Can the Urine Dipstick Test Reduce the Need for Microscopy for Assessment of Systemic Lupus Erythematosus Disease Activity?

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ABSTRACT. ***Objective.*** Urine microscopic examination is an important component of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). We investigated whether the urine dipstick test can reduce the need for microscopy for the assessment of SLEDAI.

Methods. We studied 269 urine samples from 259 SLE patients with Albustix™ and Hemastix™ reagent strips. The results were compared to concomitant microscopic examination of urinary sediment.

Results. When trace red blood cell was defined as the cutoff, the sensitivity, specificity, and negative predictive value (NPV) of the Hemastix urine test were 0.98, 0.53, and 0.99, respectively, for hematuria; 0.82, 0.47, and 0.90, respectively, for the presence of pyuria; and 0.91, 0.44, and 0.98, respectively, for the presence of casts by microscopic examination. When proteinuria of 1+ was defined as the cutoff, the sensitivity, specificity, and NPV of the Albustix test were 1.00, 0.46, and 0.99, respectively, for urinary casts; and 0.82, 0.49, and 0.90, respectively, for the presence of pyuria. When both Albustix and Hemastix were applied as screening test, urine microscopy could be reduced by 27%; however, 8% of cases with normal Albustix and Hemastix tests had at least one abnormality on urine microscopy examination.

Conclusion. In patients with SLE, a combination of Albustix and Hemastix urine tests showed reasonable sensitivity to detect abnormalities in urine sediment. Based on these results, routine urine microscopy can be limited to SLE patients with abnormal Albustix or Hemastix tests. Rarer causes of abnormal renal function in lupus, such as tubulointerstitial nephritis or drug induced interstitial nephritis, would be manifested by pyuria and therefore would not necessarily be detected by changes in the blood and protein detectors on the urine dipstick. (J Rheumatol 2005;32:828–31)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS DIPSTICK HEMATURIA
PROTEINURIA SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with high morbidity and mortality[1,2]. The aberrant immune response of SLE triggers attacks to multiple organ systems, resulting in a variety of clinical manifestations[3]. SLE usually runs a course with disease flares and remissions. As a result, regular assessment of disease activity is necessary. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is one of the most commonly used clinical tools for assessment and monitoring of SLE disease activity[4]. Among other clinical and laboratory measures of the SLEDAI score, it requires microscopic examination of the urinary sediment.

Reagent strip testing of urine specimens is commonly used as a screening tool in many areas of clinical practice[5-8]. With the use of reagent strips, a preliminary assessment of possible findings in the urinary sediment can be obtained rapidly and conveniently; cost and time may be saved by reducing the need for formal microscopic examination of many normal urine specimens. The value of the urine strip test as a screening tool has been demonstrated in other clinical settings[8-10]; we investigated whether urine strip testing can be used as a screening tool for assessment of SLE disease activity.

MATERIALS AND METHODS

Patient selection. Two hundred sixty-nine consecutive urine samples were collected from 259 SLE patients. All patients fulfilled the American College of Rheumatology diagnostic criteria for SLE[11]. Disease activity of SLE at the time of urine collection was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[12] by independent clini-

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Supported in part by Chinese University of Hong Kong research accounts 6900972 and 6900570.

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Accepted for publication December 20, 2004.

cians. Notably, urinary casts, hematuria, and pyuria are measures in the SLEDAI score that required microscopic examination of urinary sediment[12]. With patients' informed consent, early morning urine specimens were collected for immediate urinalysis.

Reagent strip testing. At the time of SLEDAI assessment, a spot urine specimen was tested using Hemastix™ and Albustix™ (both from Bayer Diagnostics, Hong Kong) according to the manufacturer's instructions. Based on the degree of color change in the reagent strip, the results were scored as negative, nonhemolyzed trace, nonhemolyzed moderate, trace, small, moderate, or large for red blood cells (RBC); and negative, trace, and 1 to 4 positive for protein.

Microscopic examination of urinary sediment. Microscopic examination of urinary sediment under phase-contrast microscopy was performed on the same urine specimen by an independent examiner (CCS) who was blinded to the result of the reagent strip test. Briefly, a 12 ml aliquot of urine was centrifuged at 450 g for 5 min. The supernatant was removed and the sediment was resuspended into solution with 1 ml of supernatant. One drop of the resuspended sediment was examined under 100× and 400× magnifications. The result was interpreted as the number of RBC per high power field (hpf) (400× magnification). Hematuria and pyuria were defined as at least 5 RBC and 5 white blood cells per hpf, respectively. Urinary casts was defined as the presence of heme-granular or RBC casts under low power field (100× magnification).

