Helicobacter pylori infection and UBT-^{13}C values are associated with changes in body mass index in children and adults

MARÍA J. BRUERA[1], MARÍA V. AMEZQUITA[2],
ARNOLDO J. RIQUELME[3], CAROLINA A. SERRANO[2,a,b*],
PAUL R. HARRIS[2,*]

[1]School of Medicine, Pontificia Universidad Católica de Chile. Santiago, Chile.
[2]Deparment of Pediatric Gastroenterology and Nutrition. School oy Medicine, Pontificia Universidad Católica de Chile. Santiago, Chile.
[3]Department of Gastroenterology, School of Medicine, Pontificia Universidad Católica de Chile. Santiago, Chile.
[a]Licenciada en Ciencias Biológica.
[b]PhD en Ciencias Biomédicas.

*Both authors contribute equally to this work.

Corresponding author:
Dr. Paul R. Harris
Diagonal Paraguay 362.
Santiago, Chile.
pharris@med.puc.cl

Carolina A. Serrano
Diagonal Paraguay 362.
Santiago, Chile.
caserran@uc.cl

ABSTRACT

Background: The urea breath test (UBT-^{13}C) is a non-invasive technique that allows the diagnosis and confirmation of eradication of Helicobacter pylori infection. Aim: To evaluate H. pylori positivity and values of UBT-^{13}C among infected Chilean children and adults, and to analyze its variation in relation to sex, nutritional status, and age of the patients. Material and Methods: Retrospective study of 1141 patients aged 6 to 94 years, with an indication for a UBT-^{13}C either for diagnosis or for confirmation of eradication of H. pylori infection. [13]C enrichment was measured using an infrared spectrometer calculating the delta ^{13}C values before and after the ingestion of ^{13}C marked urea. The clinical data of the patients were obtained at the time of the examination. Results: We included 241 children and 900 adults. Infected children obtained lower UBT-^{13}C delta values than infected adults (16.1 ± 8.7 and 37 ± 52.9, respectively). The rates of infection were higher in males who were recruited for diagnosis. Significant differences were obtained between positivity for H. pylori in overweight and obese children but not adults. UBT-^{13}C titers were significantly associated with the body mass index (BMI) only in adults. Conclusions: H. pylori infection rates are similar between sexes and are higher in children probably because of selection bias. In children, H. pylori positivity is associated with higher BMI and excess malnutrition although with similar UBT-^{13}C values. In adults, H. pylori infection is not related with BMI, but a higher BMI impacts UBT-^{13}C titers.

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Key words: Body Mass Index; Breath Tests; Urea; Helicobacter pylori.

La infección por *Helicobacter pylori* y los valores de UBT-^{13}C se asocian con el índice de masa corporal en niños y adultos

Antecedentes: La prueba de aliento con urea (UBT-^{13}C) es una técnica no invasiva que permite el diagnóstico y confirmación de erradicación de la infección por Helicobacter pylori. Objetivo: Evaluar los valores de UBT- [13]C en niños y adultos chilenos infectados y analizar su variación en relación al sexo, diagnóstico nutricional y edad de los pacientes. Material y Métodos: Estudio retrospectivo de 1.141 pacientes de 6 a 94 años. El enriquecimiento de[13]C se midió usando un

*espectrómetro de infrarrojos, calculando el delta ^{13}C antes y después de la ingesta de urea marcada con ^{13}C. Los datos clínicos de los pacientes se obtuvieron al momento del examen. **Resultados**: Incluimos 241 niños y 900 adultos con valores delta de UBT-^{13}C de 16,1 ± 8,7 frente a 37 ± 52,9, respectivamente. Las tasas de infección fueron mayores en los hombres reclutados para el diagnóstico. Se obtuvieron diferencias significativas entre la positividad para H. pylori en niños con sobrepeso y obesidad, pero no en adultos. Los títulos de UBT-^{13}C se asociaron significativamente con el índice de masa corporal (IMC) solo en adultos. **Conclusiones**: Las tasas de infección por H. pylori son similares entre los sexos y aumentan en los niños probablemente debido al sesgo de selección. En niños, la positividad para H. pylori se asocia con un IMC más alto y malnutrición por exceso, aunque con valores similares de UBT-^{13}C. En los adultos, la infección por H. pylori no se relaciona con el IMC ni con la obesidad, pero el aumento del IMC afecta los títulos de UBT-^{13}C.*

Palabras clave: *Helicobacter pylori; Índice de Masa Corporal; Pruebas Respiratorias; Urea.*

*H*elicobacter pylori infection is highly prevalent worldwide[1]. In Chile, up to 73% of asymptomatic population shows antibody titers compatible with the infection with variable rates according to age groups[2-5,9,10]. This bacterium has been associated with chronic gastritis and gastroduodenal ulcers in children and adults[1,6,7] and is the main risk factor for the development of gastric cancer, which is also highly prevalent in Chile[8], comprising a relevant public health issue for our country[9,11].

