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Relationship between *Helicobacter pylori* status and serum pepsinogens as serologic markers in atrophic gastritis

Atrofik Gastritte serolojik bir gösterge olarak serum pepsinojenleri ile *Helicobacter pylori* arasındaki ilişki

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Background/aims: *Serum pepsinogen levels are considered as a non-endoscopic blood test in the diagnosis of atrophic gastritis. The objective of the present study was to investigate whether there is any difference between pepsinogen levels in Helicobacter pylori-positive and -negative patients with atrophic gastritis, and to analyze the relationship between histopathology and pepsinogen levels after treatment in H. pylori-positive patients with atrophic gastritis.* ***Methods:*** *The study enrolled a total of 30 cases with atrophic gastritis (18 H. pylori-positive and 12 H. pylori-negative). The H. pylori-positive cases received a one-week eradication treatment. Initially for all and after the treatment for H. pylori-positive cases, serum pepsinogen I and II levels, anti-H. pylori IgG titration and histopathologic analysis were carried out.* ***Results:*** *In the H. pylori-positive patients with atrophic gastritis, the levels of pepsinogen I and pepsinogen I/II ratio were lower while the levels of pepsinogen II were higher compared to the H. pylori-negative patients ($p<0.05$ for all). The post-treatment serum pepsinogen I levels and pepsinogen I/II ratios did not change in the H. pylori-positive group, while the levels of pepsinogen II, H. pylori antibody titration and gastric atrophy degree remarkably decreased ($p<0.05$ for all).* ***Conclusions:*** *In atrophic gastritis, the levels of serum pepsinogen and pepsinogen I/II ratio show a difference in H. pylori-negative versus –positive cases. Additionally, the usage of pepsinogen II as a serum marker in predicting the eradication of H. pylori with atrophic gastritis could be more reliable than pepsinogen I or the I/II ratio.*

Key words: Pepsinogen, atrophic gastritis, *Helicobacter pylori*, eradication, serology

Amaç: *Serum pepsinojen düzeyleri atrofik gastrit tanısında non-endoskopik bir kan testi olarak kabul edilmektedir. Bu çalışmada Helicobacter pylori pozitif ve negatif atrofik gastritlilerde pepsinojen düzeylerinde fark olup olmadığını ve Helikobacter pylori pozitif atrofik gastritlilerde tedavi sonrası histopatoloji ile pepsinojen düzeyleri arasındaki ilişkiyi incelemek amaçlanmıştır.* ***Yöntem:*** *On sekizi Helicobacter pylori pozitif ve 12'si negatif toplam 30 atrofik gastritli olgu çalışmaya alındı. Helicobacter pylori pozitif olgular 1 haftalık eradikasyon tedavisi aldılar. Inisyal tüm olgularda ve Helicobacter pylori pozitiflerde tedavi sonu 6.ayda serum pepsinojen I ve II düzeyi, anti- Helicobacter pylori IgG titrasyonu ve endoskopik biopsilerde histopatolojik inceleme yapıldı.* ***Bulgular:*** *Helicobacter pylori pozitif atrofik gastritlilerde pepsinojen I düzeyleri ve pepsinojen I/II oranı Helicobacter pylori negatiflere göre daha düşük iken serum pepsinojen II düzeyleri daha yüksekti ($p<0.05$, tümü için). Helicobacter pylori pozitiflerde tedavi sonrası serum pepsinojen I düzeyleri ve I/II oranları değişmediği halde serum pepsinojen II düzeyleri, Helicobacter pylori antikor titrasyonları ve atrofik gastrit düzeyleri belirgin olarak azaldı ($p<0.05$, tümü için).* ***Sonuç:*** *Atrofik gastritte, serum pepsinojen düzeyleri ve pepsinojen I/II oranı Helicobacter pylori negatiflerde pozitiflerden farklıdır. Ek olarak, atrofik gastritlilerde helicobacter pylori eradikasyonunu belirlemede bir serum göstergesi olarak pepsinjen II düzeylerinin kullanımı pepsinojen I ve pepsinojen I/II oranına göre daha uygun olabilir.*

Anahtar kelimeler: Pepsinojen, atrofik gastrit, *Helicobacter pylori*, eradikasyon, seroloji

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INTRODUCTION

Gastric cancer remains the second greatest cause of cancer death worldwide. The most common type of gastric cancer, the intestinal type, is usually preceded by chronic atrophic gastritis. Gastritis serology is, therefore, of crucial importance in population-based screening and prevention studies (1).

Atrophic gastritis is a condition characterized by a histopathological decrease in the number of gastric glands and replacement of connective tissue among the glands by plasma cells, lymphocytes and eosinophils (2). In atrophic gastritis, the loss of glands is accompanied with intestinal metaplasia (3). The relation between *Helicobacter pylori* (*Hp*) and atrophic gastritis has been demonstrated in several studies, although contrary studies are also available (4-6). Demonstration of a reversal in the atrophy following *H. pylori* eradication has further contributed to this relation (7, 8).

Pepsinogens are strong pro-enzymes that are activated to the pepsin by the effect of the acid in the gastric lumen released to be effective particularly in protein digestion in the stomach. Under normal conditions, they randomly leak to the blood, and are usually found in the serum as pepsinogen I (PI) and pepsinogen II (PII) (9, 10). PI is synthesized solely by chief cells in the oxyntic glands and mucous neck cells of the gastric corpus. PII is formed in glands of the entire stomach and also in Brunner glands (11, 12). It has been shown that there is a relation between *H. pylori* infection and high PI and PII; their levels decrease as a result of bacteria eradication while the PI/PII ratio increases (13, 14). Also, the circulating levels of both pepsinogens decrease with the development of atrophy; particularly lower serum PI levels are valuable findings of chronic corpus atrophy (11).

