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The diagnostic accuracy of urine IgG antibody tests for the detection of *Helicobacter pylori* infection in Turkish dyspeptic patients

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Background/aims: *There is increasing interest in noninvasive tests for the assessment of Helicobacter pylori infection, and urine-based tests have been widely used as noninvasive tests to detect Helicobacter pylori infection. The aim of this study was to evaluate the adaptation and usefulness of urine antibody enzyme-linked immunosorbent assay and urine card tests in the clinical setting to detect anti-Helicobacter pylori IgG antibody excreted into urine in Turkish adult patients with dyspepsia.* ***Materials and Methods:*** *One-hundred twenty-four patients who were admitted and referred for upper endoscopy to Dokuz Eylül University Hospital, Gastroenterology Clinic were studied. Antrum and corpus biopsies were taken, and Helicobacter pylori status was defined in the presence of at least two positive results of rapid urease test, histopathology and culture. Urine and serum specimens of 124 patients were collected and examined for anti-Helicobacter pylori IgG antibody by URINELISA, RAPIRUN (Otsuka Pharmaceutical, Tokyo, Japan) and anti-Helicobacter pylori enzyme-linked immunosorbent assay (Euroimmun, Lübeck, Germany) tests, respectively.* ***Results:*** *Helicobacter pylori infection was positive in 82 (66.1%) patients according to the gold standard methods. Among 82 Helicobacter pylori infection-positive patients, 69 patients were positive by both URINELISA and RAPIRUN; 109 of 124 patients were positive by anti-Helicobacter pylori IgG enzyme-linked immunosorbent assay. The sensitivity and specificity of URINELISA, RAPIRUN and anti-Helicobacter pylori IgG enzyme-linked immunosorbent assay were 74.4%, 73.2%, 100% and 81.0%, 78.6%, 35.7%, respectively. However, the urine antibody test cut-off values were searched for the best concordance with the results of gold standard methods. This yielded that the sensitivity and specificity of URINELISA with our new cut-off value (0.530) were 90.2% and 71.4%, respectively.* ***Conclusions:*** *As a first study among Turkish adult patients with dyspepsia, the efficacy of URINELISA was related with the determination of a new cut-off value for pretreatment as a screening test value. We suggest that the cut-off value of the URINELISA test should be evaluated and considered for each patient group and each country. The URINELISA (OD 0.530) and RAPIRUN tests were found useful for the diagnosis of Helicobacter pylori infection in our patients with dyspepsia.*

Key words: *Helicobacter pylori,* URINELISA, RAPIRUN

İdrar IgG antikor testlerinin Türk dispeptik hastalarda *Helikobakter pilori* enfeksiyonunun saptanmasındaki tanısal doğruluğu