H. pylori diagnosis is based on direct or invasive testing (endoscopy dependent) and indirect or non-invasive testing. Invasive testing requires a trained operator, cost is higher and has several risks associated with the procedure. Their main advantage is that they allow diagnosing the infection but also the observation of gastric mucosal changes associated with the infection like peptic ulcer disease and the appearance of neoplastic lesions[12], while indirect testing only allows for bacterial detection. Most used non-invasive tests include the stool antigen test, the urea breath test (UBT) and serum antibody detection. Their maximum usefulness occurs in the execution of epidemiological studies and in the evaluation of the success of antibiotic therapy for eradication[13].

The UBT is a non-invasive test that detects active H. pylori infection with a sensitivity of 89-95% and specificity of 95%-100%[14-16]. It is easy, safe, and more economical to perform, than invasive methods[17]. The test is based on H. pylori ability to change ingested ^{13}C or ^{14}C marked urea. If H. pylori is present in the gastric mucosa, marked urea will be hydrolyzed by bacterial urease producing ammonium and bicarbonate which ultimately will be exhaled by the patient as marked CO_2 and measured thus determining the infection presence[6,12,17,18]. Initially $^{14}CO_2$ was used as a marker and has since been replaced by $^{13}CO_2$, which in turn is non-radioactive thus safer, increasing the applicability of the test to children, pregnant women, and older subjects[6,12].

The test results are quantitative since the value obtained from the assay are numerical values that show the difference of marked C before and after ingesting the urea (delta value). Nonetheless the informed result of the test is dichotomic as a cut-off value to determine positivity is used. Regardless, the titers obtained through the delta value can be used to get additional information than the state of the infection positivity. Manfredi et al, have shown that children infected by H. pylori have less intensive gastritis and a minimal amount of severe pathogenic changes in the gastric mucosa which might be associated with lower delta UBT-^{13}C values in this subset of patients[19]. Nonetheless there is scarce evidence in the literature that shows the association of delta UBT-^{13}C values and age, sex, or nutritional status.

The aim of this study is to evaluate the quantitative aspect of the UBT test and analyze any possible association between H. pylori positivity, delta UBT-^{13}C values with demographic

and anthropometric determinations in referred patients.

Materials and Methods

Study design

Retrospective study of 1,141 patients; 241 children and 900 adults that entered the endoscopy unit of the clinical hospital of the Pontificia Universidad Católica de Chile between the years 2014 and 2020, with indication for a UBT-13C test by their doctors. We obtained data regarding age, sex, weight, and height of the patients.

Patients

We included patients between 6 and 94 years of age, with medical indication for UBT-13C test. Exclusion criteria were antibiotic use during the last 4 weeks prior to UBT-13C test, proton pump inhibitors or histamine type 2 receptors antagonist use for 7 days prior to UBT-13C test, and food consumption for 2 hours prior to UBT-13C test.

UBT-13C

Basal levels of CO_2 were determined at t = 0. Patients ingested a 50 mg 13C marked urea in 80-100 ml of cold water. After 30 minutes in a resting state without food consumption the patient exhaled a second time (t = 30 min). Both samples were measured to determine 13C in an IR-Force Infrared Spectrometer 200 (UBiT-IR200, Otsuka Electronics Co, Ltd., Osaka, Japan). The test was considered positive for *H. pylori* infection when the difference in the measurements of parts per thousand (‰) of $^{13}CO_2$ in the sample at t = 30 minus $^0/_{00}$ of $^{13}CO_2$ in the sample at t = 0 was ≥ 4.0 ± 0.4, with a saturation limit of 170.