Statistical analysis. Statistical analysis was performed using SPSS for Windows software, version 10.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD unless otherwise specified. A conventional receiver-operating characteristic (ROC) curve was constructed to determine the area under the curve (AUC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at various definitions of the cutoff point for blood and protein on dipstick.

RESULTS

We studied 269 urine samples from 259 SLE patients in total; 250 (96%) patients were female. The average age was 37.6 ± 10.8 years (range 17–80 yrs). The average SLEDAI score was 6.1 ± 6.0 (range 0–32). On microscopic examination, 63 urine samples (23%) had hematuria, 60 (22%) pyuria, and 21 (8%) urinary casts.

Detection of hematuria by Hemastix test. With the Hemastix test, 159 out of 269 (59%) urine specimens showed trace or more RBC. With this definition, the sensitivity and specificity of the Hemastix urine tests were 0.98 and 0.53 for hematuria by microscopy, respectively. The PPV and NPV of the Hemastix urine tests were 0.39 and 0.99, respectively. By the ROC curve analysis, the AUC was 0.97 (Figure 1). Of the 110 urine specimens that were negative by Hemastix test, concurrent urine microscopy found that only one had hematuria.

Prediction of pyuria by dipstick tests. When positive Hemastix test was defined as trace or more RBC, the sensitivity and specificity of the Hemastix tests were 0.82 and 0.47, respectively, for detection of pyuria. The PPV and NPV were 0.31 and 0.90, respectively. By ROC curve analysis, the AUC was 0.82 (Figure 2A). Of 110 urine specimens that were negative by Hemastix test, concurrent urine microscopy found that 11 (10%) had pyuria.

In the Albustix test, 155 of 269 (58%) urine specimens showed proteinuria of 1+ or more. With this definition, the sensitivity and specificity of urine Albustix tests were 0.82 and 0.49, respectively, for pyuria. The PPV and NPV were 0.31 and 0.90, respectively. By ROC curve analysis, the AUC was 0.82 (Figure 2B). Of 114 urine specimens that were negative by Albustix test, concurrent urine microscopy revealed that 12 (11%) had pyuria.

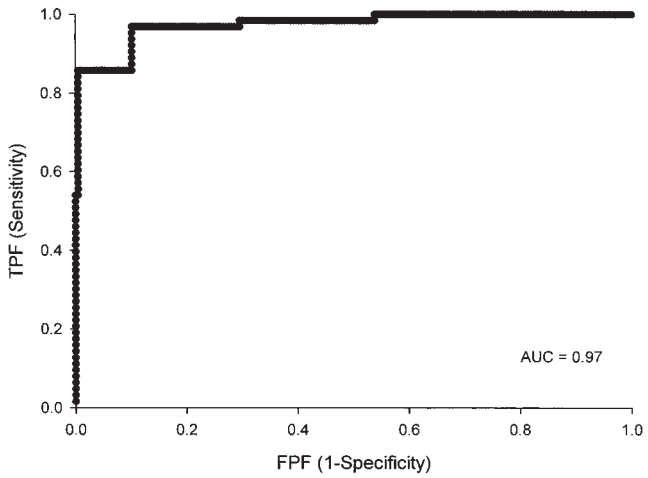

Figure 1. ROC curve for the detection of hematuria by Hemastix™ reagent strip test. When trace red blood cell was defined as the cutoff, the sensitivity, specificity, negative predictive value, and area under the curve were 0.98, 0.53, 0.99, and 0.97, respectively. TPF: true-positive finding; FPF: false-positive finding.

Prediction of urinary casts by dipstick tests. When positive Hemastix test was defined as trace or more RBC, the sensitivity and specificity of the Hemastix tests were 0.91 and 0.44, respectively, for detection of urinary casts. The PPV and NPV were 0.12 and 0.98, respectively. By ROC curve analysis, the AUC was 0.89 (Figure 3A). Of 110 urine specimens that were negative by Hemastix test, concurrent urine microscopy found that only 2 had urinary casts.

When positive Albustix test was defined as 1+ or more protein, the sensitivity and specificity of urine Albustix tests were 1.00 and 0.46, respectively, for the detection of urinary casts. The PPV and NPV of urine Albustix test were 0.13 and 0.99, respectively. By the ROC curve analysis, the AUC was 0.88 (Figure 3B). Of 114 urine specimens that were negative by Albustix test, concurrent urine microscopy found that only one had urinary casts.

Overall assessment. Of the 269 urine specimens, 73 (27%) had negative Hemastix and Albustix tests. Concurrent urine microscopy showed that 6 of them (8%) had at least one abnormality (hematuria, pyuria, or presence of cast).

