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Utility of the Dipstick Micraltest II™ in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension

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ABSTRACT

Background. In Mexico, diabetes mellitus type 2 and hypertension are leading causes of end-stage renal disease. Diagnosis of early renal damage with detection of microalbuminuria (microAlbU) is fundamental for treatment and prevention, and so avoiding the catastrophes of renal failure. For screening purposes, several simplified tests, including dipstick methods, fulfill the accuracy requirements for microAlbU detection compared with gold standards; however, no study has established the reliability of such tests in our setting. **Aim.** To evaluate the utility of micraltest II™ as a screening test for microAlbU compared with nephelometry in patients with diabetes mellitus type 2 and non-diabetic patients with essential hypertension. **Patients and methods.** Patients with diabetes mellitus type 2 as well as patients with essential hypertension of any age, sex and time of evolution, attending to three primary health-care units (UMF No. 3, 92 and 93, Guadalajara, Jalisco) were included. Patients with transitory albuminuria, secondary hypertension and serum creatinine ≥ 2 mg/dL were excluded. Micraltest II™ was performed in the first morning urine sample, and nephelometry was performed in a 24-h urine collection. Diagnostic accuracy of the dipstick test was then determined. **Results.** 245 patients were studied: 71 (29%) were diabetics without hypertension, 95 (39%) were diabetics with hypertension, and 79 (32%) had only essential hypertension. In diabetic patients, micraltest II™ sensitivity was 83%, specificity 96%, and positive and negative predictive values were 95% and 88%, respectively. Correlation between nephelometry and micraltest II™ results was 0.81 ($p < 0.001$). The best cut-off point for microAlbU was 30.5 mg/L, and area under the curve (± SEM) was 0.91 ± 0.03 (confidence interval 95%: 0.85-0.96). In non-diabetic patients with essential hypertension, micraltest II™ sensitivity was 75%, specificity 95%, and positive and negative predictive values were 43% and 99%, respectively. Correlation between nephelometry and micraltest II™ results was 0.43 ($p < 0.001$). The best cut-off point for microAlbU was 28.2 mg/L, and area under the curve was 0.85 ±

Utilidad de la tira reactiva Micraltest II™ en el escrutinio de microalbuminuria en diabetes mellitus tipo 2 e hipertensión esencial

RESUMEN

Antecedentes. *En México, la diabetes mellitus tipo 2 y la hipertensión son las principales causas de insuficiencia renal crónica terminal. El diagnóstico temprano con detección de microalbuminuria (microAlbU) es fundamental para el tratamiento y prevención, y así evitar las catástrofes de la falla renal. Con el fin de tamizaje, varias pruebas simples, incluyendo las tiras reactivas, cumplen con los requerimientos de exactitud para detección de microAlbU comparados con estándares de oro; sin embargo, ningún estudio ha establecido la confiabilidad de dichos métodos en nuestro medio.* ***Objetivo.*** *Evaluar la utilidad del micraltest II™ como prueba de tamizaje para microAlbU comparada con nefelometría en pacientes con diabetes mellitus tipo 2 y pacientes no diabéticos con hipertensión arterial esencial.* ***Pacientes y métodos.*** *Se incluyeron pacientes con diabetes mellitus tipo 2, así como pacientes con hipertensión arterial esencial de cualquiera de los dos sexos, sexo y tiempo de evolución que atendían a tres unidades de Medicina Familiar (UMF No. 3, 92 y 93, Guadalajara, Jalisco). Se excluyeron pacientes con albuminuria transitoria, hipertensión secundaria y creatinina sérica ≥ 2 mg/dL. El micraltest II™ se realizó en la primera muestra matutina de orina, y la nefelometría en recolecciones de orina de 24 horas. La exactitud diagnóstica de la tira reactiva fue luego determinada.* ***Resultados.*** *Doscientos cuarenta y cinco pacientes fueron estudiados: 71 (29%) eran diabéticos sin hipertensión, 95 (39%) eran diabéticos con hipertensión, y 79 (32%) tenían sólo hipertensión arterial esencial. En los pacientes diabéticos, el micraltest II™ tuvo una sensibilidad de 83%, especificidad de 96%, y valores predictivos positivo y negativo de 95% y 88%, respectivamente. La correlación entre la nefelometría y el micraltest II™ fue 0.81 ($p < 0.001$). El mejor punto de corte para la detección de mi-*

0.13 (0.60-1.10). **Conclusion.** Micraltest II™ dispstick is a rapid, valid and reliable method for albuminuria screening in patients with diabetes mellitus type 2 and in those non-diabetic patients with essential hypertension in our setting.