Giriş ve Amaç: *Helikobakter pilori enfeksiyonunun değerlendirilmesinde invaziv olmayan testlere ilgi artmış ve idrar temelli testler Helikobakter pilori enfeksiyonunu saptamada invaziv olmayan testler olarak sık kullanılmaktadır. Bu çalışmada Türk erişkin dispeptik hastalarda idrarda salınan anti-Helikobakter pilori IgG antikorunu saptamada hasta başı idrar kart testi ve idrar antikor enzim-bağlı immünosorbent ölçüm testlerinin adaptasyonu ve kullanışlılığının değerlendirilmesi amaçlanmıştır.* ***Gereç ve Yöntem:*** *Dokuz Eylül Üniversitesi Hastanesi, Gastroenteroloji Kliniği'ne başvuran ve endoskopi endikasyonu konulan 124 hasta çalışmaya alındı. Antrum ve korpus biyopsileri alındı ve hızlı üreaz testi, histopatoloji ve kültürün en az iki test pozitifliğinde Helikobakter pilori olumlu kabul edildi. 124 hastanın idrar ve serum örnekleri toplandı. Anti- Helikobakter pilori IgG antikor varlığı URINELISA, RAPIRUN (Otsuka Pharmacautical, Tokyo, Japan) ve anti-Helikobakter pilori enzim-bağlı immünosorbent ölçüm (Euroimmun, Lübeck, Germany) testleri ile araştırıldı.* ***Bulgular:*** *Altın standart yöntemlere göre 82 (%66.1) hasta Helikobakter pilori enfeksiyonu pozitif saptandı. 82 Helikobakter pilori enfeksiyonu pozitif hastanın, 69'u hem URINELISA hem de RAPIRUN testleri ile, 109 ise anti-Helikobakter pilori IgG enzim-bağlı immünosorbent ölçüm testi ile pozitif bulundu. URINELISA; RAPIRUN ve anti Helikobakter pilori IgG enzim-bağlı immünosorbent ölçümün duyarlılık ve özgüllüğü sırasıyla %74.4, %73,2, %100 ve %81.0, %78.6, %35.7 saptandı. Ayrıca, idrar antikor test cut-off değeri altın standard yöntemlerle uyumuna göre en iyi cut-off değeri araştırıldı ve URINELISA'nın yeni cut-off değeri (0.530) ile duyarlılık ve özgüllüğü %90.2 ve %71.4 belirlendi.* ***Sonuç:*** *Türk dispeptik hastalarında ilk çalışma olarak, tedavi öncesi tarama testi olarak URINELISA'nın etkinliği yeni cut-off değerinin saptanması ile ilişkilidir. URINELISA'nın cut-off değeri her bir hasta grubu ve her bir ülke için yeniden değerlendirilmesini önermekteyiz. URINELISA (OD 0.530) ve RAPIRUN testleri dispeptik hastalarımızda Helikobakter pilori enfeksiyonu tanısında kullanılabilir olduğu kanısına varıldı.*

Anahtar kelimeler: *Helikobakter pilori,* URINELISA, RAPIRUN

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INTRODUCTION

Helicobacter pylori (H. pylori) is etiologically associated with gastritis, gastric and duodenal ulcers, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma (1-6). *H. pylori* infection is very common worldwide, occurring in 40-50% of the population in developed countries and 80-90% of the population in developing regions (7,8). Urea breath test (UBT) and culture are gold standard methods for detecting *H. pylori* infection (1-4,6,9-11). Easy and noninvasive methods for screening *H. pylori* infection were determined necessary (11). In addition to the invasive tests, stool antigen test, urine antibodies test and serum antibody test are available as noninvasive tests in the diagnosis of *H. pylori* infection (1-4,6,9-11). A single test is not sufficient to diagnose *H. pylori* infection without culture. The European guidelines indicate that the gold standard is positivity of at least two different tests. Endoscopy was generally used in the diagnosis of *H. pylori*, but it is an expensive and invasive method. The test and treat strategy recommends a noninvasive test in patients without alarm symptoms who are <55 years old and not using nonsteroidal anti-inflammatory drugs (NSAIDs). Endoscopy is recommended for patients with alarm symptoms who are >55 years old (4). Noninvasive tests have become part of the management strategies for patients with dyspepsia (12), and they can be active or passive. Active tests detect the presence of *H. pylori* and provide evidence of a current infection. Passive tests that detect antibodies provide evidence of exposure to *H. pylori* but do not necessarily indicate an active infection (4). Serological tests are based on the detection of a specific anti-*H. pylori* immunological response, mostly by IgG antibodies, in the patient's serum (13). Recently, new methods for the detection of anti-*H. pylori* IgG antibody in urine were developed, and their clinical usefulness has been noted in adult populations (6,13).

An enzyme immunoassay method (URINELISA, Otsuka Pharmaceutical, Tokyo, Japan) as well as a serum antibody testing and immunochromatographic method (RAPIRUN, Otsuka Pharmacautical, Tokyo, Japan) have been used for the detection of *H. pylori* infection (7). Noninvasive screening for IgG antibodies in urine has many potential advantages over blood- based antibody tests in terms of convenience and use in children (12). The advantages of urine antibody tests are that urine can be collected easily and centrifugation is not required, and they combine the simplicity, cost-effectiveness and applicability under circumstances in which serological testing is impractical (7).

