Value of a standard urinary dipstick test for detecting microalbuminuria in patients with newly diagnosed hypertension

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Summary

Principles: Microalbuminuria may indicate target organ damage in hypertensive patients. However, testing for microalbuminuria is not yet consistently used in general practice. This may be partly due to a lack of data regarding the diagnostic value of practice-based dipstick testing in newly diagnosed hypertension. Objectives were to assess the diagnostic value of a standard dipstick test for urinary protein excretion.

Method: 186 patients who had been newly diagnosed with hypertension were screened for microalbuminuria. A spot urine sample from each of the subjects was evaluated by using a standard dipstick test (Combur 10, Roche Diagnostics GmbH, Mannheim, Germany) in a primary care setting. The albumin/creatinine ratio was used as the "gold standard".

Results: Dipstick testing for protein was positive in 31 urine samples (16.7% of the test samples). The albumin/creatinine ratio was elevated in 33 samples (17.7% of the test samples). The sensitivity of detecting microalbuminuria was 26%, specificity 89%, positive predictive value 45%, and the negative predictive was 88%. Repeated dipstick testing 48 hours after the initial testing in 40 randomly selected patients showed a good reproducibility (98%).

Conclusions: In a primary care setting a positive standard dipstick test of a random spot urine in patients with newly diagnosed hypertension may indicate the presence of microalbuminuria with high specificity. However, because of its low sensitivity, the standard urinary dipstick test can not be recommended as the sole method of screening for renal target organ damage. In addition standard dipstick testing is important to exclude confounding factors that can falsify the measurement of urinary protein excretion.

Key words: microalbuminuria; hypertension; target organ damage; primary health care; sensitivity and specificity

Introduction

The detection of microalbuminuria in the assessment of hypertensive individuals qualifies for aggressive blood-pressure-lowering treatment [1, 2]. Microalbuminuria is classified as target organ damage in hypertensive patients [3], as are left ventricular hypertrophy [4], ischaemic heart disease [5], and increased carotid wall thickness [6]. It predicts cardiovascular events and the development of renal insufficiency in hypertensive patients [7–9]; and it is also associated with an increased, adjusted relative risk for major cardiovascular events in high-risk patients (1.8-fold), all-cause mortality (2.1-fold), and hospitalisation for heart failure (3.2-fold) [10].

The identification of individuals with previously unknown arterial hypertension, as well as the assessment of cardiovascular risk factors and hypertensive target organ damage (such as microalbuminuria) are common tasks in general practice.

In an ambulatory setting, screening needs to be simple, low-cost, and useful. Standard dipstick tests are excellent point-of-care tests [11] and should be performed anyway to exclude confounding illnesses (eg, urinary tract infections).

Urinary albumin excretion was usually assessed by collecting urine continuously over a 24-hour period. However, this method is not only onerous for patients, it is also unreliable if the urine sample is incomplete. For this reason, collection of a random, single-voided, spot urine sample and subsequent measurement of the albumin/creatinine ratio (ACR) for the assessment of microalbuminuria is used increasingly [12] as an alternative test for this condition [13, 14]. The ACR results correlate well with the results of 24-hour urine collection [15, 16] but the ACR method is more expensive than dipstick testing. Albumin-specific dipsticks with a low threshold for detection of uri-

nary albumin excretion have been developed as another test method; however, these tests are not able to exclude confounding factors such as urinary tract infections. Standard dipstick testing of urine, measuring urinary protein excretion, is more readily available, less expensive than other methods, and can be performed by physicians in private practice without the need for sophisticated laboratory techniques. However, the threshold for detection of urinary proteins is higher (>300 mg/l) compared to albumin-specific dipsticks (>20 mg/l).

Therefore, the aim of the study was to assess the diagnostic performance (sensitivity, specificity, negative and positive predictive values, reproducibility) of a semi-quantitative standard dipstick assay (Combur 10 Test®) for detection of urinary protein excretion in patients with newly diagnosed arterial hypertension.

Materials and methods

Patients

Subjects were recruited from the Medical Outpatient Department of the University Hospital, Basel, Switzerland. The study was approved by the local Ethical Committee. Written informed consent was obtained from all subjects. We prospectively enrolled 2615 walk-in patients for arterial hypertension during twelve months. Every patient attending our Department was screened for elevated blood pressure by the treating physician.

Of the 2615 walk-in patients surveyed, 580 (22.2%) subjects had elevated blood pressure readings at the initial screening visit. Of these 580 patients, 209 (36.0%) were already being treated for hypertension and 35 (6.0%) had normal blood pressure readings on the second screening visit and were classified normotensive. Of the remaining 336 patients, 96 patients did not give consent to be tested further and 54 patients were excluded from the study because pertinent data were unavailable (41) or for other reasons (13), such as urinary tract infections. 186 patients with newly diagnosed, elevated, blood pressure measurements according to JNC 7 and ESC guidelines were included in the study. The response rate was 55% (186 patients included in 336 patients meeting the inclusion criteria).

