# Delta values of the $^{13}$C-urea breath test in Helicobacter pylori positive persons with and without dyspepsia

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***Dedicated to Professor Bohumil Fixa, MD, DSc, on the Occasion of his 75th Birthday***

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***Abstract.*** *The possible role of Helicobacter pylori (Hp) in functional dyspepsia is still controversial. Some authors hypothesize that excessive gastric urea production by Hp could be responsible for dyspeptic complaints. The aim of this study was to investigate the difference (delta) of the $^{13}CO_2$ / $^{12}CO_2$ ratio in $^{13}$C-urea breath test ($^{13}$C-urea-UBT) among Hp-positive persons with and without dyspepsia. Hp status was investigated by means of $^{13}$C-urea-UBT in 2,478 persons, 1,230 men and 1,248 women (4 - 100 year-old, mean 40, median 38 years), randomly taken from a general non-selected population. Breath samples were analyzed by means of isotope ratio mass spectrometry (AP 2003, Analytical Precision, UK). Cut-off was 3.5 (grey zone range 3.3 - 3.7). Health status was evaluated based on data given by particular persons into their structured questionnaires. A total of 1,015 (41.0 %) persons were Hp positive and 1,399 (56.4 %) Hp negative. Sixty-four subjects (2.6 %) had a grey zone result. There was no significant difference of dyspepsia rate between Hp positive and Hp negative persons. Among Hp-positive subjects, there were 529/1,015 persons (52.1 %) symptom free, 61/1,015 patients (6.0 %) had dyspepsia as the only long-lasting symptom and 63/1,015 subjects (6.2 %) had dyspepsia associated with other co-morbidity. There was no significant difference of delta values between symptom-free Hp-positive persons and Hp-positive patients with sole long-lasting dyspepsia. Thus our results do not support the hypothesis that gastric urea overproduction could be a causative factor originating dyspeptic symptoms.*

***Key words:*** *Helicobacter pylori, $^{13}$C-urea breath test, delta over baseline, functional dyspepsia*

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***Souhrn.*** *Možná role infekce Helicobacter pylori (Hp) u funkční dyspepsie je stále kontroverzní. Někteří autoři vyslovili domněnku, že výrazná produkce močoviny v žaludku účinkem Hp by mohla způsobovat dyspeptické obtíže. Cílem této studie bylo vyšetřit hodnoty delta, jako rozdílu poměrů $^{13}CO_2$ / $^{12}CO_2$ dechového testu s $^{13}$C-ureou u Hp pozitivních osob s dyspepsií a bez dyspepsie. Přítomnost infekce Hp byla vyšetřena pomocí dechového testu s $^{13}$C-ureou u 2478 osob, 1230 mužů a 1248 žen (ve věku 4 - 100 let, průměr 40, medián 38 let), vybraných z neselektované všeobecné populace. Vzorky dechu byly analyzovány poměrovou hmotnostní spektrometrií (AP 2003, Analytical Precision, Velká Británie). Rozhraní pozitivního a negativního výsledku (cut-off) bylo 3,5, šedá zóna byla 3,3 - 3,7. Hodnocení zdravotního stavu bylo provedeno na základě údajů jednotlivých vyšetřených osob, které uvedli do strukturovaného dotazníku. Celkem 1015 osob (41,0 %) bylo Hp pozitivních a 1399 (56,4 %) bylo Hp negativních. Šedesát čtyři vyšetření (2,6 %) měl hraniční výsledek v šedé zóně. Nebyl zjištěn signifikantní rozdíl v prevalenci dyspepsie u Hp pozitivních a Hp negativních osob. Mezi Hp pozitivními bylo 529/1015 vyšetřených (52,1 %) bez subjektivních zdravotních potíží, 61/1015 (6,0 %) osob mělo dyspepsii jako jediný dlouhodobě trvající příznak a 63/1015 (6,2 %) vyšetřených mělo dyspepsii spolu s jiným onemocněním. Nebyl zjištěn signifikantní rozdíl delta hodnot dechového testu mezi Hp pozitivních osob bez dyspepsie a Hp pozitivních osob s dyspepsií jako jediným dlouhodobě trvajícím příznakem. Naše výsledky nepodporují teorie, že by močovina vytvořená v žaludku účinkem Hp byla příčinným faktorem při vzniku dyspeptických obtíží.*