Key words. Microalbuminuria. Micraltest™. Nephelometry. Diabetes mellitus 2. Essential Hypertension. Early nephropathy.

croAlbU fue 30.5 mg/L, y el área bajo la curva (± EE) fue 0.91 ± 0.03 (intervalo de confianza 95%: 0.85-0.96). En los pacientes no diabéticos con hipertensión esencial, el micraltest II™ tuvo una sensibilidad de 75%, especificidad de 95%, y valores predictivos positivo y negativo de 43 y 99%, respectivamente. La correlación entre los resultados de nefelometría y micraltest II™ fue 0.43 (p < 0.001). El mejor punto de corte para microAlbU fue 28.2 mg/L, y el área bajo la curva fue 0.85 ± 0.13 (intervalo de confianza 95%:0.60-1.10). ***Conclusión.*** *La tira reactiva micraltest II™ es un método rápido, válido y confiable para el tamizaje de albuminuria en pacientes con diabetes mellitus tipo 2 y pacientes no diabéticos con hipertensión arterial esencial en nuestro medio.*

Palabras clave. *Microalbuminuria. Micraltest™. Nefelometría. Diabetes Mellitus 2. Hipertensión arterial esencial. Nefropatía temprana.*

INTRODUCTION

Albumin excretion rate (AER) has been widely advocated as a means for diagnosis of early renal damage in diabetes and essential hypertension.[1,2] Microalbuminuria (microAlbU), defined as an AER of 20-200 mg/minute, is associated with development of clinical proteinuria, chronic renal failure, and premature cardiovascular mortality in patients with diabetes mellitus type 1 and type 2.[3,4] Annual microAlbU screening in diabetic patients is currently recommended by several national and international organizations.[5-7] In non-diabetic subjects with essential hypertension, elevated AER have been found to be a strong predictor for cardiovascular disease and nephropathy.[8]

Early detection of microAlbU requires the use of radioimmunoassay, nephelometry or inmunoturbidimetry.[7,9] Such methodologies are expensive and not always available in all settings, making difficult to test large numbers of patients. Therefore, for screening purposes, it is necessary to count with simpler methods that provide a safe approximation to AER. Several simplified tests are currently available for microAlbU detection, including the dipstick micraltest II™.[10,11] This test is based on a competition for gold-labelled anti-albumin antibodies (IgG) between specimen albumin an albumin molecules immobilized in the test strip. The final detection area is colored by excess free antibodies after IgG binding with urinary albumin.[10]

In Mexican population, diabetes mellitus type 2 and hypertension are highly prevalent[12,13] and, as in many parts of the world, they are leading causes of end-stage renal disease.[14,15] Detection of early stages of renal disease is fundamental for establishing treatment and prevention measures in order to avoid the clinical and economical catastrophes of end-stage renal disease. Several studies about prevalence of microAlbU in diabetic and hypertensive patients have been performed in our country;[16-18] most of them were based on the determination of microAlbU using dipstick tests. However, to the best of our knowledge, no study has established the reliability of dipstick methods compared with gold standards for AER in our setting. Therefore, the aim of this study was to evaluate the utility of micraltest II™ as a screening test for microAlbU compared with nephelometry in patients with diabetes mellitus type 2 and essential hypertension.

