Eradication of Helicobacter pylori increases childhood growth and serum acylated ghrelin levels

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Abstract

AIM: To determine whether Helicobacter pylori (H. pylori)-infected children have reduced body weight (BW) and height (BH) growth, and if H. pylori eradication may restore growth while improving serum acylated ghrelin.

METHODS: This longitudinal cohort study with one-year follow-up enrolled 1222 children aged 4 to 12 years old into an observation cohort (18 with and 318 without H. pylori) and intervention cohort (75 with and 811 without). The 7-d triple therapy was used for eradication in the intervention cohort. The net increases of BW and BH as well as serum acylated ghrelin after one-year follow-up were compared between successful eradicated H. pylori-infected children and controls.

RESULTS: In the observation cohort, the H. pylori-infected children had lower z score of BW (-1.11 ± 0.47 vs 0.35 ± 0.69, P = 0.01) and body mass index (BMI) (0.06 ± 0.45 vs 0.44 ± 0.73, P = 0.02) at enrollment and lower net BW gain after one-year follow-up (3.3 ± 2.1 kg vs 4.5 ± 2.4 kg, P = 0.04) than the non-infected controls. In the intervention cohort, the H. pylori-infected children had lower z score of BMI (0.25 ± 1.09 vs 0.68 ± 0.87, P = 0.009) and serum acylated ghrelin levels (41.8 ± 35.6 pg/mL vs 83.6 ± 24.2 pg/mL, P < 0.001) than the non-infected controls. In addition to restoring decreased serum ghrelin levels (87.7 ± 38.0 pg/mL vs 44.2 ± 39.0 pg/mL, P < 0.001), the H. pylori-infected children with successful eradication had higher net gains (P < 0.05) and increase of z scores (P < 0.05) of both BW and BH as compared with non-infected controls after one-year follow-up.

CONCLUSION: H. pylori-infected children are associated with low serum acylated ghrelin and growth retardation. Successful eradication of H. pylori restores ghrelin levels and increases growth in children.

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Key words: Child; Clinical trial; Ghrelin; Growth retardation; Helicobacter pylori

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**INTRODUCTION**

Primary infection with *Helicobacter pylori* (*H. pylori*) usually occurs during childhood[2,3]. This organism has been proven to cause chronic gastritis, peptic ulcer diseases, and has a high correlation with gastric cancer in humans[4-5]. In children, the *H. pylori* prevalence rate was relatively lower than adults[6,7]. Besides the link with gastric diseases, the association between *H. pylori* infection and growth retardation in children has raised clinical attention to this issue and caused some debate recently. Some cross-sectional analyses have indicated that *H. pylori*-infected children had subnormal growth retardation as compared with non-infected children[8-13], but some others did not support such findings[10,11]. Long-term observational studies have reported that children with persistent *H. pylori* infection have reduced body weight (BW) and height (BH) growth than the non-infected peers[9,10]. Therefore, to further support the causal relationship between *H. pylori* infection and growth retardation in children, interventional trials involving *H. pylori* eradication may provide new insights using a rigorous study design.

Ghrelin, a growth-hormone-releasing peptide biosynthesized mainly in the fundic mucosa, regulates appetite and body composition and is affected by inflammatory and atrophic events associated with *H. pylori* infection[14,15]. Previous studies showed conflicting results regarding the correlation between plasma ghrelin levels and *H. pylori* infection after eradication of bacteria[16-19]. This controversy may be caused by the measurement of total plasma ghrelin, which contains both acylated and desacylated forms. Acylated ghrelin is a more potent agonist on the growth-hormone-stimulating receptor than the desacylated form and undergoes a compensatory elevation in patients with chronic atrophic gastritis[19,20]. This study seeks to examine active ghrelin levels and its relationship with growth in patients before and after *H. pylori* eradication.

Although eradication of *H. pylori* can restore body mass index (BMI) and serum albumin in adult patients with infection[21,22], such improvement has not yet been documented in *H. pylori*-infected children. Moreover, it is unclear whether the improving growth parameters after *H. pylori* eradication are subsequently linked to increase serum acylated ghrelin levels. Therefore, this study sought to examine whether *H. pylori* eradication improves BW and BH growth in children in parallel with increases in serum acylated ghrelin levels.