***Klíčová slova:*** *Helicobacter pylori, dechový test s $^{13}$C-ureou, hodnota delta, funkční dyspepsie*

The $^{13}$C-urea breath test ($^{13}$C-urea-UBT) is the most accurate non-invasive method to diagnose Helicobacter pylori (Hp) infection (23). The test is based on the gastric urease activity of Hp, which splits non-radioactive stable $^{13}$C-labelled urea ingested by investigated persons into $NH_4^+$ and $^{13}$C-labelled $HCO_3^-$, which is expired as $^{13}CO_2$ in the exhaled breath. Expired $^{13}$C-labelled carbon dioxide is measured as a $^{13}CO_2$ / $^{12}CO_2$ ratio and results are expressed as the excess delta (difference between $\delta$ $t_i$ and $\delta$ $t_0$). The $^{13}$C-urea-UBT correlates with gastric density of Hp infection (4,6,9,18,31,34,37).

The possible role of Hp infection in functional dyspepsia is still controversial (7,8,10,28,29,38,39,43). Some authors hypothesize that excessive gastric urea production by Hp could be responsible for dyspeptic complaints (5,13). The aim of this study was to assess delta values of $^{13}$C-urea-UBT in Hp-positive persons with and without dyspepsia.

## Materials and methods

### Subjects

Nineteen general practitioner centres (7 for children & adolescents and 12 for adults) took part in the Project. A total number of 30,012 persons created this general non-selected population. In two-step random selection, carried out centrally, 2,956 individuals older than 4 years were chosen for the study. All persons selected were invited (in writing) to participate in the study. Four hundred and forty-seven (15.1 %) of the subjects were excluded: 172 did not respond the invitation, 72 moved, 58 died (within a 6-month period between the selection and study), 55 refused to participate, 49 were employed far from their place of residency, 19 were abroad for a long-term stay, 1 was staring at an asylum elsewhere, 19 persons did not complete the breath test and 2 subjects did not fill out the questionnaire. Another 31 persons (1 %) were excluded as complete data (either from the breath samples analysis or questionnaires) was not available. All participants got detailed written information about the Project in advance and signed written consent (parents on behalf of their children).

Overall, 2,478 persons, 1,230 men and 1,248 women (4 - 100 year-old, mean 40, median 38 years) were evaluated. Health status was assessed based on data given by particular subjects on their structured questionnaires. For all data obtained, all personal identification information was deleted in compliance with the laws for the protection of confidentiality in the Czech Republic.

### Urea breath test

Urea breath tests were performed in the morning after overnight fasting. Citric acid solution (3 g dissolved in 150 mL of still water) as a test drink was given initially. Five minutes later two baseline exhaled breath samples were collected into 20-mL vacutainers using a straw. Thereafter all persons ingested 100 mg $^{13}$C-urea for adults (Helicobacter Test Hp Plus, Utandningstester i Sverige AB, Göteborg, Sweden) or 75 mg $^{13}$C-urea for children and adolescents (Helicobacter Test INFAI, INFAI GmbH, Köln, Germany) dissolved in 50 mL of still water with 1 g citric acid (at time 0). Breath samples were collected in duplicate using a straw into 20-mL vacutainers after 30 minutes. Tubes with breath samples were sent to a single analytical centre by post and measured within a one-week period. Breath samples were analyzed by means of isotope ratio mass spectrometry (AP 2003, Analytical Precision, United Kingdom). Cut-off was 3.5 (grey zone range 3.3 - 3.7).

### Statistics

Data were statistically treated by a Mann-Whitney test, analysis of variance and a Chi-square test using statistical software (SigmaStat, Jandel Corporation, Germany).