Because of the widespread prevalence of *H. pylori* infection, simple, convenient, and noninvasive techniques are required as a screening tool for *H. pylori* infection. URINELISA and RAPIRUN have been proven to have sufficient accuracy so as to be used clinically (14,15). Urine-based enzyme-linked immunosorbent assay (ELISA) for the detection of IgG antibody to *H. pylori* has already been shown to have high sensitivity and specificity in adults (2).

We evaluated the efficacy and diagnostic value of URINELISA and RAPIRUN for the screening of *H. pylori* infection as well as how the diagnostic accuracy of a new cut-off value would influence the determination of *H. pylori* infection in adult patients with dyspepsia admitted to our hospital.

MATERIALS AND METHODS

Patients

One hundred twenty-four patients with dyspepsia (31 males, 93 females; mean age: 46 ± 12 years) who admitted to the Gastroenterology Clinic at Dokuz Eylül University Hospital and were referred for upper endoscopy were included in this study. Urine specimens and sera were collected on the same day as endoscopy. Patients were excluded if they had received proton pump inhibitors (PPIs) or antibiotic in the previous one month, had prior gastric surgery, were pregnant or lactating, had gastrointestinal malignancy, alcohol abuse, drug addiction, or chronic use of corticosteroids or NSAIDs. Six biopsy samples were taken from all patients (3 from the antrum, 3 from the corpus). Each antrum and corpus biopsy specimen was used for rapid urease test (RUT), histopathology and culture. After endoscopy, urine specimens and sera were collected on the same day. All patients gave their written informed consent in this study. *H. pylori* infection was defined as positivity of at least two of RUT, histopathology and culture results as gold standard methods. A patient was classified as *H. pylori* infection-negative when RUT, histopathological examination and culture were all negative or only one (histopathology or RUT result) was positive.

Rapid Urease Test and Histopathology

Three antrum and three corpus biopsy specimens were taken at endoscopy: One antrum and one

corpus specimens were used for the RUT and the other two were immediately fixed and transported in 10% buffered formalin solution for histopathologic examination. Hematoxylin-eosin, Alcian blue and Giemsa stains were used for morphologic examination of Helicobacter-like organisms (HLO) according to the Updated Sydney System (16).

Culture

Each patient's antrum and corpus gastric biopsy specimens were collected into transport media (Brucella broth with 20% glycerol). These were homogenized separately and cultured separately on Columbia Blood Agar (Oxoid) plates containing 7% defibrinated horse blood (Oxoid) and supplemented with *H. pylori* selective supplement (DENT) (Oxoid). The inoculated plates were incubated at 37°C in anaerobic jar (Oxoid) under microaerophilic conditions (Gaspak Campy Container System; Beckton Dickinson) for 3-7 days. Cultured *H. pylori* strains were identified based on colony morphology, by microscopic examination for motility and morphology, and by Gram staining and positive reaction with oxidase, catalase and urease tests.

Serum Antibody Tests

Sera were collected on the same day as when biopsies were taken from patients undergoing endoscopy. Serum samples were aliquotted and stored at -20°C until used. Anti-*H. pylori* IgG ELISA (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany) was used to detect the presence of *H. pylori*-specific serum antibodies according to the manufacturer's instructions. The recommended cut-off values were used.