PATIENTS AND METHODS

This is an observational, cross-sectional, and comparative study on a diagnostic test. Patients with previous diagnosis of diabetes mellitus type 2 (according with the American Diabetes Association criteria[19]) with or without hypertension, as well as patients with essential hypertension without diabetes mellitus (according with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[20]), of any age, sex and time since diagnosis were included. Patients were randomly selected from the total diabetes mellitus type 2 and essential hypertension population attending to three primary health-care units (Unidades de Medicina Familiar No. 3, 92 and 93) in the metropolitan area of the city of Guadalajara, Jalisco. Patients were excluded if they had cardiac failure or renal tract disease, acute febrile illnesses, urinary tract infection, hematuria (women were not examined during menstruation), abnormal urinary sediment, any level of proteinuria in urinalysis, and serum creatinine > 2 mg/dL.

Determination of microAlbU

Before determination of AER, recommendation was made about adequate fluid intake and avoiding excessive physical exercise three days previous to urine sampling. Results obtained by micraltest II™ dipstick (*Roche Diagnostics GmbH*, Germany) were compared with nephelometry (*Behring Nephelometer Analyzer II, Behring Diagnostics GmbH*, Germany) which was considered as the gold standard in this study. Patients were instructed to collect a 24-h urine sample, but they were asked to collect separately the last voiding sample (first sample of the next morning). In this first voiding urine sample, a micraltest II™ dipstick was submerged during five seconds, and a reading was performed one minute later by only one investigator (LCS). The result of this assay was read in a semiquantitative manner as 0 mg/L, 20 mg/L, 50 mg/L or 100 mg/L. A reading of 0 mg/L was interpreted as negative, and a reading of 20 mg/L or more was considered positive (microAlbU is defined as 20-200 mg/L by the micraltest II™). After the micraltest II™ reading, the first voiding urine sample was mixed with the rest of the 24-h urine collection for the nephelometry measurement, which had a detection inferior limit of 2.3 μ/mL and a coefficient of variation of 2.1%. Normal AER by this method is defined as < 20 μg/min, microAlbU is 20-200 μg/min, and macroalbuminuria is > 200 μg/min. To compare nephelometry results with those of micraltest II™, the latter values were converted from μg/min to μg/L. All the nephelometry measurements were performed in the Central Laboratory of the Hospital de Especialidades, CMNO, IMSS, by only one person blinded to the micraltest II™ results.

Statistical analysis

Data are shown as frequencies, percentages, mean ± standard deviation, and median (percentiles 25-75%) as appropriate. Validity was studied by the sensitivity, specificity, and the positive and negative predictive values. Relationship between nephelometry and micraltest II™ measurements was calculated by the Pearson correlation coefficient. Determination of diagnostic accuracy of the test was performed by means of drawing Receiver Operating Characteristic (ROC) curve. Analyses were performed using SPSS 10.0 for Windows. A p value < 0.05 was considered as significant.

RESULTS

Two hundred forty-five patients attending to primary health-care units were studied; 71 (29%) had diabetes mellitus type 2 without hypertension, 95 (39%) had diabetes mellitus type 2 with hypertension, 79 (32%) had only essential hypertension (without diabetes). Demographic and clinical data of patients are shown in table 1.

From the whole sample of patients, 162 (69%) had no albuminuria, 51 (21%) had microAlbU, and 25 (10%) had macroalbuminuria; median urinary AER was 7.3 (3.6–31.8) μg/min.

Table 1. Demographic and clinical data of the patients.

Variable	Diabetes mellitus	Hypertension
N	166	79
Age (years)	59 ± 11	60 ± 11
Female Sex	103 (62%)	61 (77%)
With hypertension, N (%)	95 (57%)	79 (100%)
Essential hypertension, N (%)		79 (100%)
Duration of diabetes (years)*	8.0 (3 - 13)	
Duration of hypertension (years)*	5.0 (2 - 10)	8.0 (4 - 13)
Systolic blood pressure (mm Hg)	120 ± 18	133 ± 19
Diastolic blood pressure (mm Hg)	74 ± 10	80 ± 9
Antihypertensive drugs, N (%)	0.72 ± 0.84	1.62 ± 0.72
ACE inhibitors, N (%)	60 (36%)	59 (75%)
ARB, N (%)	13 (8%)	10 (13%)
Serum creatinine (mg/dL)	1.00 ± 0.43	0.93 ± 0.21
GFR (mL/min/1.73m^2)	79 ± 25	87 ± 31

* In those with the corresponding disease; GFR: glomerular filtration rate; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers.

