding.

Acknowledgements

Potential conflicts of interest

None.

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ความเที่ยงตรงของการตรวจปัสสาวะด้วยแถบจุ่มสำหรับ microalbuminuria ในผู้ป่วยเบาหวานชนิดที่ 2

อุดม ไกรฤทธิชัย, สมเกียรติ โพธิสัตย์, อัมพร จงเสรีจิตต์, ชาญเวช ศรัทธาพุทธ

ภูมิหลัง: การตรวจ microalbuminuria (MA) เป็นวิธีการตรวจหา diabetic nephropathy ระยะเริ่มแรกการตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA นิยมใช้เป็นเครื่องมือในการคัดกรองโรคแต่วิธีดังกล่าวยังไม่เคยมีการทำการทดสอบความเที่ยงตรงของเครื่องมือในผู้ป่วยเบาหวานคนไทย

วัตถุประสงค์: ต้องการทดสอบความเที่ยงตรงของการตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA ในผู้ป่วยเบาหวานชนิดที่ 2 โดยเปรียบเทียบกับการตรวจมาตรฐาน urinary albumin to creatinine ratio (UACR)

วัสดุและวิธีการ: คัดเลือกผู้ป่วยเบาหวานชนิดที่ 2 จากห้องตรวจผู้ป่วยนอกในโรงพยาบาลของรัฐ 7 แห่ง นำไปตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA (Combi-Screen®) และตรวจหา UACR

ผลการศึกษา: ปัสสาวะ 6,223 ตัวอย่างจากผู้ป่วยเบาหวานชนิดที่ 2 จำนวน 899 คน ได้ทำการตรวจหา MA จากข้อกำหนดของ UACR สามารถแบ่งปัสสาวะออกเป็น normoalbuminuria (4,016 ตัวอย่าง, 64.5%), MA (1,795 ตัวอย่าง, 28.8%) และ macroalbuminuria (412 ตัวอย่าง, 6.6%) การตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA มี sensitivity เท่ากับ 83.7%, specificity เท่ากับ 92.6%, positive predictive value เท่ากับ 83.4% และ negative predictive value เท่ากับ 92.7% พื้นที่ใต้ ROC curve ของการตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA เท่ากับ 0.9427

สรุป: การศึกษานี้พบว่าการตรวจปัสสาวะด้วยแถบจุ่มสำหรับ MA น่าจะมีประโยชน์สำหรับคัดกรองหา MA ในผู้ป่วยเบาหวานชนิดที่ 2