Nutritional assessment

Nutritional status assessment was performed concomitantly to the UBT-13C test. For children and teenagers, nutritional status was determined using reference standards by the World Health Organization (WHO) in 2007. Standard deviation was expressed as Z score. Calculations were performed using the WHO Anthro plus 2009 (http://www.who.int/growthref/tools/en/) software. For adults BMI cut off values used were defined by WHO in 2013 and are underweight < 18.5, normal 18.5-24.9, overweight ≥ 25-29.9 and obesity ≥ 30.

Statistical analysis

Data are shown as media, standard deviation, and range or as medians and interquartile range as appropriate. Comparison was performed using Mann-Whitney test or performed using Kruskal-Wallis and Dunn multiple comparison post-test. Categorical data was analyzed using Chi square test. Correlation analysis was performed using Spearman non-parametric tests. All analyses were performed using GraphPad Prism v5.

Ethics

This study was performed according to Helsinki declaration and approved by the local ethics committee CEC MED-UC (project ID: 200608006) of the Pontificia Universidad Católica de Chile.

Results

General characteristics of the patients

We included 241 (21.1%) children with a media of 9.6 ± 2.3 years of age, 60.2% of females and 900 adults (78.9%) with a media age 49.2 ± 15.5 years. General characteristics such as age, sex, height, weight, and BMI are described in Table 1.

Medical prescription for UBT-13C

We determined the reason for UBT-13C prescription in a 1,000 of the analyzed patients. In 773 (77.3%) patients UBT-13C test was performed to confirm bacterial eradication after antibiotic treatment. Two hundred and fifteen (27.8%) patients remained infected after treatment. In 227 (22.7%) patients UBT-13C was performed to diagnose the infection with 101 (44.5%) patients infected by *H. pylori*. Interestingly, all patients that received treatment and effectively eradicated the bacteria showed UBT-13C titers similarly to the titers observed by non-infected patients referred to UBT-13C for diagnosis (Table 2).

H. pylori infection status

One hundred (41.5%) of children and 254 (28.2%) of adults were infected by *H. pylori* (p = 0.001; OR 1.8; 95%IC: 1.3-2.4). Out of the 687 women, 213 (31%) and 141 (31%) of the 454 men, included in this study were positive for the infection. (Table 3). We then analyzed sociodemographic characteristics depending on medical

Table 1. Sociodemographic characteristics of the patients included in this study

	Children (< 18 years)	Adults (≥ 18 years)	Total
N° patients (%)	241 (21.1)	900 (78.9)	1141 (100)
Age, years (X + SD)	9.6 +2.3	49.2 + 15.5	40.8 + 21.2
Sex, N° (%)			
- Female	145 (60.2)	542 (60.2)	687 (60.2)
- Male	96 (39.8)	358 (39.8)	454 (39.8)
Weight, kg* (X + SD)	40.9 + 13.1	70.2 + 12.5	67.4 + 15.2
Height, cm* (X + SD)	141.2 + 16	163.1 + 18.1	161 + 19
BMI, kg/m2* (X + SD)	20.1 + 3.5	25.8 + 3.9	25.3 + 4.2

*Nutritional assessment was performed in a total of 79 pediatric patients and 761 adult patients.

Table 2. Delta value according to medical prescription of the UBT-[13]C[&]

Medical prescription for UBT N (%)	Delta Value Non-infected 686 (76.7) **	Delta Value *H. pylori*-infected 316 (32.3) **
Diagnostic 227 (22.7) **	0.6 ± 0.5 (0- 3.5)* 126 (12.6; 55.5)**	27.1+40.3 (4-170)* 101 (10.1; 44.5)**
Eradication 773 (77.3) **	0.6 ± 0.6 (0- 3.9)* 558 (55.8; 72.2)**	35.2 ± 50.7 (4- 170)* 215 (21.5; 27.8)**

[&]Medical prescription of the test was only available for 1000 patients; *Data are presented as media ± SD (range). **N (% of total patients; % of medical prescription).

prescription for UBT-[13]C. For patients that used UBT-^{13}C for diagnosis, 46 (57.5 %) of children and 55 (37.4 %) of adults were infected by *H. pylori* (p = 0.03; OR 1.6; 95%IC: 1.05-2.5). Out of the 130 women, 51 (39.2%) and 50 (51.5%) of the 97 men, included in this study were positive for the infection. For patients that used UBT-^{13}C for eradication confirmation, 41 (37.6 %) of children and 157 (27.1%) of adults were infected by *H. pylori* (p = 0.0001; OR 2.3; 95%IC: 1.3-3.9). Out of the 427 women, 124 (29%) and 74 (28.2%) of the 262 men, included in this study were positive for the infection (Table 3).