Table 2. Validity results of the micraltest II™ in the case of diabetes mellitus type 2.

Micraltest II™	24-h Nephelometry Positive	Negative	Total
Positive	59	3	62
Negative	12	92	104
Total	71	95	166

Sensitivity: 83%
Specificity: 96%
Positive predictive value: 95%
Negative predictive value: 88%
Prevalence: 42%
Exactitude: 90%

Table 3. Validity results of the micraltest II™ according to the duration of diabetes mellitus type 2.

Duration of DM2	Sensitivity (%)	Specificity (%)	PP Value (%)	NP Value (%)	Prevalence (%)	Exactitude (%)
≤ 5 years	68	98	91	91	23	91
6-10 years	87	95	91	93	42	92
> 10 years	87	95	97	81	63	90

PP: positive predictive; NP: negative predictive.

Table 4. Comparison of urinary album concentration determined by micraltest II™ and nephelometry in the case of diabetes mellitus type 2.

Micraltest II™ (mg/L)	n	24-h Nephelometry (mg/L) < 20 n (%)	≥ 20 n (%)	Median (percentiles 25-75%)
0	176	163 (93)	13 (7)	4.23 (2.7 – 8.2)
20	13	5 (38)	8 (62)	20.40 (13.4 – 27.9)
50	21	3 (14)	18 (86)	74.30 (29.4 – 164.5)
100	35	1 (3)	34 (97)	261.0 (99.4 – 1140)

Results in patients with diabetes mellitus type 2

Sensitivity, specificity, positive and negative predictive values, and exactitude of micraltest II™, and prevalence of albuminuria in diabetic patients are shown in table 2. Validity results of the micraltest II™ according with the time of evolution of diabetes are shown in table 3; sensitivity and positive predictive value seemed to improve with longer duration of diabetes (which increases the prevalence of albuminuria), however, specificity and exactitude of the test were roughly the same throughout this time. Correlation between nephelometry and micraltest II™ measurements was 0.81 ($p < 0.0001$). Comparison of urinary album concentration determined by micraltest II™ and nephelometry is shown in table 4. Figure 1 shows the ROC curve results for nephelometry and micraltest II™ for albuminuria in diabetic patients. When the performance of micraltest II™ as a diagnostic test for microAlbU was analyzed, the calculated mean area under the ROC curve (± SEM) was 0.91 ± 0.03 (confidence interval 95%: 0.85-0.96), and the corresponding best cut-off point value was 30.5 mg/L.

Results in patients with essential hypertension

Sensitivity, specificity, positive and negative predictive values, and exactitude of micraltest II™, and prevalence of albuminuria in patients with essential hypertension are shown in table 5. Validity results of the micraltest II™ according with the time of evo-

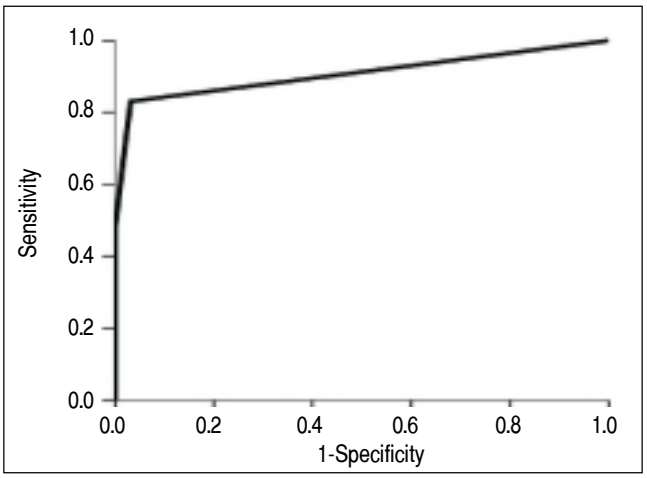

Figure 1. *Diagnostic accuracy of micraltest II™ as determined by the receiver operating characteristic (ROC) curve in the case of diabetes mellitus type 2.*