Urine Antibody Tests

Urine samples were collected on the day of endoscopy. Urine samples were stored at 4°C before analysis. RAPIRUN *H. pylori* Antibody Test (Otsuka Pharmaceutical, Tokyo, Japan) is an immunochromatographic test for the detection of anti-*H. pylori* IgG antibody in urine. The urine sample (0.5 ml) was transferred into a sample diluent tube containing the sample diluent and mixed by pipetting using the same syringe; then, 0.2 to 0.3 ml of the mixture was added to the sampling part of the test device, and results were determined. The samples were considered positive when two red bands at the test line and control line were observed within 20 minutes (min), and samples were considered negative when only the control line was observed in 20 min (1,5,12,13,17-20). URINELISA *H. pylori* antibody test (Otsuka Pharmaceutical, Tokyo, Japan) is an ELISA for the detection of anti-*H. pylori* IgG antibody in urine. A solid phase of an antigen, a protein extracted from an *H. pylori* strain isolated from a Japanese patient with gastritis, was used. The assay procedure was performed according to the manufacturer's recommendations. Absorbance was determined at a wavelength of 450 nm by an ELISA reader (Organon Technica Microwell System). Two positive controls and three negative controls were measured simultaneously. In the cut-off value index used, <1.0 was negative and ≥1.0 was positive according to manufacturer's instructions (2,6,7,9,12-14). Meanwhile, we also searched for a new cut-off value to determine the best cut-off value result in concordance with the results of gold standard methods by receiver operating characteristic (ROC) analysis.

Consequently, the results of URINELISA were independently evaluated for kit cut-off value according to the manufacturer's instructions and our determined new cut-off value. All urine tests were performed without knowledge of the other test results.

Statistical Analysis

The McNemar χ^2 test was used. The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and diagnostic accuracy were calculated (version 15.0; Statistical Package for the Social Sciences [SPSS]). A calculation of the ROC curve analysis was used to determine the best cut-off value for URINELISA.

Ethics

The research protocol was approved before the study began by the Institutional Review Board and the Ethical Committee of Dokuz Eylül University, Faculty of Medicine (03.02.2006/01).

RESULTS

H. pylori infection was positive in 82 patients (66.1%) according to the gold standard methods. Sixty-nine patients (55.6%) were positive and 55 patients (44.4%) were negative for anti-*H. pylori* IgG antibody by URINELISA and RAPIRUN. The sensitivity and specificity were 74.4%, 73.2% and 81.0%, 78.6%, respectively (κ=0.515; κ=0.481). One hundred nine patients (87.9%) were positive and 15 patients (12.1%) were negative by anti-*H. pylori* IgG ELISA test. The sensitivity and specificity were 100% and 35.7%, respectively (κ=0.424) (Table 1; Figure 1).

Table 1. Results of 124 urine and serum antibody tests compared to the gold standard invasive tests

	True-Positive n (%)	True-Negative n (%)	False-Positive n (%)	False-Negative n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
URINELISA*	61 (74.4)	34 (81.0)	8 (19.1)	21 (25.6)	74.4	81.0	88.4	61.8
RAPIRUN	60 (73.2)	33 (78.6)	9 (21.4)	22 (26.8)	73.2	78.6	87.0	60.0
IgG ELISA	82 (100)	15 (35.7)	27 (64.3)	0 (0)	100.0	35.7	75.2	100.0

* URINELISA was evaluated according to the manufacturer's instructions (OD 1).

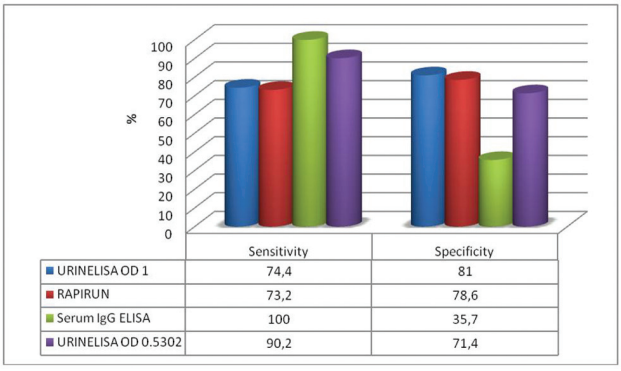

Figure 1. Comparison of sensitivity and specificity of all tests.