Demographic characteristics and UBT-^{13}C titers in infected patients.

Infected children showed lower delta UBT-^{13}C values than infected adults (16.1 ± 8.7‰ versus 37 ± 52.9‰ respectively, p = 0.07), (Figure 1A). In children the highest delta value reported was 39.9‰, while in adults the highest value was determined by the saturation limit of the infrared detector. Significantly higher titers for UBT-^{13}C were detected in the 61-70 and over 70 year-old group in comparison to the 11-20 year-old patients (66.9 ± 72.7‰ versus 12 ± 8.1‰, p < 0.05 and 62.4 ± 69.2‰ versus 12.8 ± 8.8‰, p < 0.05 respectively) (Figure 1B) and a significant correlation showing increased titers with age was found (Spearman r = 0.15, p = 0.002) (Figure 1C).

Although no significant differences were found between UBT- C[13] delta values in children and adults between sex (Figure 2A, B), in adults infected men showed in average higher values with more dispersion than (44.2 ± 60.5 versus 22.8 ± 30.5‰, respectively) women (Figure 2B).

Nutritional status in H. pylori infection

To determine BMI, we analyzed nutritional parameters in a total of 840 patients (79 children and 761 adults) available. For non-infected children 59.1% were normal, 22.7% were overweight and only 11.4 % were obese. When comparing to *H. pylori* infected children 25.7% were normal, 25.7%

Table 3. Sociodemographic variables according to *H. pylori* infection status

	H. pylori (-)	*H. pylori* (+)	Total
Total patients Age, p = 0.0001; OR 1.8; 95%IC: 1.3-2.4			
Children	141 (58.5)	100 (41.5)	241 (21.2)
Adults	646 (71.8)	254 (28.2)	900 (78.8)
Patients evaluated for Diagnosis* Age, p = 0.03; OR 1.6; 95%IC: 1.05-2.5			
Children	34 (42.5)	46 (57.5)	80 (35.2)
Adults	92 (62.6)	55 (37.4)	147 (64.8)
Patients evaluated for Eradication* Age, p = 0.0001; OR 2.3; 95%IC: 1.3-3.9			
Children	68 (62.4)	41 (37.6)	109 (15.8)
Adult	423 (72.9)	157 (27.1)	580 (84.2)
Total patients Sex, p = 0.98; OR 0.99; 95%IC: 0.77-1.3			
Female	474 (69)	213 (31)	687 (60.2)
Male	313 (69)	141 (31)	454 (39.8)
Patients evaluated for Diagnosis* Sex, p = 0.006; OR 0.6; 95%IC: 0.3-1			
Female	79 (60.8)	51 (39.2)	130 (57.3)
Male	47 (48.5)	50 (51.5)	97 (42.7)
Patients evaluated for Eradication* Sex, p = 0.8; OR 1; 95%IC: 0.4-1.5			
Female	303 (71)	124 (29)	427 (62)
Male	188 (71.8)	74 (28.2)	262 (38)

*Medical prescription of the test was only available for 1000 patients. Data presented N° (row %). Data were analyzed with chi square test.

overweight, and 42.9% were obese (p = 0.001) (Figure 3A). No significant differences were found in children regarding UBT- C[13] delta values when comparing different nutritional status (Figure 3B)

In adults no significant differences were found when comparing *H. pylori* status with nutritional assessment (Figure 3C), nonetheless UBT-^{13}C delta values were significantly higher between normal and overweight patients (28.9 ± 44.5‰ versus 60.1 ± 69.3‰ respectively (p < 0.05) (Figure 3D).

When comparing BMI for the different age groups between infected and non-infected patients, only infected children showed significantly increased BMI (19.4 + 3.3 versus 21 + 3.6; p = 0.02 respectively) (Figure 3E)

Finally, we analyzed if there was correlation between UBT-^{13}C delta values and BMI and showed a non-significant positive correlation between the two only in adults. (Spearman r = 0.1, p = 0.07) (Figure 3F).