**MATERIALS AND METHODS**

**Subject enrollments in the two cohorts**

This study enrolled 1292 students, aged 4 to 12 years old from three elementary schools and their associated pre-school kindergartens in Tainan City, Taiwan. The participants were consecutively enrolled into two study cohorts. Each participant provided informed consent documentation that was signed by her/his parents.

The first cohort (observation cohort) enrolled 400 children in 2005 to screen for the *H. pylori* infection, and they were then scheduled to return for follow-up growth status by a half-year interval of up to one year. The second group was an interventional cohort which enrolled 892 children in 2006 to screen for the *H. pylori* infection. Moreover, the *H. pylori*-infected subjects were invited to receive one-week of triple therapy for *H. pylori* eradication. As well, the children in the 2nd cohort were scheduled to return for follow-up growth status by a half-year interval of up to one year.

In each cohort, both the enrolled children and their parents were reviewed with a questionnaire to record data on underlying medical diseases, *H. pylori* infection status, and a range of demographic variables, including socioeconomic status, such as number of family members[23], and annual household income (low income indicated less than $15,000 US/year). The same nursing assistant provided the introduction of questionnaire to the enrolled subjects. Children with pre-established and severe medical/organic conditions predisposing to the failure of thrive, such as genetic/metabolic disorders and cyanotic congenital heart diseases, were not included. The study also excluded children with a known past history to receive anti-*H. pylori* therapy and children underwent eradication therapy or acid suppressors, during the follow-up period in the observation group. In both groups, the control cases were randomly selected (1:4 in the observation and 1:3 in the interventional cohorts) and were matched by age and gender to children with 13C-labeled urea breath test (13C-UBT)-confirmed *H. pylori* infection. Moreover, for the *H. pylori*-infected (confirmed by a positive 13C-UBT) children at entry, the *H. pylori* status was assessed with a 13C-UBT after 6 mo (intervention cohort) and one year follow-up (both cohort).

**BMI and z scores of weight, height and BMI**

For each participant, the overnight fasting BW and BH were serially measured at enrollment and at the follow-up period on the 6th mo and the 12th mo, respectively. The BMI was defined as BW in kilograms/squared of body length in meter (kg/m^2^). The z scores (SD scores) of BW, BH and BMI were calculated using the reference population of 2003 Taiwanese boys and girls based on health-related physical fitness and based on 2006 World Health Organization standards[24]. The net changes of BW, BH and BMI were calculated by the value of each parameter at follow-up minus the corresponding value at enrollment. We also defined the increase of z score means that z scores of BW, BH and BMI were upgrade at the one-year follow-up than at the enrollment (the net change > 0).

**Serological screening of *H. pylori* infection and confirmation by urea breath test**

In each enrolled child, the serum was tested for anti-*H. pylori*...
IgG antibodies (HEL-p TEST™ II, AMRAD Biotech, Australia) by enzyme-linked immunosorbent assay (ELISA) methods. The serologic kit has been validated with a favorable sensitivity and specificity (> 90%) in detecting *H. pylori* infection in our previous studies[8,26]. The seropositive children further confirmed by 13C-UBT to diagnose ongoing *H. pylori* infection[13]. The cut-off value of positive 13C-UBT was defined as excess 13CO2/12CO2 ratio more than 3.5‰[9,20].

**Eradication therapy for *H. pylori*-infected children**

For the *H. pylori*-infected children in the intervention cohort, lansoprazole (1 mg/kg per day, max. 30 mg bid), amoxicillin (50 mg/kg per day, max. 1 g bid), and clarithromycin (15 mg/kg per day, max. 500 mg bid) were prescribed for one week[26]. We have educated the participants and their parents for the compliance and report of complications. Successful eradication therapy was defined by a negative result of 13C-UBT on both the 6th and the 12th mo follow-up, respectively[7].

**Serial serum acylated ghrelin levels before and after *H. pylori* eradication**

The serum acylated ghrelin levels of the interventional cohorts at enrollment were compared between children with and without *H. pylori* infection. In addition, the serial serum acylated ghrelin levels of the children with *H. pylori* eradication collected at enrollment, the 6th mo, and the 12th mo follow-up were compared. Each blood sample of child was collected in the morning before breakfast and was incubated in the ice-bath container immediately. The sera were separated by centrifugation within 2-3 h and were stored in a -80 °C refrigerator until use. These samples’ serum acylated ghrelin levels were analyzed in duplicate by a commercial kit (LINCO Research, St. Charles, Missouri, United States), using ELISA methods.

