

## Gender-associated differences in urea breath test for *Helicobacter pylori* infection referrals and results among dyspeptic patients

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### Abstract

**AIM:** To verify whether there is a gender difference in the  $^{13}\text{C}$ -urea breath test results in a large cohort.

**METHODS:** The test results of dyspeptic patients referred for  $^{13}\text{C}$ -urea breath testing between January and December, 2007 were evaluated. Testing was carried out at the health insurance organization branches and evaluated at a central laboratory in Israel.

**RESULTS:** Of a total of 28 746 test results, 18 122 (63.04%) were from females and 10 624 (36.95%) from males. Overall, 10 188 (35.4%) results [expressed as delta over baseline (DOB)] were positive ( $\text{DOB } ^{13}\text{C} > 5$ ), 18,326 (63.7%) were negative ( $\text{DOB } ^{13}\text{C} < 3.5$ ) and 232 (0.8%) were borderline ( $\text{DOB } ^{13}\text{C} 3.5-5$ ). There was a significant difference between the total positive rate among females and males (34.8% vs 37.2%, respectively,  $P = 0.0003$ ). The mean test value was increased by approximately 10 units for females compared to males ( $P < 0.01$ ) and this difference was consistent for

all age groups (i.e., between 10-80 years of age,  $P < 0.01$ ).

**CONCLUSION:** More females were referred to  $^{13}\text{C}$ -urea breath testing. More males had positive results. The mean test values were significantly higher among females of all age groups, possibly representing an increased bacterial load among females and suggesting gender-associated differences in *Helicobacter pylori* host interactions.

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**Key words:** *Helicobacter pylori*; Urea breath test; Gender; Dyspepsia

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### INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is the major cause of peptic ulcer disease as well as being implicated in the pathogenesis of gastric cancer<sup>[1]</sup>. The  $^{13}\text{C}$ -urea breath test ( $^{13}\text{C}$ -UBT) is considered the most accurate non-invasive diagnostic tool for the presence of *H. pylori*<sup>[2,3]</sup> and one that is widely used in clinical practice. By measuring the intragastric urease activity, potential advantages of  $^{13}\text{C}$ -UBT are threefold: it allows assessment of the *H. pylori*

bacterial load, which, according to several reports, might be a risk factor in the development of peptic ulcer disease<sup>[4-7]</sup>; it serves to determine the severity of gastritis activity<sup>[4-6]</sup>; and it influences the efficacy of *H. pylori* eradication therapy<sup>[8-11]</sup>. A significant elevation of <sup>13</sup>C-UBT values among females infected with *H. pylori* compared to males was recently reported, suggesting gender-associated differences in *H. pylori* host interaction<sup>[12]</sup>. The aim of our current study was to evaluate the pattern of <sup>13</sup>C-UBT referrals among a large cohort of dyspeptic males and females and to verify whether or not there is such a difference in <sup>13</sup>C-UBT results.

## MATERIALS AND METHODS

Maccabi Health Services is the second largest health insurance organization (HMO) in Israel, providing health services to approximately 2 million citizens. Its central laboratory provides <sup>13</sup>C-UBTs for its subscribers nationwide. The sample for the current study consists of <sup>13</sup>C-UBTs collected at the HMO branches and evaluated at MHC's central laboratory from January to December, 2007. The <sup>13</sup>C-UBT was performed with a mass spectrometer (Analytical Precision 2003, UK) using 75 mg of urea labeled with <sup>13</sup>C in 200 mL of orange juice. Breath samples were collected twice from each patient (at 0 and 30 min) and the ratio of <sup>12</sup>C to <sup>13</sup>C was measured at both time points. The difference was calculated by subtraction and termed the excess delta or the delta over the baseline (DOB). A DOB > 5.0 was considered positive for *H. pylori* infection, a DOB < 3.5 was considered negative for *H. pylori* infection and a DOB of 3.5-5 was considered as a borderline result. All the study patients were asked to stop the use of H<sub>2</sub> antagonists, proton pump inhibitors or any antibiotics one week prior to undergoing the breath test.