Baseline characteristics for the 186 subjects and their blood pressure readings are displayed in table 1 and table 3.

The inclusion criteria for the trial were a patient age of over eighteen years and a diagnosis of previously undetected and untreated hypertension. Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg as an average of two blood pressure readings, as specified by JNC 7 guidelines [17]. Patients who were being treated with antihypertensive medication, had an acute urinary tract infection or acute febrile illness, had clinically overt heart failure or exhausting physical exercise the day before sampling were excluded from the study.

A random, single-void spot urine specimen was collected from each patient in the study group. For further stratification, ambulatory blood pressure was also measured in all of these patients. Patients with daytime 24-hour ambulatory blood pressure values >135/85 mm Hg were classified as definite hypertensives; patients with daytime ambulatory blood pressure values below <135/85 mm Hg were classified as "white coat hypertensives".

Assessment of urinary protein excretion

Definitions [14]

The term "mircoalbuminuria" refers to albumin excretion that exceeds the normal range (>20 mg/l) but is below the minimum level for detection by standard dipsticks (usually <200–300 mg/l). "Albuminuria" refers specifically to increased urinary excretion of albumin (>20 mg/l). "Proteinuria" indicates increased urinary excretion of albumin or any other specific protein. Proteinuria also refers to urinary protein excretion that is detectable by standard dipstick test (usually >200–300 mg/l).

Assays for protein and albumin by dipstick

The Combur10 dipstick test (Combur10, Roche Diagnostics GmbH, Mannheim, Germany) evaluated in our study is a commonly used screening method for elevated urinary protein excretion, especially among general practitioners. Furthermore, Combur 10 dipstick tests are frequently used to exclude urinary tract infection by measuring, semi-quantitatively, the leucocyte count in urine. The Combur10 dipsticks were used according to the manufacturer's instructions. The dipstick includes a reagent pad that is treated with 3',3",5',5"-tetrachlorphenol-3,4,5,6-tetrabromsulfophthalein dye, which detects albumin at concentrations ≥300 mg/l. The Combur 10 dipstick is usually designated as the standard dipstick, which

Table 1

Characteristics of the patients with newly diagnosed, untreated arterial hypertension (n = 186); SD = Standard deviation.

Characteristic	description
Age (SD)	53 (13) years
Gender (male/female)	108 male/78 female (58.1%/41.9%)
Body mass index (SD)	26.9 (4.7) kg/m^2
Positive family history of hypertension	118 patients (43%)
Patients with diabetes mellitus	9 patients (4.8%)
Renal function (serum creatinine in μmol/l) (SD)	84.3 (22.7)

Table 2

Diagnostic performance of standard dipstick testing for detection of microalbuminuria (as a marker of a hypertensive renal target organ damage) compared to albumin/creatinine ratio (assumed as gold standard for microalbuminuria).
* PPV = positive predictive value;
** NPV = negative predictive value;
*** LR+ = positive likelihood ratio;
**** LR– = negative likelihood ratio.

	Dipstick one-cross (+) positive (≥300 mg/l and <1 g/l)	Dipstick two-cross (++) positive (≥1 g/l and <5 g/l)	all positive dipstick tests
Sensitivity	24%	30%	26%
Specificity	91%	98%	89%
PPV*	36%	67%	45%
NPV**	87%	88%	88%
LR+***	3.2	11.1	3.8
LR–****	0.1	0.7	0.6

Table 3

Blood pressure readings during screening visit and at time of 24-hour ambulatory blood pressure. Monitoring.

* ABPM: Ambulatory blood pressure monitoring;
** OBP: Newly diagnosed hypertension (determined according to JNV 7 and European guidelines);
*** WCH: "White coat" hypertension (mean daytime ABPM <135/85 mm Hg);
**** aHT: Arterial hypertension confirmed by ABPM (mean daytime ABPM ≥135/85 mm Hg); Standard deviation in parenthesis.

Blood pressure group	n	Mean BP Screening visits (systolic)	mean BP screening visits (diastolic)	mean ABPM* (daytime systolic)	mean ABPM (daytime diastolic)
OBP**	186 (100%)	157 (15) mm Hg	98 (8) mm Hg	139 (12) mm Hg	87 (9) mm Hg
WCH***	45 (24%)	155 (96) mm Hg	96 (8) mm Hg	126 (6) mm Hg	76 (6) mm Hg
aHT****	141 (76%)	157 (16) mm Hg	99 (8) mm Hg	144 (10) mm Hg	90 (7) mm Hg

detects the higher concentrations of proteins [18] (as opposed to the more expensive albumin-specific dipsticks that can detect lower protein concentration levels). The stick is dipped into the urine specimen for one second, and one minute later, the color change of reagent in the pad is assessed visually. Theoretically, a one-cross positive (1+) corresponds to a urine protein value of ≥300 mg/l; a two-cross positive (2++) corresponds to a value ≥1000 mg/l; and a three-cross positive (3+++) corresponds to a value ≥5000 mg/l. Therefore, urine protein values <300 mg/l are not detectable by using the Combur 10 dipstick and are assumed to be false negative in terms of microalbuminuria. To assess reproducibility, the dipstick test was repeated 48 hours later under identical conditions in 40 patients who were selected at random from the larger study group of 186 patients.