### Results

A total of 1,015 (41.0 %) persons were Hp-positive and 1,399 (56.4 %) were Hp-negative. Sixty-four subjects (2.6 %) had a grey zone result. Among children & adolescents (4 - 18 year-old) 190/664 subjects (28.6 %) were Hp positive, among adults (over 18 years) 825/1,814 persons (46.5 %) were Hp positive ($\chi^2 = 20.754$, $p < 0.001$). There was no significant difference in the prevalence of Hp between males (516/1,230, 42.0 %) and females (499/1.248, 40.0 %), $\chi^2 = 0.369$, $p = 0.544$. There was no significant difference of dyspepsia rate between Hp-positive and Hp-negative persons. Among Hp-positive subjects, there were 529/1,015 persons (52.1 %) symptom free who themselves felt healthy, 61/1,015 patients (6.0 %) had dyspepsia as the only long-lasting symptom (over one year) and 63/1,015 subjects (6.2 %) had dyspepsia associated with other co-morbidity and/or treatment. Remaining 362/1,015 (35.7 %) persons have had various, mostly minor health problems without dyspepsia (like allergy, arthralgias, recurrent respiratory infections, headache, low back pain, chronic bronchitis, hypertension, diabetes mellitus or ischaemic heart disease etc.).

Delta values were significantly higher in persons tested with higher (100 mg) compared to lower dose (75 mg) of $^{13}$C-urea both for Hp-positive and Hp-negative subjects (Table 1). There was no significant relationship between delta values and age either among Hp-positive children ($r = - 0.202$, NS) or Hp-positive adults ($r = - 0.107$, NS). Delta values were significantly higher in Hp-positive males when compared with Hp-positive females (Table 2). This difference was still significant when delta values were related to the body-mass index of particular subjects, median 0.520 (interquartile range 0.303 - 0.718) vs. 0.438 (0.236 - 0.675), $p = 0.009$. Baseline values of the $^{13}CO_2$ / $^{12}CO_2$ ratio were significantly lower in adult males (-23.805 ± 1.231) compared with adult females (-23.992 ± 1.000), $p = 0.044$, and between adult persons in total (-23.893 ± 1.131) and children & adolescents (-24.272 ± 1.085), $p < 0.001$. There was no significant difference of delta values between symptom-free Hp-positive persons and Hp-positive patients with sole long-lasting dyspepsia (Table 3).

### Discussion

The $^{13}$C-urea-UBT correlates with gastric density of Hp infection (4,6,9,18,31,34,37) although not proved by all authors (22). The aim of our study was to evaluate delta values of $^{13}$C-urea-UBT in Hp-positive subjects with and without dyspepsia. We found no significant difference of delta values between symptom-

Table 1
**Delta values in Helicobacter pylori positive and negative children & adolescent persons ($^{13}$C-urea 75 mg) and adults ($^{13}$C-urea 100 mg administered), expressed as median and interquartile range. Sixty-four persons with grey zone results are not included.**

| Delta | $^{13}$C-urea 75 mg (n = 633) | $^{13}$C-urea 100 mg (n = 1,781) | Significance |
|---|---|---|---|
| Hp-negative (n = 1,399) | 0.525 (0.24 - 0.12) | 1.560 (0.81 - 2.29) | $p < 0.001$ |
| Hp-positive (n = 1,015) | 6.110 (4.55 - 12.74) | 13.285 (7.84 - 18.79) | $p < 0.001$ |

Table 2
**Delta values in Helicobacter pylori positive males and females, expressed as mean ± SD and median & interquartile range.**

| | **Males** n = 516 | | **Females** n = 499 | | **Significance** |
|---|---|---|---|---|---|
| | mean ± SD | median interquartile range | mean ± SD | median interquartile range | |
| **Adults** n = 825 | 13.785 ± 6.024 | 13.970 8.615 - 19.272 | 12.906 ± 7.192 | 11.800 7.160 - 18.182 | p = 0.015 |
| **Children & adolescents** n = 190 | 9.962 ± 6.192 | 8.200 5.003 - 13.920 | 8.335 ± 5.779 | 5.320 4.333 - 10.425 | p = 0.011 |
| **Total** n = 1,015 | 13.200 ± 6.199 | 13.215 7.580 - 18.825 | 11.888 ± 7.155 | 10.650 5.560 - 17.300 | p < 0.001 |