### Statistical analysis

Categorical variables were summarized with number and percentage of patients. The  $\chi^2$  and Fisher exact tests were used to compare categorical variables and the Kruskal-Wallis one-way analysis of variance was used to analyze the demographic data. Significance was set at a *P* value < 0.05. The data were analyzed using SPSS version 15.0 (SPSS Inc. Chicago, IL).

## RESULTS

A total of 28 746 <sup>13</sup>C-UBTs were performed, 18 122 (63.04%) in females and 10 624 (36.95%) in males, during the one year study period. Figure 1 demonstrates the number of <sup>13</sup>C-UBT referrals according to the patients' age. Overall, 10 188 (35.4%) <sup>13</sup>C-UBTs were positive ( $\Delta^{13}\text{C} > 5$ ), 18 326 (63.7%) were negative ( $\Delta^{13}\text{C} < 3.5$ ) and only 232 (0.8%) were borderline ( $\Delta^{13}\text{C}$  3.5-5). The difference between the total positive rate among females and males (34.8% vs 37.2%) was highly significant (*P* = 0.0003) (Figure 2).

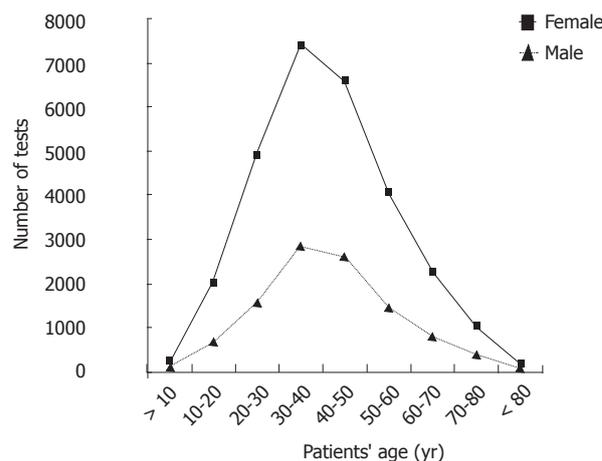


Figure 1 Number of <sup>13</sup>C-urea breath test referrals according to gender and age group.

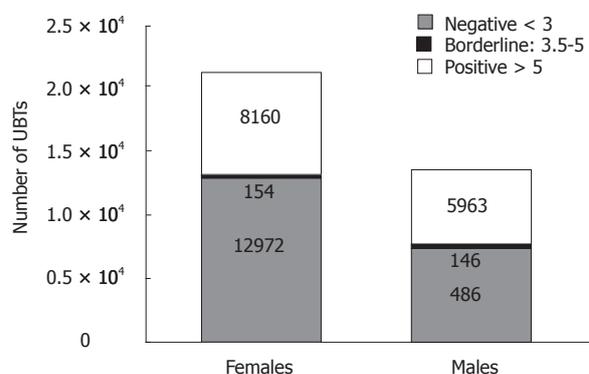


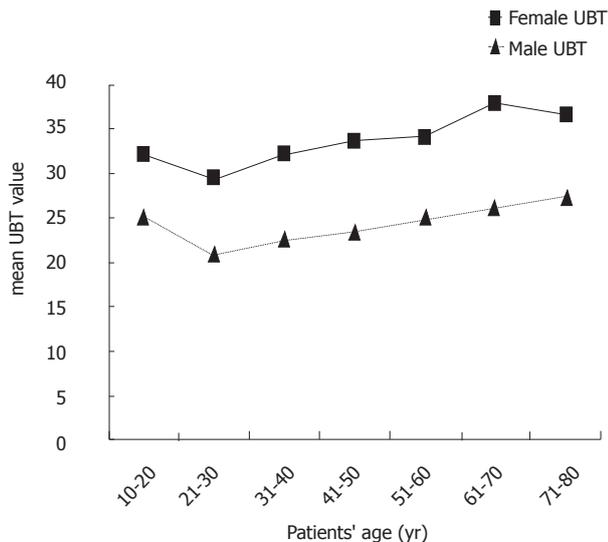
Figure 2 Distribution of <sup>13</sup>C-urea breath test results according to gender. UBT: Urea breath test.