DISCUSSION

SLE is a systemic autoimmune disease with a relapsing and remitting clinical course. Regular monitoring of disease activity of SLE patients is necessary. Traditionally, microscopic examination of urinary sediment has been an indispensable component in the assessment of SLE disease activ-

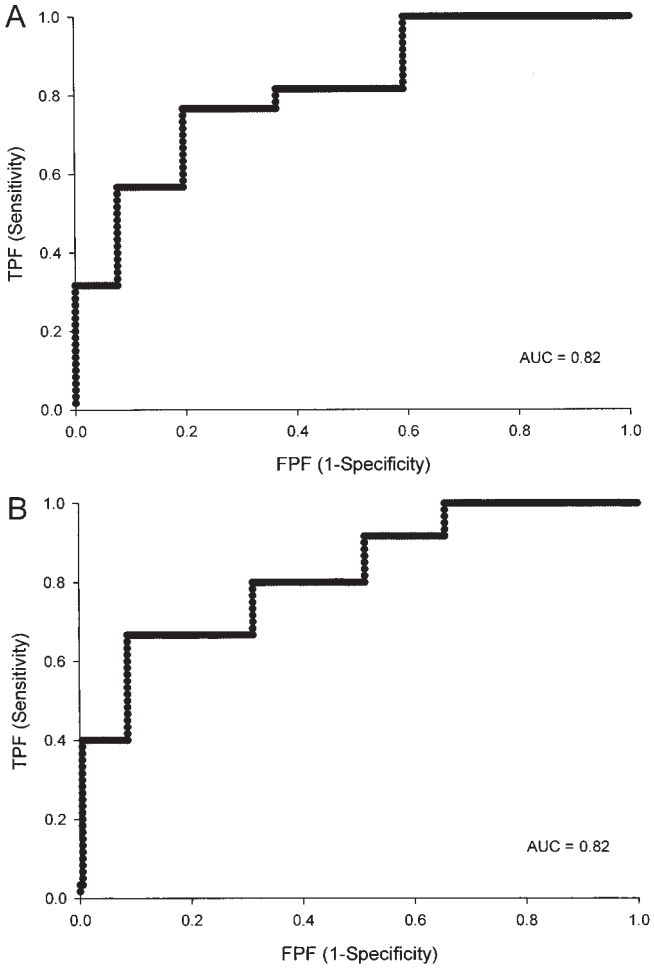

Figure 2. ROC curve for the detection of pyuria: (A) By Hemastix™. When trace red blood cell was defined as the cutoff, the sensitivity, specificity, negative predictive value, and area under the curve were 0.82, 0.47, 0.90, and 0.82, respectively. (B) By Albustix™. When proteinuria of 1+ was defined as the cutoff, the sensitivity, specificity, negative predictive value, and area under the curve were 0.82, 0.49, 0.90, and 0.82, respectively. TPF: true-positive finding; FPF: false-positive finding.