Table 3
**Delta values in 1,015 Helicobacter pylori positive persons with and without dyspepsia, expressed as mean ± SD and median & interquartile range (IQR).**

| **Delta values** | **Mean ± SD** | **Median (IQR)** |
|---|---|---|
| (A) Symptom-free subjects (n = 529) | 12.022 ± 6.413 | 10.935 (5.880 - 17.450) |
| (B) Various diseases without dyspepsia (n = 362) | 12.764 ± 6.244 | 11.820 ( 6.845 - 18.521) |
| A + B (n = 891) | 12.312 ± 6.354 | 11.330 (6.265 - 17.782) |
| (C) Sole long-lasting dyspepsia (n = 61) | 13.182 ± 11.195 | 11.540 (6.412 - 17.347) |
| (D) Other dyspepsia + co-morbidity (n = 63) | 13.454 ± 5.945 | 13.320 (8.170 - 18.380) |
| C + D (n = 124) | 13.331 ± 8.682 | 12.720 ( 7.893 - 18.118) |

**Significance:**
A vs B: NS (p = 0.061); A vs C: NS (p = 0.824); A vs D: p = 0.050; B vs C: NS (p = 0.455);
B vs D: NS (p = 0.359); C vs D: NS (p = 0.222); A+B vs C+D: NS (p = 0.296).
NS - not significant.

free Hp-positive persons and Hp-positive patients with sole long-lasting dyspepsia. Based on structured health questionnaire, 61 patients have been suffering from sole long-lasting dyspeptic symptoms (one year or longer), with no evidence of organic disease and no alarm symptoms. We suppose that these patients have had functional dyspepsia, although in a substantial part of cases it was in fact an uninvestigated dyspepsia (not investigated at upper GI endoscopy), thus not-fulfilling the Rome II criteria (33). Dyspepsia in the other 63 persons was associated with other complaints, co-morbidity and/or medical treatment and was considered to be organic or secondary dyspepsia. There was a difference of delta values between this group of Hp-positive patients and Hp-positive symptom-free subjects. This finding must be interpreted with caution as these 63 persons form a very heterogeneous group of different conditions (known organic gastrointestinal disease, NSAIDs or other medical treatment for different co-morbidity etc). There was also a significant difference of delta values between Hp-positive males and females, both for children & adolescents and adults (Table 2). This difference still remains significant even when delta values are related to body-mass index and a slight difference of baseline values is considered. Klein et al. (17) found higher urea hydrolysis rate in males and concluded that results of $^{13}CO_2$ / $^{12}CO_2$ ratio are critically dependent on the amount of dilution by endogenous CO2 production (higher in males than females) (17). According to another study (1), breath test results are not influenced by CO2 production in otherwise healthy persons (unlike children with cystic fibrosis) and/or in case of a normal metabolic rate. Furthemore if we use mass spectrometry for the analysis, delta values are not influenced by $^{12}CO_2$ concentration as single particles are measured (as opposed to infrared spectrometry). Based on our previous study (20) we hypothesize that different time peaks in men and women are the most plausible explanation for

the difference of delta values between males and females.

Koskenpato et al. (21) found that high delta-over-baseline values were associated with antrum-predominant Hp-positive chronic gastritis and functional dyspepsia (in a subgroup of 36 patients out of 136 subjects). These patients gained symptom improvement one year after successful anti-Hp eradication therapy. Similarly as in our case, Braden et al (3) found no association between dyspeptic symptoms and density of gastric Hp colonization in their study of 1,500 persons. Chang et al. (5) studied 100 dyspeptic patients by means of $^{13}$C-urea-UBT and concluded that patients with functional dyspepsia and high delta values (> 58.2) could benefit from Hp eradication therapy. Franceschi et al. (13) found an increase of frequency and intensity of dyspeptic symptoms according to delta-over-baseline values (in 1,688 Hp-positive patients out of 2,520 dyspeptic subjects).

The possible role of Hp infection in the pathogenesis of functional dyspepsia is still very controversial. Several clinical studies have been published both with positive (21,24,25,30) and prevailing negative results (2,11,12,14-16,19,26,32,40,41). There are several concepts for the possible causative role of Hp in functional dyspepsia hypothesizing that dyspeptic symptoms are caused by mediators of chronic inflammation (25), virulent strains of Hp (42), neuroplastic changes in the afferent neural pathway (leading to visceral hyperalgaesia) (36), gastric dysmotility caused by Hp (27,35) or excessive gastric urea production by Hp (5,13).

To summarize our study, there was no significant difference of delta values between symptom-free Hp-positive persons and Hp-positive patients with sole long-lasting dyspepsia. Thus our results do not support the hypothesis that gastric urea overproduction would be a causative factor originating symptoms in dyspepsia.

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