**Statistical analysis**

The χ2 test with the odds ratio (OR) and 95% confidence interval (CI) and logistic regression test were applied as an estimate of the possibly related factors between *H. pylori*-infected and non-infected children. The Student’s *t* test and one-way analysis of variance with least significant difference test correction were used as appropriate to compare the differences of ghrelin, BW, BH, BMI and their net changes during one-year follow-up periods among different study groups. The paired *t* test was used to analyze the difference of the serial serum acylated ghrelin levels before and after eradication therapy within the same study group. A *P* value less than 0.05 was considered statistically significant.

**RESULTS**

**Participants and *H. pylori* infection**

There were 84% (336/400) children in the observation and 99% (886/892) children in the intervention cohorts who completed the questionnaires and provided their sera for the anti-*H. pylori* IgG antibodies tested, respectively. In Figure 1, the case numbers of each cohort were serially summarized during the one-year follow-up. One hundred and twenty-one (27 in the observation cohort, 94 in the intervention cohort) were defined with seropositive of *H. pylori* infection. Among them, 113 children received 13C-UBT, of which only 93 (82%) children were positive (18 in the observation cohort and 75 in the intervention cohort). Accordingly, the overall *H. pylori* prevalence was 7.6% in these two cohorts.

For the 18 *H. pylori*-positive children in the observation cohort, the infection was persisted with a positive 13C-UBT until the end of follow-up on the 1st year. Among the 75 *H. pylori*-infected children in the intervention cohort, 57 children were enrolled to receive the 7-d eradica-
Low income: Indicated < $15000 US/year. Increase of z score means that z scores of body weight, height and body mass index (BMI) were upgrade at the one-year follow-up than at the enrollment (the net change > 0). The difference of the body weight, height, BMI and ghrelin level among the three groups were analyzed by oneway analysis of variance model with least significant difference correction. The difference of the up-shift of the z scores of body weight, height and BMI were analyzed by χ² test. *P < 0.05 between H. pylori-positive subjects with eradication failure and controls, **P < 0.05 between H. pylori-positive subjects with eradication success and controls.

Low income: Indicated < $15000 US/year. Increase of z score means that z scores of body weight, height and body mass index (BMI) were upgrade at the one-year follow-up than at the enrollment (the net change > 0). The difference of the body weight, height, BMI and ghrelin level among the three groups were analyzed by oneway analysis of variance model with least significant difference correction. The difference of the up-shift of the z scores of body weight, height and BMI were analyzed by χ² test. *P < 0.05 between H. pylori-positive subjects with eradication failure and controls, **P < 0.05 between H. pylori-positive subjects with eradication success and controls.
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**Figure 2** Comparison of the serum acylated ghrelin levels (mean) at enrollment, at 6 mo and at 12th mo follow-ups between the two groups of *Helicobacter pylori*-infected children with success (A) and with failure (B) of eradication therapy. The significance was analyzed by paired t-test.

Despite the current study should have not encountered a significant bias of social backgrounds on growth limitations [29]. Other studies have argued that lower socioeconomic status is conjunction with the presence of *H. pylori* accounts for poor growth in children [29]. For overcoming the influencing bias of poor socioeconomic status, indicated by low income, to child growth, multiple logistic regression confirmed that *H. pylori* infection was closely related to both z scores of BW and BMI independent to socioeconomic status. Accordingly, the current study should have not encountered significant bias of social backgrounds on growth limitation in children.

Based on the data of the observation cohort, the *H. pylori*...
Figure 3

*H. pylori* infection in children causes not only gastric inflammation and peptic ulcer diseases but also extragastric disorder. Longitudinal observational have found that children with persistent *H. pylori* infection have reduced body weight (BW) and height (BH) growth than the non-infected children. Even though some *H. pylori*-infected children had a failure of triple therapy, there was still existed an increase of BW, BH, and serum acylated ghrelin levels at the 6th and the 12th mo. Triple therapy can decrease bacterial loads or gastric inflammation [15,33]. We have analyzed the 51 pairs of 13C-UBT and ghrelin levels (at enrollment, the 6th and 12th mo follow-up) in 17 children with a failure of triple therapy. The result shows the bacterial loads, indicated by the values of 13C-UBT are not correlated well to the ghrelin levels ($r^2 = 0.03, P = 0.25$). Therefore, it is possibly due to transient improvement of gastric inflammation to restore serum acylated ghrelin levels. Lack of endoscopic evidence in children with failure of therapy is the limitation in this study. A longer follow-up period is thus needed to clarify this transient improving effect in children with failure of therapy.