Discussion

In this study, we analyzed the quantitative aspect of the UBT test and its association with *H. pylori* positivity, delta UBT-13C values with demographic and anthropometric determinations in referred patients. In Chile, reported prevalence for *H. pylori* in non-symptomatic population are 18.1%-20% in school aged children[11,20], and 72.9%-75% in adults[2,9,10] although different technical testing and timing of sampling might influence this difference. On the other hand, reported prevalence in symptomatic populations described in endoscopy based studies with consecutive patient recruitment show lower rates of infection varying 26%-60% of positivity depending on age status and location of the recruitment center[21-23]. In this study, we showed the percentage of *H. pylori* infection is higher in symptomatic children (41%) than in symptomatic adults (28%)

and also different to asymptomatic patients reports. In a separate cohort of 177 adult patients recruited in the same endoscopic center between the years 2019 and 2021, *H. pylori* positivity rates determined by rapid urease testing in endoscopic biopsies show a similar positivity rate (35% infection; data not shown) to the infection rate in our study (37.4% infection in adults referred for diagnosis testing) suggesting both test results are comparable and that the decrease in *H. pylori* infection rates in adults is a new phenomenon that warrants further investigation. Additionally, high levels of *H. pylori* positivity in symptomatic children by UBT-^{13}C suggest *H. pylori* testing might be performed in children with pronounced symptomatology increasing their probability to be infected by *H. pylori* in comparison to non-symptomatic population.

Regarding UBT-^{13}C titers, infected children showed in average lower delta UBT-^{13}C values with a lower maximum titer than infected adults, suggesting that endogenous production of CO_2 depends on the basal metabolism which is directly related with the weight and body surface area of the individual[24,25]. Since UBT-^{13}C determines the quantity of expired CO_2 it is expected that individuals with higher weight and height such as adults show increased delta titers. One interesting finding is that although the loss of ecological niche is predicted in adults that belong in the higher age groups, titers of UBT-^{13}C were the highest for this age group.

Alternatively, UBT-^{13}C titers might be associated with bacterial load. The association between bacterial load determined by *H. pylori* culture, histopathological quantification or qPCR from the biopsies and UBT has been analyzed by several research groups demonstrating a positive correlation between them[26-29]. Boltin conducted a study that showed the bacterial density of the patients was correlated with UBT-^{13}C titers with similar results described by several authors[27,31-33]. In our study, most patients came to confirm eradication. However, those uninfected patients who came for diagnosis of the infection, and who had never received treatment previously, obtained UBT-^{13}C delta values similar to those infected who achieved successful eradication after antibiotic treatment, suggesting that successful eradication is associated with levels of UBT-^{13}C similar to those subjects who were never infected.

Regarding sex and *H. pylori* infection Eisdorfer et al. and Perri et al found no association[25,30] between them. We only found significant differences between sexes when analyzing infection rates in patients referred to UBT-^{13}C for diagnosis and
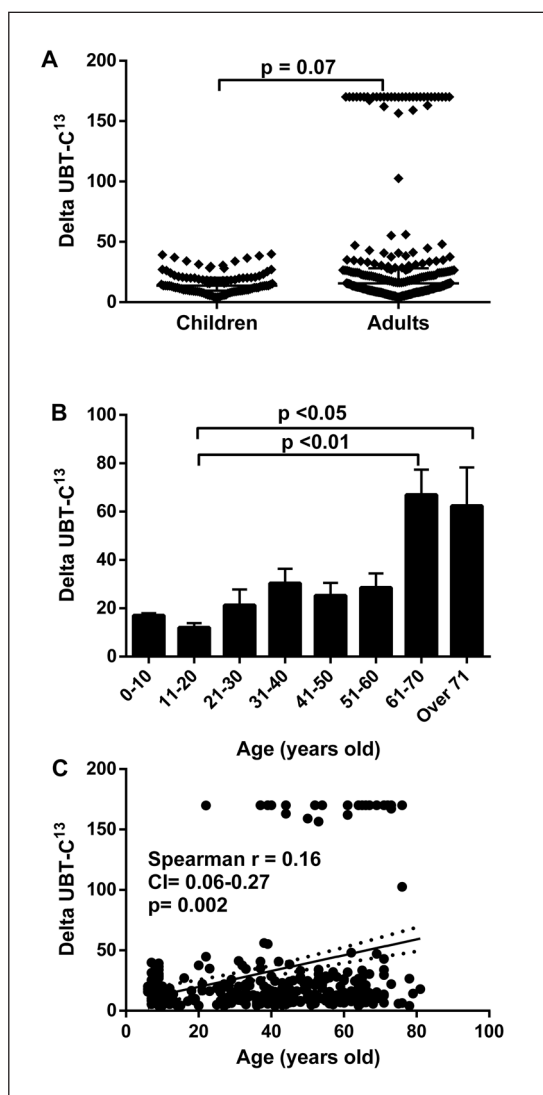

