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Original Research Article

Pepsinogen testing for evaluation of the success of *Helicobacter pylori* eradication at 4 weeks after completion of therapy

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ABSTRACT

Background and objective: Pepsinogen levels in plasma are increased by inflammation in the gastric mucosa, including inflammation resulting from *Helicobacter pylori* infection. A decrease in pepsinogen II level has been suggested as a reliable marker to confirm the successful eradication of infection. The aim of our study was to evaluate the potential role of pepsinogens I and II, gastrin-17 and *H. pylori* antibodies in confirming successful eradication.

Material and methods: Altogether 42 patients (25 women, 17 men), mean age 45 years (range 23–74), were enrolled. Pepsinogens I and II, gastrin-17 and *H. pylori* IgG antibodies were measured in plasma samples using an ELISA test (Biohit, Oyj., Finland) before the eradication and 4 weeks after completing the treatment. The success of eradication was determined by a urea breath test.

Results: Eradication was successful in 31 patients (74%) and unsuccessful in 11 patients (26%). Pepsinogen II decreased significantly in both the successful ($P = 0.029$) and unsuccessful ($P = 0.042$) eradication groups. Pepsinogen I decreased significantly in the successful ($P = 0.025$) but not the unsuccessful ($P = 0.29$) eradication group. The pepsinogen I/II ratio increased in the successful eradication group ($P = 0.0018$) but not in the group in which treatment failed ($P = 0.12$). There were no differences in gastrin-17 or *H. pylori* antibody values.

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Conclusions: A decrease in pepsinogen II levels cannot be used as a reliable marker for the successful eradication of *H. pylori* 4 weeks after the completion of treatment. The increase in pepsinogen I/II ratio reflects differences in pepsinogen production following the eradication irrespective of improvement in atrophy.

1. Introduction

The accuracy of diagnostic tests for *Helicobacter pylori* (*H. pylori*) is influenced by various conditions including the use of acidity-lowering agents and antibiotics, so the recommended tests for initial detection of the microorganism differ from the follow-up tests to confirm the success of eradication therapy. The ^{13}C urea-breath test (UBT) and laboratory-based monoclonal stool antigen test are considered the non-invasive tests of choice for follow-up [1]. According to Maastricht-IV recommendations, the time for testing the success of *H. pylori* eradication after the end of treatment should be at least 4 weeks and PPI should be stopped for 2 weeks before testing [1].

Although follow-up testing to evaluate the success of eradication is recommended, these recommendations are quite often not followed in routine practice [2]; one reason for this could be the unavailability of the tests in particular locations. Therefore new non-invasive tests to confirm the success of eradication would be useful.

Earlier research suggested the detection of *H. pylori* antibody in serum/plasma for judging the success of eradication [3–5], but in a large proportion of patients the antibody levels remain high for a substantial period even after successful eradication [6,7]. In addition, simple comparison between the initial and follow-up sample results may be not reliable owing to daily variations in the results if comprehensive methods to quantify the antibody are not used or the samples are not run in pairs. Therefore, the existing guidelines do not recommend serology tests for follow-up [1].

Most of the diagnostic tests for *H. pylori* (UBT, stool antigen test, biopsy-based tests) are dependent on the density of the microorganisms in the stomach mucosa, so a decrease in that density following therapy with antibiotics and/or proton pump inhibitors could lead to a false-negative result [2,8]. Therefore, a test independent of the density of *H. pylori* would be of particular interest. Pepsinogens (Pgs) are inactive pepsin precursors; the clinically relevant Pgs in humans are pepsinogen I (PgI) and pepsinogen II (PgII). PgI is synthesized by the chief cells and neck cells of the gastric corpus, while PgII is also synthesized in the cardiac, pyloric and Brunner gland cells in the proximal duodenum [9]. Active inflammation caused by *H. pylori* increases the blood levels of Pgs [10,11]. Atrophy of the corpus part is related to decreased PgI levels [11,12]; the ratio between PgI and PgII (PgI/PgII) is considered a better marker for corpus atrophy [13–15].

Gatta et al. recently suggested that the PgII level 8 weeks after eradication therapy is a reliable marker of successful eradication [9]. The cut-off value they used (22.7% decrease) resulted in 100% sensitivity and 96.6% specificity for detecting the success of eradication, while the other markers they evaluated (PgI, gastrin-17) did not give acceptable results. However, the authors acknowledged the need for additional studies to test their hypothesis that measuring the PgII level constitutes a method for determining whether eradication has been successful.