Quantitative assays for albumin/creatinine ratio (ACR)

Creatinine concentrations in urine specimens were measured by using enzymatic methods (Wako, Pure Chemical Industries Ltd., Osaka, Japan) with a chemistry analyser (Hitachi 917, Japan). Albumin concentrations in urine specimens were determined by using nephelometric methods (Beckman-Coulter, California, USA). Microalbuminuria as a marker for renal target organ damage was defined as an albumin to creatinine ratio >2.26 mg/mmol in a clean, midstream, sample [13]. Confounding urinary protein or albumin excretion (eg, as a result of haematuria, urinary tract infection, or vaginal fluid contaminating urine samples) were excluded before analysis.

Statistical analysis

Results are expressed as means ± standard deviation (SD). Qualitative parameters are expressed as percentages. Evaluation of the sensitivity, specificity, and positive and negative predictive values were performed with GB-STAT for Windows, version V6.0, Dynamic Microsystem Inc. (Silver Spring, Maryland, USA). To compare the group of definite hypertensives with the group of "white coat hypertensives", the t-test was applied.

Results

Standard dipstick testing for urinary protein excretion was positive in 31 (16.7%) of the 186 urine samples analysed; 22 (11.9%) were one-cross (+) positive and 9 (4.8%) were two-cross positive (++). The albumin/creatinine ratio (ACR) was elevated (>2.26 mg/mmol) in 33 (17.7%) samples. One of nine patients with diabetes had a positive dipstick test and pathological ACR (2.98 mg/mmol), the other diabetic patients had a normal ACR and negative dipstick tests.

The sensitivity of standard dipstick testing for the detecting of microalbuminuria (as a marker of hypertensive renal target organ damage) compared to albumin/creatinine ratio (assumed as the gold standard for microalbuminuria) was 26% and specificity was 89%. The negative predictive value of a negative dipstick test in terms of (micro)albuminuria was 88%. Patients with a two-cross positive (++) dipstick test had a likelihood ratio (LR+) of 11.1 for a pathological albumin/creatinine ratio (>2.26 mg/mmol) (table 2).

Patients with "white coat" hypertension and patients who are definite hypertensives were analysed separately as subgroups (table 3). Office blood pressure readings were comparable in both groups. Patients who were definitely hypertensive had higher albumin/creatinine values than subjects with "white coat" hypertension (2.9 (1.4–4.4) mg/mmol vs. 1.3 (0.8–1.9) mg/mmol). Sensitivity and specificity of standard dipstick testing with regard to detect microalbuminuria did not differ considerably in "white coat hypertensives" compared to patients with definite hypertension. Positive and negative predictive values were almost equal in these subgroups (PPV 43% vs. 46%; NPP 92% vs. 86%).

Reproducibility of the dipstick test results was good, 39 of 40 patients showed identical results 48 hours after initial testing under same conditions.

Discussion

In the larger population of patients with arterial hypertension, early detection of those patients with target organ damage (who are, thus, at increased risk for cardiovascular morbidity and mortality) is essential. To assess microalbuminuria testing of spot urine specimens by dipstick testing is a quick, accurate, and not burdensome method for the patient [13, 15, 16]. Generally, the prevalence of microalbuminuria in hypertensive patients has been estimated to range widely between 6% and 40% depending on severity and duration of hypertension [19]. The frequency of microalbuminuria (17.7%) observed in the present study was similar to prevalence reported in comparable subjects [20–22]. To our knowledge, there are no other data available with respect to standard dipstick testing for proteinuria in patients with newly diagnosed hypertension in a primary care setting. The high value of specificity is similar to data reported in the literature using albumin-specific dipsticks [23–25]. Albumin-specific dipsticks are also simple bedside tests, but there are limitations to their use: they are more expensive (five fold in Switzerland) than standard dipstick tests, and they only measure albumin in urine, whereas standard dipstick testing also can exclude evidence of urinary tract infections or other confounding factors at the same time. According to guidelines regarding the evaluation of proteinuria [14], confounding factors have to be excluded before urine can be accurately assessed for microalbuminuria. Thus, the use of a standard dipstick test provides valuable information in bifocal perspectives that are important particularly in a primary care setting: Evidence or exclusion of confounding factors disturbing the assessment of urinary proteins and information about urinary protein excretion as a marker of renal end organ damage in hypertensives.