Figure 1. Delta UBT-^{13}C values according to age in *H. pylori* infected patients. **A)** UBT-^{13}C values in children and adults. Data are presented as individual patients plus median + IQR and were analyzed using Mann-Whitney test. **B)** UBT-^{13}C values in different age groups. Data are presented as mean + SEM and were analyzed using Kruskal-Wallis test with Dunn´s multiple comparison test. **C)** Correlation between UBT-^{13}C delta values and age in *H. pylori* infected patients. Spearman correlation coefficient was used for analysis.
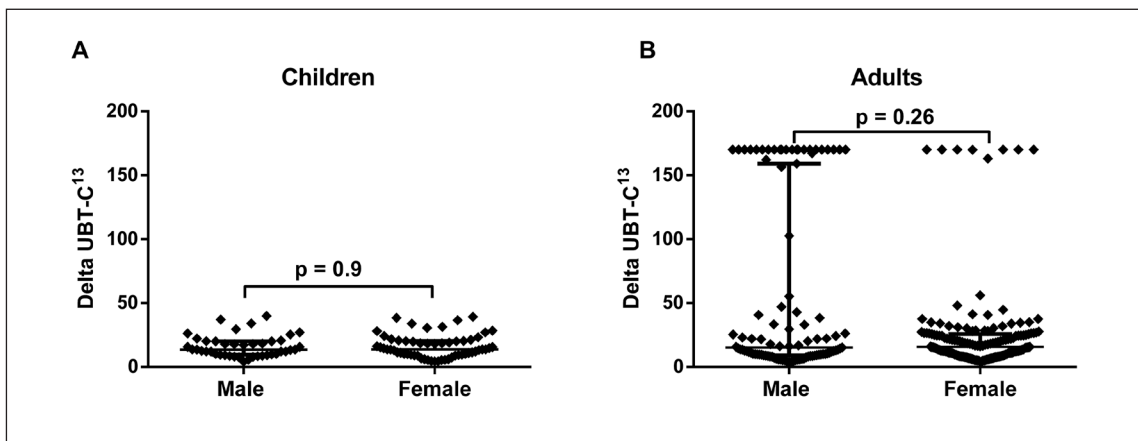
Figure 2. Delta UBT-^{13}C values according to sex in *H. pylori* infected patients. **A)** UBT-^{13}C values in according to sex in children. Data are presented as individual patients plus median + IQR and were analyzed using Mann-Whitney test. **B)** UBT-^{13}C values in according to sex in adults. Data are presented as individual patients plus median + IQR and were analyzed using Mann-Whitney test.
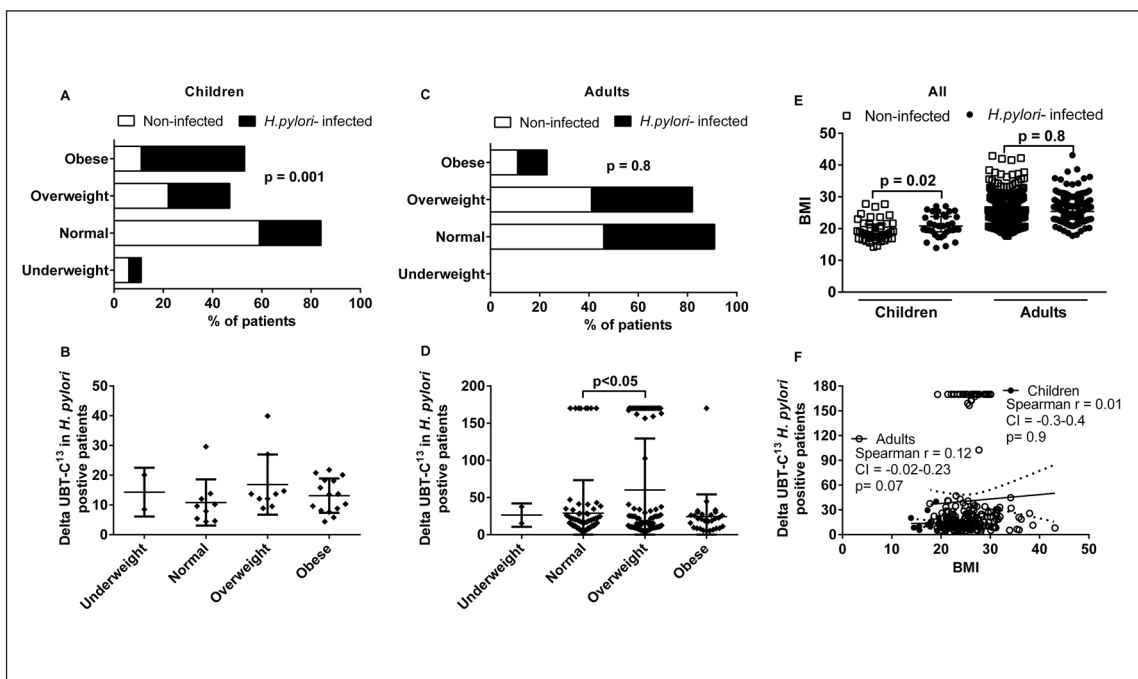