The objective of the present work was to evaluate changes in PgI, PgII and PgI/PgII as well as gastrin-17 (G-17) and *H. pylori* IgG antibody levels at 4 weeks after the completion of *H. pylori* eradication compared to the levels at baseline, and to evaluate the potential of these parameters as markers for the success of eradication.

2. Material and methods

Adult patients with upper gastrointestinal complaints referred for upper endoscopy were prospectively invited to participate in the study; patients having failed 1st line eradication therapy beforehand were excluded. Upper endoscopy was performed at the time of inclusion. Blood samples for detection of biomarkers were drawn prior to the endoscopy. Biopsy samples were taken during the initial endoscopy and analyzed according to the updated Sydney classification [16]. The presence of *H. pylori* was evaluated by histology at inclusion. All the slides were stained with hematoxylin and eosin as well as Giemsa (the latter was used to evaluate the presence or absence of *H. pylori* infection).

Standard eradication therapy was offered to *H. pylori*-infected individuals in whom this treatment was clinically indicated, consisting of lansoprazole (30 mg), clarithromycin (500 mg), amoxicillin (1000 mg), all BID for 7 days.

The success of eradication was determined by UBT 4 weeks after the completion of treatment; the use of proton pump inhibitors was not allowed during this period. Another blood sample for biomarker detection was withdrawn prior to the UBT. Only those patients who complied with the protocol were included in the analysis.

For the laboratory work-up, plasma samples were taken during a fasting state and before the follow-up UBT. The samples were frozen immediately and kept frozen at −80 °C pending tests. The initial and the follow-up plasma samples were tested at the same run and on the same test-plate. Biohit, Oyj. (Finland) reagents were used to test for PgI, PgII, G-17 and *H. pylori* IgG using the methods recommended by the manufacturer.

All patients gave a signed informed consent and the study was approved by the Ethics Committee of the Institute for

Experimental and Clinical Medicine, University of Latvia, Riga, Latvia.

Data were arranged and processed in tables using Microsoft Office Excel (Microsoft Corporation, Redmond, USA) and analyzed with R-project software (R Development Core Team, Austria, Vienna 2011). Frequency distributions were evaluated for the categorical variables (e.g., gender, age, diagnoses). Median values and the range of distribution were used to characterize categorical variables. The proportionality between the groups (e.g. gender, age, diagnosis) was analyzed by χ^2 tests with Mantel-Haenszel odds ratios used to test for independence between factors of interest. For comparative purposes a *t* test was applied. Summary statistics included point estimates and 95% confidence intervals (CI). The significance levels were set at $P < 0.05$.

3. Results

Altogether 42 patients (25 women; 59.5%/17 men; 40.5%), median age 45 years (range 23–74), were available for the study. Of these patients, 16 (38.1%) had peptic ulcers and 26 (61.9%) had functional dyspepsia; 15 patients (35.7%) reported symptoms of gastroesophageal reflux. Atrophy in the corpus (of any grade) was found in 5 cases (11.9%), atrophy in the antrum in 3 cases (0.7%), and 1 patient (0.2%) had atrophy in either corpus or antrum.

Compliance (self-reported) with the eradication therapy was 100%. All patients completed the therapy. On the basis of the UBT results, eradication was successful in 31/42 patients (74%) and unsuccessful in 11/42 patients (26%). The proportions of unsuccessful eradication were 41.2% in men and 16.0% in women; the sex difference did not reach statistical significance ($P = 0.09$).

One patient had a PgI/PgII below 3 (PgI/PgII = 1.2) at inclusion; this ratio increased to 3.6 following the eradication treatment even though the eradication was unsuccessful.

The biomarker test results and dynamics following eradication therapy are given in Table 1, with the data divided between the successful and unsuccessful eradication groups. The mean PgI value decreased by 28.8 μg/l (95% confidence interval [CI] 10.9–46.9; $P = 0.012$) or by 29.6% (Fig. 1). The mean decrease in PgII value was 5.2 μg/l (95% CI, 2.0–8.4; $P = 0.0042$) or 38.8% (Fig. 2). There was no significant difference in the magnitude of decrease between PgI and PgII ($P = 0.19$). The mean PgI/PgII increased from 9 to 12.4 or by 37.8% ($P < 0.001$) (Fig. 3); this increase was significant in the successful eradication group ($P = 0.0018$) but not in the treatment failure group ($P = 0.12$).