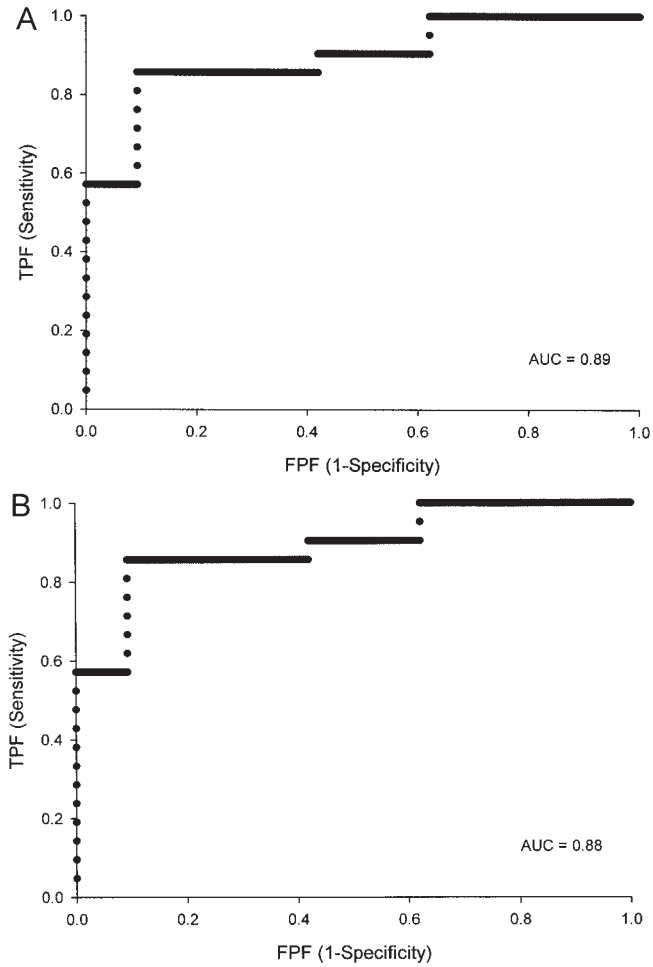

Figure 3. ROC curve for the detection of casts: (A) By Hemastix™. When trace red blood cell was defined as the cutoff, the sensitivity, specificity, negative predictive value, and area under the curve were 0.91, 0.44, 0.98, and 0.89, respectively. (B) By Albustix™. When proteinuria of 1+ was defined as the cutoff, the sensitivity, specificity, negative predictive value, and area under the curve were 1.00, 0.46, 0.99, and 0.88, respectively. TPF: true-positive finding; FPF: false-positive finding.

ity because urinary casts, hematuria, and pyuria are the renal indicators for the SLEDAI score, a widely used objective assessment of SLE disease activity. It is obvious that examination of urinary sediment by trained personnel is invaluable. However, freshly-voided urine samples are needed and the examination requires a certain degree of laboratory expertise; it would be cumbersome to screen a large number of samples in a busy clinic. Urine reagent strip tests are widely used in general and nephrology practice in view of the obvious advantages in terms of sensitivity, cost, time, and convenience. Many reports have evaluated the reliability of various reagent strip tests[5,6,8,12-15]. It has been shown that strip tests could provide high sensitivity, with over 90% of negative predictive values, but low positive predictive values, which ranged from 17% to 96%, on average. High false-positive findings were common in reagent strip tests; nevertheless the dipstick is a sensitive screening tool for detection of proteinuria, hematuria, and pyuria. In other chronic renal diseases, urine reagent strip test has been routinely used as a screening and monitoring tool[16-20].

We investigated the reliability of urine reagent strip test as a screening tool for assessment of SLE disease activity. We demonstrated that urine microscopy can be reduced by about one-third after screening with the reagent strip test and suggest that a combination of urine Albustix and Hemastix tests could be an adequate screening strategy to detect abnormalities in urine microscopy. The high negative predictive values we found are in accord with the correct usage of a urine dipstick for sieve testing, which is consistent with the findings reported from various other clinical settings[5,6,8,12-15].

We found the urinary reagent strip test had a high sensitivity for detection of urinary casts, and the Hemastix strip test had high sensitivity for detection of hematuria in

patients with SLE. Our finding is similar to studies on patients with other kinds of chronic kidney diseases[9,21]; a high false-positive rate for detection of hematuria in SLE patients was found in this study. The reagent strip test for hemoglobin is based on the oxidation reaction between the organic peroxide on the strip and hemoglobin in urine. However, myoglobin in urine has peroxidase-like activity similar to that of hemoglobin. Therefore, myoglobinuria could change the pad color and result in a false-positive finding. In addition, it should be noted that hemolysis may take place in urine, particularly in dilute or alkaline urine, during the time between voiding and microscopy[22]. Since the fragments of RBC are easily missed under bright-field microscopy, while both lysed and unlysed cells are detected by the reagent strip test, this may account for the inconsistency between the 2 methods. It is important to note, however, that the urine Hematstix test cannot replace urine microscopy, which distinguishes hematuria from hemoglobinuria, and glomerular from urologic origin of hematuria.

It is the routine clinical practice in many countries to screen for urinary abnormalities by Hemastix and Albustix in all outpatient services. Because of economic considerations and practical convenience, the dipstick test for leukocytes (for example, by leukocyte esterase) has not been routinely adopted because it is largely used for the diagnosis of urinary tract infection in general practice. In our study, only Hemastix and Albustix reagent strip tests were used, to mimic the everyday clinical practice of our locality. The combination of Hemastix and Albustix reagent strip tests was taken as a surrogate screening test for pyuria because of pathophysiological considerations. Briefly, after the initiation of renal injury such as immune complex deposition, there follows infiltration and activation of lymphocytes and macrophages. The inflammatory process leads to damage of the glomerulus and tubulointerstitium, with glomerular bleeding, abnormality in glomerular filtration barrier, and interstitial infiltration occurring simultaneously, resulting in inflammatory kidney lesions with proteinuria, hematuria, and pyuria.

In our study, we did not examine the role of urine Albustix testing for screening of proteinuria in patients with SLE. Although proteinuria testing is an integral part of the SLEDAI, and Albustix is a reasonable screening tool for proteinuria in other chronic kidney diseases, quantification of proteinuria by timed urine collection provides additional diagnostic and prognostic information that cannot be replaced by a dipstick test. Furthermore, the recently validated spot urine protein-to-creatinine ratio is highly convenient for daily clinical practice[23].

ACKNOWLEDGMENT

We thank Lee Wai Ching for clerical assistance.

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