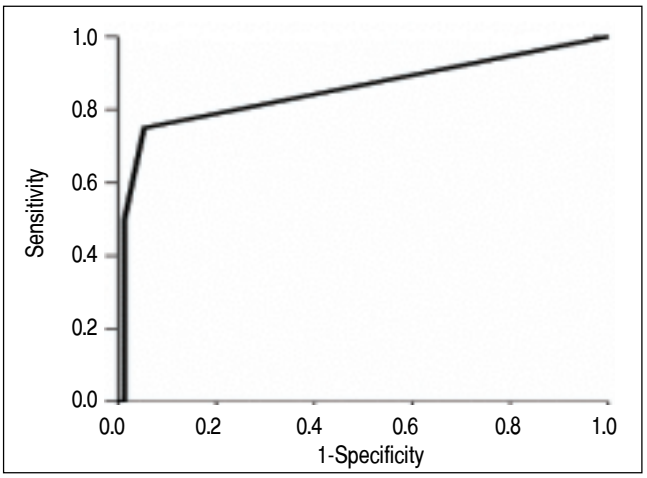

Figure 2. *Diagnostic accuracy of micraltest II™ as determined by the receiver operating characteristic (ROC) curve in the case of essential hypertension.*

Table 5. Validity results of the micraltest II™ in the case of essential hypertension.

Micraltest II™	%	24-h Nephelometry Positive	Negative	Total
Positive		3	4	7
Negative		1	71	72
Total		4	75	79
Sensitivity:	75			
Specificity:	95			
Positive predictive value:	43			
Negative predictive value:	99			
Prevalence:	5			
Exactitude:	94			

Table 6. Validity results of the micraltest II™ according to the duration of essential hypertension.

Duration of hypertension	Sensitivity (%)	Specificity (%)	PP Value (%)	NP Value (%)	Prevalence (%)	Exactitude (%)
≤ 5 years	50	89	25	96	6.9	86
6-10 years	67	96	67	96	7.4	92
> 10 years*	-	-	-	-	0.0	-

PP: positive predictive; NP: negative predictive. * at this period of time, all the cases (23) were true negatives; therefore, it was not possible to calculate validity results.

lution of hypertension are shown in table 6; sensitivity, specificity, positive predictive value and exactitude seemed to improve with longer duration of hypertension. No calculations could be performed with a duration of this disease > 10 years as all the 23 cases present with this evolution of hypertension were true negative cases (no cases of albuminuria). Essential hypertensive patients with longer duration of hypertension displayed a non-significant trend to use more antihypertensive drugs (≤ 5 years: 1.41 ± 0.63; 6-10 years: 1.70 ± 0.77; >10 years: 1.78 ± 0.74), and to have lower diastolic blood pressure

Table 7. Comparison of urinary album concentration determined by micraltest II™ and nephelometry in the case of essential hypertension.

Micraltest II™ (mg/L)	n	24-h Nephelometry (mg/L) < 20 n (%)	≥ 20 n (%)	Median (percentiles 25-75%)
0	70	70 (97)	2 (3)	4.28 (2.6-7.7)
20	4	2 (50)	2 (50)	16.0 (10.6-23.9)
50	2	0 (0)	2 (100)	72.3 (31.6-113.0)
100	1	1 (100)	0 (0)	5.64

(≤5 years: 81 ± 10 mm Hg; 6-10 years: 82 ± 8 mm Hg; >10 years: 78 ± 10 mm Hg) than the others. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers were not different between patients with different duration of hypertension. Correlation between nephelometry and micraltest II™ measurements was 0.43 ($p < 0.0001$). Comparison of urinary album concentration determined by micraltest II™ and nephelometry is shown in table 7. Figure 2 shows the ROC curve results for nephelometry and micraltest II™ for albuminuria in patients with essential hypertension. When the performance of micraltest II™ as a diagnostic test for microAlbU was analyzed, the calculated mean area under the ROC curve was 0.85 ± 0.13 (0.60-1.10), and the corresponding best cut-off point value was 28.2 mg/L.

DISCUSSION

Our results show that micraltest II™ dipstick is a valid and reliable test for albuminuria (microAlbU and macroalbuminuria) detection in patients with diabetes mellitus type 2 and essential hypertension in our setting.