Figure 3. *H. pylori* infection and nutritional status. **A**) Percentage of patients according to *H. pylori* status and nutritional assessment in children. Data are presented as percentage of patients and were analyzed using Chi-square test. **B**) Delta UBT-^{13}C values and nutritional assessment in *H. pylori* infected children. Dara are presented as individual patients plus median + IQR and were analyzed using Kruskal-Wallis test with Dunn´s multiple comparison test. **C**) Percentage of patients according to *H. pylori* status and nutritional assessment in adults. Data are presented as percentage of patients and were analyzed using Chi-square test. **D**) Delta UBT-^{13}C values and nutritional assessment in *H. pylori* infected adults. Data are presented as individual patients plus median + IQR and were analyzed using Kruscal-Wallis test with Dunn´s multiple comparison test. **E**) BMI values according to *H. pylori* infection status. Data are presented as individual patients plus median + IQR and were analyzed using Mann-Whitney test. **F**) Correlation between UBT-^{13}C delta values in *H. pylori* infected patients with BMI in different age groups. Spearman correlation coefficient was used for analysis.

not for eradication. A significant rate of infection was shown in males as previously reported for asymptomatic adults in our country[9]. De Martel et al in 2006[34], showed in a meta-analysis, a higher prevalence of infection in male adults (16% higher than female adults). However, in children no significant differences were found between both sexes. When comparing UBT-^{13}C delta values no differences were found between sexes. In contrast to our results, Eisdorfer et al., found that the average UBT- C[13] value was significantly higher in women than in men.

In this study, we show overweight infected adults had higher delta UBT-^{13}C values than infected normal weight adults. However, there are no differences in relation to the number of infected and uninfected overweight patients suggesting that although overweight patients have higher delta values than normal weight patients, being overweight is not a factor that determines a greater probability of being infected. In addition, there were no differences in BMI according to *H. pylori* status, but we found a positive non-significant correlation between BMI and UBT-^{13}C titers suggesting adult patients with high BMI may have increased basal metabolism that account for these differences. Report between the relationship for BMI in *H. pylori* infection in adults are varied with mixed results. Suki et al, and Xu et al both reported the infection associated with higher risks of obesity or higher values of BMI, but several other studies report contradictory results. These studies were performed all around the globe suggesting that local factors might contribute to the issue.

In children, this study also showed less malnutrition due to excess than reported nationwide in children of the same age, which in 2019 reached 52.9% (30.1% overweight and 27.4% obese)[35]. Significant differences were observed between nutritional status and *H. pylori*. 68.6% of infected children presented malnutrition due to excess (25.7% overweight and 42.9% obesity respectively). Although we did not find increased levels of UBT-^{13}C levels by nutritional status as in adults nor any correlation between BMI and UBT-^{13}C suggesting children regardless of weight do not increase UBT-^{13}C titers and that these titers relate more with the infection than with basal metabolism. Two previous studies in children showed an inverse relationship between *H. pylori* colonization and overweight or obesity among symptomatic children or no relationship at all suggesting again a great variation between the studies[36,37].

In conclusion, higher values of delta UBT-^{13}C were observed in adults, males and overweight children. These results can be explained from the higher CO_2 production by basal metabolism that depends on weight and height, higher bacterial density, changes in gastric pH or several unknown local factors suggesting further studies that will incorporate histology, microbiological techniques for bacterial quantification, and clinical variables that can better explain the physiological basis of these findings are required.

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