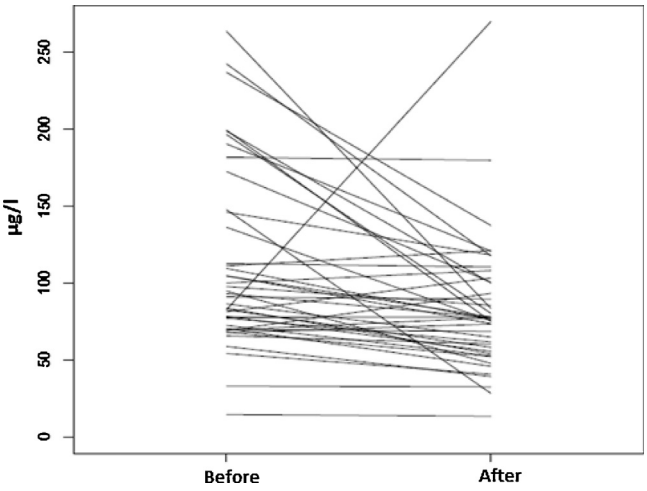

Fig. 1 – Pepsinogen I levels before and 30 days after *H. pylori* eradication completion in the total patient sample ($P = 0.012$).

No statistically significant difference was found between the successful eradication cases and the treatment failures in respect of the magnitude of decrease in PgI ($P = 0.96$) or PgII ($P = 0.91$), or the increase in PgI/PgII ($P = 0.49$). The initial (baseline) PgII values did not differ between the groups ($P = 0.92$) and the results in the two groups overlapped completely after the completion of therapy (Fig. 4).

Table 1 – Changes in mean biomarker levels before and 30 days after completing *H. pylori* therapy.

Biomarker	Mean before eradication	Mean after eradication	Change in units	95% CI	P
Pepsinogen I, μg/L, entire group	111.6	82.7	−28.9	−46.9; −10.9	0.012
Pepsinogen I, μg/L, eradication successful	112.3	81.6	−30.7	−54.2; −7.2	0.025
Pepsinogen I, μg/L, eradication unsuccessful	109.6	85.8	−23.7	−47.9; 0.5	0.29
Pepsinogen II, μg/L, entire group	13.4	8.2	−5.2	−8.4; −2.0	0.0042
Pepsinogen II, μg/L, eradication successful	13.4	8.3	−5	−9.1; −0.9	0.029
Pepsinogen II, μg/L, eradication unsuccessful	13.6	7.8	−5.8	−10.8; −0.8	0.041
PgI/PgII, entire group	9	12.4	3.4	2.3; 4.5	0.00041
PgI/PgII, eradication successful	9.1	12.7	3.6	2.2; 5.0	0.0018
PgI/PgII, eradication unsuccessful	8.8	11.5	2.7	0.6; 4.8	0.12
Gastrin-17, pmol/L, entire group	9.5	5.2	−4.3	−8.0; −0.6	0.11
Gastrin-17, pmol/L, eradication successful	7.8	4.8	−2.9	−7.4; 1.6	0.33
Gastrin-17, pmol/L, eradication unsuccessful	14.5	6.3	−8.2	−15.2; −1.2	0.18
Hp IgG ab, EIU, entire group	77.7	69.7	−8	−12.8; −3.2	0.079
Hp IgG ab, EIU, eradication successful	77.8	69.4	−8.4	−15.0; −1.8	0.11
Hp IgG ab, EIU, eradication unsuccessful	77.5	70.5	−7	−10.3; −3.7	0.47

PgI/PgII, pepsinogen I/pepsinogen II ratio; Hp IgG ab, IgG group antibodies to *H. pylori* infection; 95% CI, 95% confidence interval.

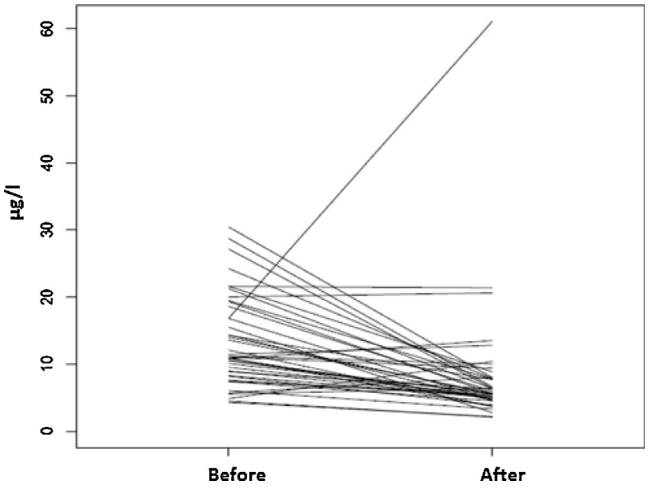

Fig. 2 – Pepsinogen II levels before and 30 days after *H. pylori* eradication completion in the total patient sample (*P* = 0.0042).