In summary, *H. pylori* infection can be associated with decreased serum acylated ghrelin levels, BW and BH in children. Successful *H. pylori* eradication can restore ghrelin levels and the growth of BW and BH in the infected children with growth retardation.

### COMMENTS

**Background**

*Helicobacter pylori* (*H. pylori*) infection in children causes not only gastric inflammation and peptic ulcer diseases but also extragastric disorder. Longitudinal observational have found that children with persistent *H. pylori* infection have reduced body weight (BW) and height (BH) growth than the non-infected

| Table 3 | The differences of the baseline serum acylated ghrelin levels between the children with body weight above and below the cut-off point selected based on the different age ranges of children (mean ± SD) |
|---------|------------------------------------------------------------------------------------------------|
| Age ranges (yr) | H. pylori infection | Non-H. pylori infection |
| 4-7 | 8-12 | 4-7 | 8-12 |
| BW cut-off point, kg (n) | 26 (31) | 26 (32) | 26 (47) | 26 (67) |
| Baseline serum acylated ghrelin (pg/mL) | 51.3 ± 40.9 | 51.8 ± 40.9 | 78.2 ± 12.0 | 85.9 ± 26.9 |
| Above or equal to the BW cut-off point | 47.8 ± 36.5 | 23.8 ± 22.1 | 82.5 ± 17.2 | 83.8 ± 31.2 |
| 1P value | 0.93 | 0.02 | 0.31 | 0.78 |
| z score of BW cut-off point (n) | 0.5 (18) | 0.5 (35) | 0.5 (28) | 0.5 (106) |
| Baseline serum acylated ghrelin (pg/mL) | 53.4 ± 40.6 | 46.8 ± 38.9 | 81.3 ± 14.1 | 81.7 ± 19.7 |
| Above or equal to the z score of BW cut-off point | 45.9 ± 33.6 | 27.3 ± 26.5 | 81.9 ± 16.6 | 89.6 ± 36.4 |
| 1P value | 0.68 | 0.09 | 0.91 | 0.15 |

1The P value indicated the difference of serum acylated ghrelin levels between the children with body weight (BW) and z score of BW above or equal to the cut-off point and those with below the cut-off point within the same age ranges, analyzed by the Student’s t test. The BW (z score of BW) cut-off point was determined by the mean (median) of non-*Helicobacter pylori* (*H. pylori*) infected children within the same age ranges.
ones. In addition, previous studies showed conflicting results regarding the correlation between plasma ghrelin levels and H. pylori infection after eradication of bacteria. Therefore, long-term follow-up the childhood growth as well ghrelin levels in H. pylori-infected children after eradication therapy can illustrate the causal relationship between H. pylori infection and growth retardation in children.

Research frontiers

Growth retardation in H. pylori-infected children without any organic diseases remains controversial for eradication therapy. The authors aimed to establish a new indication for treating H. pylori infection in children with growth retardation and to explore the serum acylated ghrelin levels correlated to eradication therapy.

Innovations and breakthroughs

This study demonstrated that H. pylori infection can be associated with decreased serum acylated ghrelin levels, BW and BH in children. In the intervention study, successful H. pylori eradication can restore serum acylated ghrelin levels and the growth of BW and BH in the infected children with growth retardation at the 1-year follow-up.

Applications

This study confirmed the causal relationship of H. pylori infection and childhood growth retardation. Therefore, we supposed that eradication therapy should be considered as a treatment strategy in H. pylori-infected children with growth retardation, which was not related to other organic diseases.

Terminology

Growth retardation is indicated by poor BW and BH growth as compared to the average and gender-matched normal population. Eradication therapy means that a treatment strategy to eradicate H. pylori from stomach. The first-line regimen consists of one proton pump inhibitor and two antibiotics.

Peer review

This is an interesting study aimed at determining whether H. pylori-infected children have reduced growth rates and lower levels of ghrelin compared to uninfected and if H. pylori eradication may reverse those changes. The study is well written and well designed.

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