We analyzed the mean <sup>13</sup>C-UBT values in both genders according to the patients' age (Figure 3). There was a significant increase of about 10 units in the mean <sup>13</sup>C-UBT value among females compared to males and that difference remained constant for all age groups between 10 years and 80 years of age (*P* < 0.01 for each).

## DISCUSSION

The main findings of the present study are that more females are referred to <sup>13</sup>C-UBTs than males, that the rate of positive results is higher among males, and that there is a highly significant increased mean <sup>13</sup>C-UBT value for females in all age groups compared to age-matched males.

The numerical results of the <sup>13</sup>C-UBT are the function of total urease activity within the stomach, so the test might serve as a quantitative index of the density of gastric *H. pylori* colonization. Previous studies have reported inconsistent results about the relationship between <sup>13</sup>C-UBT findings and histology-based semi quantitative measures of bacterial infection. Several studies



**Figure 3** Mean <sup>13</sup>C-urea breath test values in males and females according to age group. DOB: Delta over baseline.

have demonstrated a correlation between the excess of delta ( $\delta$ ) <sup>13</sup>CO<sub>2</sub> excretion and the *H. pylori* bacterial load<sup>[13-18]</sup>, while others found that the <sup>13</sup>C-UBT value has only qualitative meaning, i.e., either positive or negative for *H. pylori* infection<sup>[19-21]</sup>. Kobayashi *et al*<sup>[22]</sup> reported that the gastric mucosal density of *H. pylori* as estimated by real-time polymerase chain reaction was significantly correlated with <sup>13</sup>C-UBT results and histological grading. Some groups have shown that <sup>13</sup>C-UBT-based or histologically estimated bacterial density in gastric mucosa can predict the extension of gastric inflammation and *H. pylori* eradication<sup>[5,6]</sup>.

The observation in our study of the significantly increased mean <sup>13</sup>C-UBT value found in females of all age groups requires an explanation, whether the <sup>13</sup>C-UBT value represents bacterial load or urease enzyme activity. In <sup>13</sup>C-UBT, orally administered <sup>13</sup>C-labeled urea is hydrolyzed into ammonia and into <sup>13</sup>CO<sub>2</sub> by urease in the presence of *H. pylori* infection. The results are expressed as DOB values. Since endogenous <sup>12</sup>CO<sub>2</sub> production varies with age (i.e., adults more than children), weight, height and sex (i.e., males more than females), individuals with relatively lower body weight and height may produce smaller amounts of endogenous <sup>12</sup>CO<sub>2</sub>, whereupon their DOB values, expressed as a change in the <sup>13</sup>CO<sub>2</sub>/<sup>12</sup>CO<sub>2</sub> ratio, may consequently increase<sup>[22]</sup>. This, however, can explain only a small part of the increased mean <sup>13</sup>C-UBT values among females and not the significantly increased values (approximately 10 units) in all age groups that were found in the present study.

Most *H. pylori*-related diseases are associated with male gender. The role of gender as a risk factor for *H. pylori* infection was reviewed by de Martel and Parsonnet in a meta-analysis of large, population-based studies<sup>[23]</sup>. Those authors found that male gender was significantly associated with *H. pylori* infection (OR: 1.16, 95% CI: 1.11-1.22) and that this male predominance of *H. pylori*

infection was homogeneous and consistent across adult populations from various countries. They concluded that these findings may partially explain the male predominance of *H. pylori*-related adult diseases, such as duodenal ulcer and gastric adenocarcinoma.