When using the cut-off value of 1.000 (OD 1) as recommended by the manufacturer, the sensitivity, specificity, PPV, and NPV of the URINELISA test were 74.4%, 81.0%, 88.4%, and 61.8%, respectively. Although the sensitivity and specificity of URINELISA were acceptable, we wondered, when ROC curves were performed, whether or not it would influence the results correlated with gold standard methods. Thus, ROC curves were performed for URINELISA to reach the best new cut-off value in concordance with the results of gold standard methods in our patient groups. ROC curve allowed for the determination of the threshold, giving the best combination of sensitivity and specificity for URINELISA, indicating that the optimal cut-off value as indicated in the ROC curves was 0.530 (area under curve =0.866) for our patient population (Figure 2). When we used this optimal cut-off value of 0.530, the sensitivity, specificity, PPV, and NPV of URINELISA were 90.2%, 71.4%, 86.1%, and 79.0%, respectively (κ=0.631) (Table 2, Figure 1).

DISCUSSION

To our knowledge, our study is the first to determine the validity of URINELISA, which is a urine-based enzyme immunoassay, as a noninvasive test, among Turkish adult patients with dyspepsia in our university hospital. The advantages of urine-based enzyme immunoassays are that they are noninvasive, the sample collection is very simple (3,6,7), it does not require centrifugation, and the cost of using urine as a sample is much lower than that of serum (4,7,20). Antibody concentration in urine samples was approximately 1/10000 of antibody concentration in serum (12,21). Although anti-*H. pylori* IgG is at a low concentration in urine samples, it has been found to correlate with anti-*H. pylori* IgG in serum samples (5,20). In addition, antibodies to *H. pylori* in urine are stable for 60 days at 4°C (3,6,26) and for 3 days at 37°C (3,26) thus making routine transportation of urine samples to laboratories convenient (7). The antibody activity of URINELISA in random single-void urine in humans was comparatively constant during a day and on different days, except for first-void morning urine (3). Although it can be used with randomly collected urine samples, too much water intake before urination should be avoided, as it can produce urine with a very low concentration of IgG (3,11,20). Additionally, the patient's renal function, urine constituents and urine pH may influence the detection of urine antibodies (20). We collected urine specimens before or after endoscopy on the same day. The patients did not eat or drink anything for 8 hours before endoscopy.

Muhsen et al. (22) reported the sensitivity and specificity of URINELISA in children as 34.2% and 96.3%, respectively. However, they evaluated only the stool antigen test as the gold standard method, so these results were limited. They found a new cut-off value of 0.066 for URINELISA for healthy Israeli children. Megraud et al. (9) found a new cut-off value of 0.2 for URINELISA. The *H. pylori* antigens used for the urine-based ELISA were extracted from a Japanese strain (2,3). The different genetic background of patients and *H. pylori* strains could induce different antigen-antibody responses (7). There is no study in the literature about urine antibody tests for Turkish adult dyspeptic patients. The sensitivity of URINELISA

Table 2. Results of urine antibody tests with different cut-off values compared to the gold standard invasive tests

	True-Positive n (%)	True-Negative n (%)	False-Positive n (%)	False-Negative n (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
URINELISA (OD=1)	61 (74.4)	34 (81.0)	8 (19.1)	21 (25.6)	74.4	81.0	88.4	61.8
URINELISA (OD=0.530)	74 (90.2)	30 (71.4)	12 (28.6)	8 (9.8)	90.2	71.4	86.1	79.0

* URINELISA was evaluated according to the manufacturer's instructions (OD 1) and according to our new cut-off value (OD 0.530).