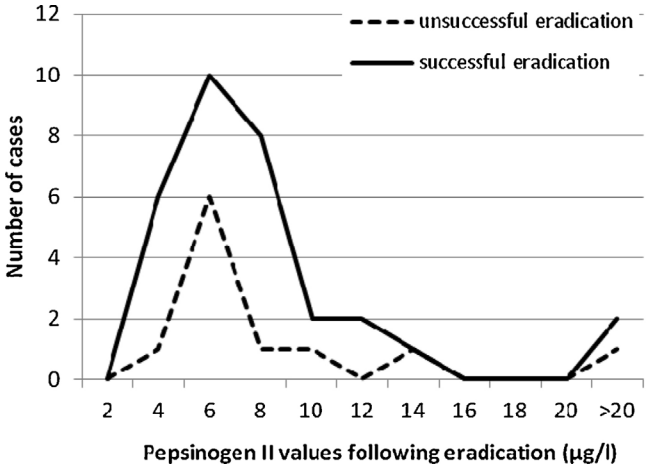

Fig. 4 – The distribution of pepsinogen II values following eradication.

In the patient group as a whole and in both subgroups, there were no statistically significant changes between baseline and the completion of treatment in G-17 level or in *H. pylori* IgG group antibodies.

In three patients all the biomarkers (PgI, PgII, G-17) increased but PgI/PgII decreased following the eradication treatment (see Table 2). According to the UBT results, the first two of these patients showed successful eradication but the third did not.

4. Discussion

Plasma pepsinogen levels are expected to decrease and remain low following successful eradication. On the contrary, the pepsinogens should remain stable or return to the baseline level after an initial drop if therapy is unsuccessful. This was demonstrated in a small group of patients by Chen et al. [17]. Further, it has been suggested that PgII could be an even better marker for this difference than PgI [9,18].

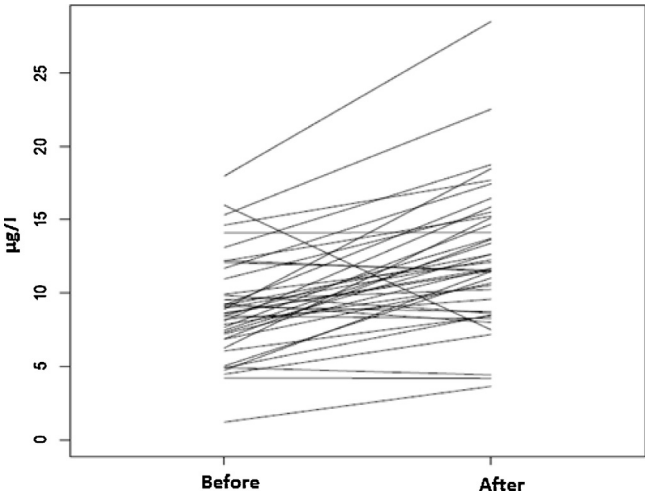

Fig. 3 – Pepsinogen I/II ratio before and 30 days after *H. pylori* eradication completion in the total patient sample (*P* = 0.00041).

The results obtained in our study clearly demonstrated that both PgI and PgII levels decreased at 4 weeks after eradication. However, a significant decrease in PgII was evident not only in the group in which eradication had been successful, but also among patients in whom treatment had failed (Table 1). The mean values for PgII before and after eradication were very close for both the groups with a successful eradication and treatment failure.

Gatta et al. [9] have reported encouraging results concerning the value of PgII measurements for distinguishing successful eradication cases from treatment failures at 8 weeks after treatment (100% sensitivity and 96.6% specificity for a 22.7% decrease in PgII). Lower accuracy has been reported by two other studies: 84.4% sensitivity and 73.3% specificity for a 15% decrease in PgII at 1 month [18] and 82% sensitivity and 62% specificity for a 25% decrease in PgII 28 days after the initiation of treatment [19]. The accuracy observed in the two latter studies would be insufficient to make the use of this parameter acceptable in clinical practice. However, our results

Table 2 – Biomarker test results in patients with increased values of all markers following eradication.