For the purposes of clinical practice, our findings may suggest that patients with positive dipstick testing microalbuminuria may have microalbuminuria with high specificity (89%). High NPV (88%) of the standard dipstick test is comparable to the albumin-specific dipsticks [24], but has to be interpreted cautiously because of low prevalence of microalbuminuria in the study population [26, 27].

Standard dipstick testing as a screening method for microalbuminuria is definitely insufficient due to low sensitivity and low positive predictive value. The detection level (one-cross positive) of the evaluated test is 300 mg/l, according to the manufacturer of the dipstick. If dipstick testing for proteins is positive (and confounding factors are excluded) albuminuria and proteinuria respectively in terms of renal organ damage may be suspected. To confirm and quantify albuminuria further testing is recommended [1, 2, 14]. According to guidelines [1, 2, 14], such patients should be tested by using either albumin-specific dipsticks (detection level 20–40 mg/l [3], PPV 53–98% [24]) or an untimed urine measurement of the albumin/creatinine ratio (ACR). Although it is more expensive, the ACR may be preferred in clinical practice because of its option to quantify microalbuminuria.

In our cohort, we identified "white coat" hypertension in 24% of the patients. Within this group, the absolute value of ACR was lower compared to the value identified in patients with definite hypertension. These data are consistent with previous studies [19, 20]. After all, 13% of the "white coat" hypertensive patients did have microalbuminuria. Although "white coat hypertensives" may represent subjects at lower cardiovascular risk than definite hypertensives [19], close monitoring of these patients and timely implementation of antihypertensive treatment are warranted. The results of standard dipstick testing (sensitivity, specificity, NPV, PPV in terms of microalbuminuria) of "white coat hypertensives" compared to results for patients with confirmed hypertension were comparable.

Our study has limitations. The diagnostic measures used in the study (sensitivity, specificity, PPN, and NPV) are crucially influenced by the prevalence of the sought condition (microalbuminuria). Values of diagnostic measures in our study will indisputably only be relevant to a population similar to our study participants. We are also aware of the moderately adequate response rate (55%). Prevalence may have been influenced by including more eligible patients. However, prevalence of microalbuminuria in the present study is comparable to prevalence reported in similar study populations [20–22].

Diagnostic tests in general, and visually readable dipstick testing in particular, are subject to individual interpretation and inter-observer variability. In the present study, clinical laboratory workers were not explicitly informed about the study; they performed the dipstick test as part of their daily routine. The dipstick testing was not standardised or controlled by the investigators. However, not intervening in the daily routine of the laboratory workers enabled us to determine the diagnostic accuracy of the dipstick test method in actual clinical practice. In our primary care setting we confirm the known low sensitivity of standard dipsticks regarding detection of microalbuminuria. Nevertheless, for the primary care physician the high negative predictive value and high specificity (few false positives) of the test detecting microalbuminuria may be useful for cardiovascular risk stratification in hypertensive patients.

We conclude that in a primary care a positive standard dipstick test of a random spot, single-void urine specimen in patients with newly diagnosed hypertension may indicate the presence of microalbuminuria with high specificity. However, due to low sensitivity, the standard urinary dipstick

test can not be recommended as the sole method of screening for microalbuminuria as a marker of renal target organ damage. In addition, the standard dipstick test is a well reproducible, readily available and inexpensive bedside test in a primary care setting and important to exclude confounding factors that can falsify the measurement of urinary protein excretion.

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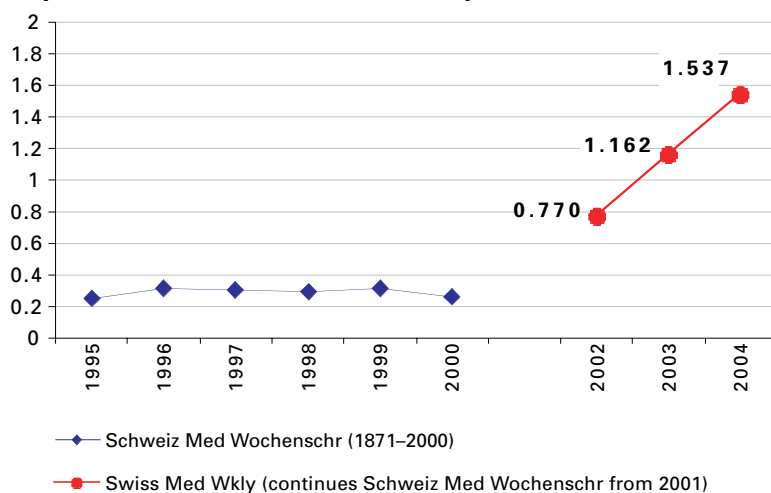- No page charges and attractive colour offprints at no extra cost

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