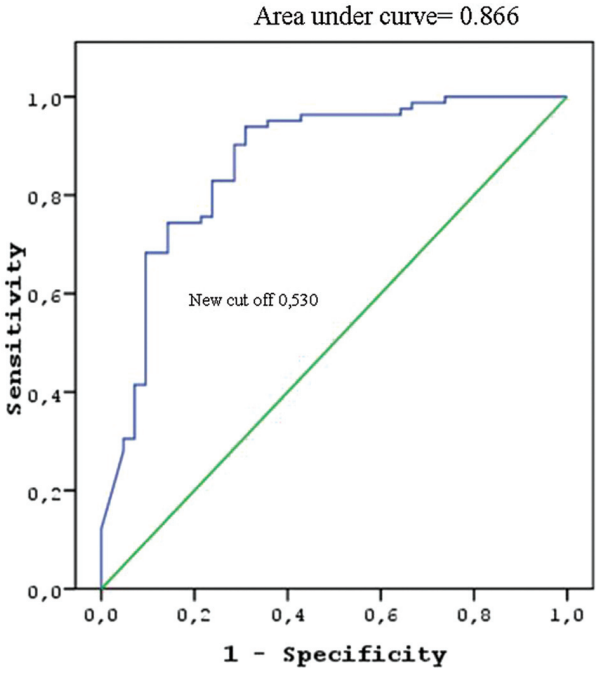

Figure 2. Receiver operating characteristic curve of the URINELISA test in comparison with the gold standard methods for diagnosis of *H. pylori* infection in 124 patients.

might change in different geographical regions. In our study, we found an optimal cut-off value of 0.530 for URINELISA for our Turkish adult patients with dyspepsia.

Leodolter et al. (12) reported the sensitivities of URINELISA and RAPIRUN in dyspeptic patients to be 90% and 82%, respectively. Adachi et al. (13) compared frozen and unfrozen urine samples for *H. pylori* detection in which the number of subjects with positive results was significantly higher for the unfrozen samples, by both URINELISA and RAPIRUN. Megraud et al. (9) reported that the sensitivities of URINELISA and RAPIRUN were 72.2% and 30.2%, respectively. In our study, we also found that sensitivities of URINELISA (OD 1) and RAPIRUN were 74.4% and 73.2%, respectively, with the higher sensitivity of URINELISA (OD 1). However, when we used our best new cut-off value (0.530), the sensitivity of URINELISA was 90.2% compared with the gold standard methods as the best concordance.

H. pylori infection can be diagnosed by a variety of invasive and noninvasive tests. Serology can be performed on noninvasively collected clinical samples. Yılmaz et al. (24) detected *H. pylori* infection by IgA, IgG and anti CagA ELISA and Western blot techniques, indicating that anti-*H. pylori* IgA testing seems clinically useless and IgG testing is not clinically meaningful. Tests for the detection of anti-*H. pylori* antibodies are widely used because they are straightforward, convenient and economical. However, serum and urine tests for the presence of antibody cannot distinguish current or past infection (25,26). The performance of an antibody detection-based kit is affected by the ethnic factor, and therefore, it is different in various patient populations (26). URINELISA assay plates and RAPIRUN membranes contain antigens from *H. pylori* strain (OHPC-040), which have important genes *(vacA, ureB and cagA)* from Japanese patients (3,9,11,18,21,22). However, the urine antibody test accuracy did not differ between Asian and Western ethnic groups (26).

Opekun et al. (25) found that sensitivities of RAPIRUN and serum IgG serology test (HM-CAP) were 90% and 85%, respectively. They concluded that RAPIRUN urine antibody test provided reliable information rapidly at the point of primary care. Nguyen et al. (5) found that the sensitivity and specificity of RAPIRUN test in 148 Vietnamese patients were 79.5% and 90.7%, respectively.

In conclusion, we found that URINELISA and RAPIRUN were highly accurate, just as accurate as the serological tests, and also that they could be used as an alternative to the serological tests for detecting *H. pylori* infection in patients with dyspepsia. Both urine-based tests, URINELISA and RAPIRUN, were found highly specific for the diagnosis of *H. pylori* infection, and they were al-

so more convenient and easy to use as a noninvasive method in clinical trials, especially at the point of primary care. Both tests would be useful for screening patients with dyspepsia. The best cut-off value of 0.530 for URINELISA was found to be more effective for the evaluation of patients with dyspepsia in our patient group. The isolates of *H. pylori* from different geographic regions can show antigenic variations, and URINELISA validated in one region may have variable results in other regions. Therefore, the optimal density value for URINELISA should be calculated and adjusted for the study population in each country.

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