Patient characteristics	G-17 (pmol/L)	PgI (µg/L)	PgII (µg/L)	PgI/PgII
Patient 1 (successful eradication)				
Before	5.5	99.9	10.8	9.3
After	8.4	107.9	13.5	8.0
Patient 2 (successful eradication)				
Before	7.9	82.7	16.9	4.9
After	13.0	269.7	61.1	4.4
Patient 3 (unsuccessful eradication)				
Before	13.3	69.0	5.7	12.0
After	19.6	93.1	8.0	11.5

G-17, gastrin-17; PgI, pepsinogen I; PgI, pepsinogen II; PgI/PgII, pepsinogen I/pepsinogen II ratio.

fell below even that level and support the conclusions from the study by Al-Assi et al.: despite a significant fall in plasma pepsinogens, no marker tested could be used reliably to determine posttherapy *H. pylori* status for an individual patient [20], at least 1 month following eradication therapy.

The discrepancy of the results could be possibly explained by the time period after eradication therapy. In the study by Gatta et al. PgII decrease was observed 8 weeks after treatment. The other studies (including the present study) have investigated the patients 1 month after eradication treatment or after the initiation of treatment.

At the same time, there are data in the literature suggesting that a 4-week interval following eradication therapy could be long enough for control [21]. A study in Japan demonstrated that both PgI and PgII levels remained higher than in the *H. pylori* negative control group at 1 month following eradication, while 2 months after eradication and thereafter the levels became similar to the cases in which *H. pylori* was initially negative [22]. This was confirmed by the study of Kawai et al., where similar PgI/PgII levels were found 2 months after eradication and were comparable at 12 and 24 months after the treatment [23].

Further, no significant difference between these two groups (with a successful eradication and treatment failure) in the extent of decrease in PgI and PgII levels in our study could be due to a decrease of the density of *H. pylori* in the stomach mucosa irrespective of the final outcome of eradication. Decreased density of bacteria could be associated with a lower activity of inflammation and further resulting in decrease of pepsinogen levels [23,24].

In the follow-up test, the PgI/PgII ratio showed an increase. This could be because the PgII levels fell more rapidly than PgI, but this possibility could not be demonstrated owing to the relatively small sample size. A more rapid decrease in PgII than PgI at 1 month following eradication has also been reported by Ohkusa et al. [22].

PgI/PgII is a widely accepted marker for atrophy, and the increase in the ratio is considered to be an indicator of improvement of atrophic changes in the gastric mucosa [15]. Kawai et al. reported a strong correlation between PgI/PgII and atrophy both prior to eradication and shortly thereafter [23]. The results of the present study suggest that the increase in PgI/PgII following eradication therapy could be more pronounced (37.8% in the total group, 39.6% in the group with successful eradication) than the improvement of atrophy. We have evaluated the dynamics of PgI/PgII over a 5-week interval, too brief for any improvement in atrophic changes as a result of mucosal recovery to be expected [25–27]. The results indicate that the value of PgI/PgII for evaluating the disappearance of atrophy could be controversial if serial evaluations are not done (e.g. 1 month after the eradication and further tests after longer periods).

Few studies have demonstrated a decrease in PgI following eradication in duodenal ulcer patients [17,18,24]. Chen et al. [17] have reported a simultaneous decrease in total gastrin starting from 1.5 months, but Perez-Paramo et al. Have demonstrated a similar decline in successfully eradicated cases 1 month after treatment [18]. Pimanov et al. [24] have found decreased levels of G-17 in these patients one year after eradication. Our results failed to demonstrate a similar decrease in G-17 at 1 month after eradication. However, only a minority of our patients suffered peptic ulcer disease. Duodenal ulcer patients mainly present with antrum-predominant gastritis, and therefore this study group could differ from those without this type of ulcer [18].

The limitation of our study is the relatively small group of patients, however this was sufficient to reveal the biomarker test dynamics at the given time interval (4 weeks after the completion of the eradication).

5. Conclusions

The decrease in PgII may not be used as a reliable marker for determining the success of *H. pylori* eradication at 4 weeks after completion of therapy due to close values of the biomarker in patients with a successful eradication and treatment failure.

To evaluate the improvement in atrophy the PgI/PgII ratio should be measured at several time-points following eradication to avoid the bias potentially caused by the effect of treatment on inflammation.

Conflict of interest

The authors state no conflict of interest.

Acknowledgments

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