Office test for detecting abnormal albuminuria should be simple in use, robust, quick, and inexpensive. Several office tests seem to fulfill the requirements of adequate sensitivity, specificity and reproducibility;[21-23] however, it is always useful to validate new tests when they are to be used in populations different from those originally probed. Some authors have compared the micraltest II™ dipstick with gold standards as radioimmunoassay or immunoturbidimetry, obtaining in general, similar results in both diabetics and in hypertensive non-diabetic patients.[10,11,21-23] Fewer data have been reported with the employment of nephelometry as the gold standard, in which micraltest II™ has shown a sensitivity of 84-97%, specificity of 72-98%, positive predictive value of 77-84%, and negative predictive value of 93-94%.[24-27] The previous results are in general comparable with ours, although Poulsen, *et al.*,[26] displayed a trend to a higher sensitivity and lower specificity. As expected, prevalence of albuminuria was higher in diabetics than in those non-diabetic patients with essential hypertension in the present study; such a finding influenced on the better negative predictive value and the poorer positive predictive value of micraltest II™ observed in patients with essential hypertension compared with diabetics. In our hands, the best cut-off point value was 30.5 mg/L in diabetics and 28.2 mg/L in patients with essential hypertension. These latter findings may explain why the highest proportion of false positives with micraltest II™ in both patient subpopulations was observed at the 20 mg/L level of micraltest II™; in other words, it could be possible that a higher proportion of albuminuria cases were precisely diagnosed if the dipstick test cut-off value was 30 mg/L instead of 20 mg/L.

Although 24-h urine collections remains the reference model for albuminuria detection, they are uncomfortable for the patient, and because of non-compliance, it may result in inadequate sample for analysis. It has been established that micraltest II™ displays comparable results when it is performed in 24-h urine collections or in a first voiding urine sample.[25] Therefre, isolated first voiding urine samples, as they are easier for the patient, may be preferable for albuminuria screening in large number of patients.[25] Once a positive result with micraltest II™ dipstick is identified, a confirmatory measurement with a quantitative method (nephelometry, radioimmunoassay or immunoturbidimetry) in 24-h urine collection may be indicated.

On the other hand, to the best of our knowledge, no study using test-strip for microAlbU in Mexico or Latin America had been previously published. Calzada-León, *et al.*,[28] reported results of the colorimetric bromphenol-blue test compared with radioimmunoassay in 82 Mexican children; these authors found a sensitivity of 60%, specificity of 83%, positive predictive value of 33%, and negative predictive value of 94%. The higher precision of the test evaluated in the present study compared with

that of Calzada-León, *et al*.,[28] confirms the advantage of the antibody-based screening methods compared to older colorimetry methods based on bromphenol dye.[29] MicroAlbU may predict later development of nephropathy in diabetics,[30] and is associated with other complications, as retinopathy, cardiovascular risk factors and coronary heart disease both in diabetics and non-diabetic patients.[31-33] On the other hand, renoprotection (i.e. general, dietary and pharmacological interventions to halt or at least to slow the progression of renal function decline) is now the cornerstone of the management of patients with renal disease, and it is mostly effective when is implemented at early stages.[5,6,34,35] In many parts of the world and our country,[14,15] diabetes mellitus type 2 and hypertension are the leading causes of end-stage renal disease. Thus, it is crucial to detect early nephropathy in these high risk populations. Results of the current study demonstrate a high proportion of diabetic and hypertensive patients with early nephropathy in our setting, which is in agreement with previous reports.[16-18] The latter urges to the implementation of measures of secondary prevention and treatment to avoid further progression of the kidney function deterioration in this kind of patients. This in turn, may be useful to halt the increasing frequency of end-stage renal disease, which constitutes one of the greatest socioeconomic and public health problems in our country.

In conclusion, results of the present study show that micraltest II™ dispstick is a rapid, valid and reliable method for the albuminuria screening in patients with diabetes mellitus type 2 and in those non-diabetic patients with essential hypertension in our setting. Routine dipstick screening for microalbuminuria might be recommended in patients at risk for renal disease attending to primary health-care units.

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