Gender differences have also been found in response to treatment. Moayyedi *et al*<sup>[24]</sup> reported that anti-*H. pylori* therapy was significantly less successful in women than in men. They hypothesized that this may relate to an increased prevalence of 5-nitroimidazole-resistant organisms in women. Alternatively, there may be gender differences in acid output and gastric blood flow that influence treatment success<sup>[25]</sup>. The findings of the current study may provide another explanation: that the increased bacterial load among females causes the decreased response to antibiotic therapy.

Several studies have shown that the presence of *H. pylori* infection is a stronger predictor of gastric cancer in females compared to males<sup>[26-29]</sup>. Smoking and alcohol consumption were significantly more prevalent in males with gastric cancer than in males without it, and these differences were not present in females. It may therefore be considered that as risk factors, smoking and alcohol consumption have a stronger impact on males than on females. Here again, the finding that females might have an increased bacterial load may provide an explanation for *H. pylori* infection having been shown to be a stronger predictor of gastric cancer in females compared to males. Ohtani *et al*<sup>[30]</sup> have shown an effect of ovarian-dependent female hormones on *H. pylori*-induced gastric cancer in hypergastrinemic INS-GAS mice and Crabtree and colleagues have demonstrated that there are gender differences in the magnitude of the gastric cytokine responses to *H. pylori*<sup>[31]</sup>.

An interesting observation in our study is that the number of total <sup>13</sup>C-UBT referrals was significantly higher among females than males in almost all age groups, but especially between the third and fifth decades (Figure 2). The increased number of <sup>13</sup>C-UBTs among females was also associated with a slightly increased rate of negative test results. Both observations might reflect the increased prevalence of functional dyspepsia among females compared to males<sup>[32-34]</sup>. It would appear that females, especially those between the third and fifth decades of life, tend to suffer more from functional disorders. This would serve to explain the increased number of females referred to *H. pylori* <sup>13</sup>C-UBTs. On the other hand, organic *H. pylori*-related diseases are more associated with male gender and this would explain the increased rate of positive <sup>13</sup>C-UBT results among males.

We found that the number of referrals to <sup>13</sup>C-UBTs was greater among females than males, especially among females between the third and fifth decades of life. This could be explained by the increased prevalence of functional dyspepsia among females. The rate of positive <sup>13</sup>C-UBT results, however, was greater among males. Another important observation was the significantly increased

mean <sup>13</sup>C-UBT values among females in all age groups. This may represent an increased bacterial load among females but this gender difference needs to be further investigated before any firm conclusions can be drawn.

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## COMMENTS

### Background

*Helicobacter pylori* (*H. pylori*) is the major cause of peptic ulcer disease and the <sup>13</sup>C-urea breath test (<sup>13</sup>C-UBT) is considered the most accurate non-invasive diagnostic tool for the presence of *H. pylori*. A significant elevation of <sup>13</sup>C-UBT values among females infected with *H. pylori* compared to males was recently reported, suggesting gender-associated differences in *H. pylori* host interaction, and the aim of the current study was to evaluate the pattern of <sup>13</sup>C-UBT referrals among a large cohort of dyspeptic males and females and to verify whether or not there is such a difference in <sup>13</sup>C-UBT results.

### Research frontiers

The main findings of the present study are that more females are referred to <sup>13</sup>C-UBTs than males, that the rate of positive results is higher among males, and that there is a highly significant increased mean <sup>13</sup>C-UBT value for females in all age groups compared to age-matched males.

### Innovations and breakthroughs

The authors found significantly increased mean <sup>13</sup>C-UBT values among females in all age groups. This may represent an increased bacterial load among females.

### Terminology

*H. pylori* is a spiral bacterium implicated in gastritis, gastric ulcer and peptic ulcer disease. UBT is a non-invasive diagnostic procedure used to identify infections by *H. pylori*. It is based upon the ability of the bacterial enzyme urease to convert urea to ammonia and carbon dioxide. UBT is recommended in leading society guidelines as a preferred non-invasive choice for detecting *H. pylori* before and after treatment.

### Peer review

The study was performed on a large cohort of patients regarding the possibility of a gender difference in the <sup>13</sup>C-urea breath test. The analysis is well conducted and the results are interesting.

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