The objective of the present study was to see whether there is any difference in pepsinogen levels between *H. pylori*-positive and -negative patients with atrophic gastritis, and to analyze the relation between histopathology and pepsinogen levels after treatment in *H. pylori*-positive patients with atrophic gastritis.

MATERIALS AND METHODS

The study included a total of 30 cases (mean age: 47.1 ± 12 years), 13 female and 17 male, with a diagnosis of atrophic gastritis in their esophagogastroduodenoscopy and histopathological analysis. The exclusion criteria were anemia, malignancy, pregnancy, lactation, history of stomach operation, *H. pylori* eradication treatment within the last six months or proton pump inhibitor (PPI) use in the last four weeks, chronic and any autoimmune disease, and compliance problem during the therapy and follow-up. All cases were duly informed and their written consent was received.

For histopathological diagnosis and demonstrating *H. pylori* presence, two biopsies were obtained from the corpus and antrum of each case and fixed with 10% formaldehyde. The cases were divided into two groups depending on the presence of *H. pylori* as: Group I: *H. pylori*-positive atrophic gastritis (18 cases with a mean age of 47.5 ± 12 years, 10 female, 8 male), and Group II: *H. pylori*-negative atrophic gastritis (12 cases with a mean age of 46.4 ± 12 years, 3 female, 9 male).

Initial blood samples were taken from both groups. Group I received one-week PPI (omeprazole 40 mg/day or lansoprazole 60 mg/day) + clarithromycin (1 g/day) + amoxicillin (2 g/day) for *H. pylori* eradication. A second endoscopy was performed after a mean period of 7.28±2.99 months in this group; similarly, two biopsies were obtained from the corpus and antrum and sent for histopathological analysis. Again, fasting bloods samples were received.

The blood samples received initially and after the treatment were separated into their serums by a centrifuge of 3000 cycles/min, and kept at –70°C until the day of analysis.

The assessment of serum PI and PII was performed using PEPSIK (P2560) and PEPSI-K (P2560) kits of SORIN Biomedica Diagnostics S.p.A, Italy and by performing radioimmunoassay (RIA) method (12). For PI, the normal range was 20-80 ng/ml and for PII it was <17 ng/ml.

The serum *H. pylori* IgG antibody levels in U/ml were determined using the ImmunoComb II kits and Orgenics Combscale of Orgenics, Israel by the method of indirect solid phase enzyme-immunoassay (EIA).

The histopathological analysis was performed by modified Sydney system (15). The *H. pylori* intensity in the presence of *H. pylori* was graded by the number of *H. pylori* in a foveola according to the loss of atrophic gland. Those analyses were carried out blindly by the same pathologist.

Data are presented as mean and SD. The statistical analyses were evaluated using the methods of Pearson's correlation test, T-test for independent series and paired T-test. P values <0.05 were regarded as statistically significant.

RESULTS

In the whole group, no correlation was observed between *H. pylori* antibody titration and serum PI levels, while there was a significantly positive correlation between *H. pylori* antibody titration and serum PII levels (r=0.56, p=0.001) and a significantly negative correlation between *H. pylori* antibody titration and PI/PII levels (r=-0.51, p=0.003).

Table 1. Comparison of findings in *Hp*-positive and -negative atrophic gastritis patients

	***Hp* (+) n:18**	***Hp* (-) n:12**	**p=**
PI ng/ml	7.27±9.2	18.22±13.5	0.013
PII ng/ml	24.17±18.2	12.39±9.08	0.048
PI/PII %	0.54±0.8	2.69±2.5	0.002
AntiHp IgG U/ml	123.05±43	54.16±27	0.001
Degree of Antrum Atrophy	2±0.7	1.83±1.2	0.65
Degree of Corpus Atrophy	1.22±1	1±1.2	0.58
Antral Activity	1.38±0.77	0.5±0.67	0.003
Corpus Activity	1.38±0.6	0.41±0.5	0.001
Antrum Inflammation	2.05±0.87	1.55±0.92	0.14
Corpus Inflammation	1.88±0.75	0.83±1.15	0.002

Data are presented as mean and SD, A p value of <0.05 was considered statistically significant, p: Pepsinogen, *Hp*: *Helicobacter pylori*

Table 2. Comparison of pre- and post-treatment findings in *Hp*-positive patients with atrophic gastritis

n=18	**Initial**	**Post-treatment**	**p=**
PI ng/ml	7.27±9.2	6.34±2.31	0.64
PII ng/ml	24.17±18.25	9.95±4.8	0.002
PI/PII %	0.54±0.83	0.86±0.6	0.12
AntiHp IgG U/ml	123.5±43.69	72.22±29.21	0.001
Degree of Corpus Atrophy	1.22±1	0.05±0.2	0.001
Degree of Antrum Atrophy	2±0.76	1.11±1.2	0.013
Corpus Activity	1.38±0.6	0.44±0.8	0.004
Antrum Activity	1.38±0.77	0.44±0.8	0.001
Intensity of Corpus *Hp*	3.22±1.5	1.1±1.8	0.003
Intensity of Antrum *Hp*	3.55±1.2	2.05±2.02	0.09

Data are presented as mean and SD, A p value of <0.05 was considered statistically significant, p: Pepsinogen, *Hp*: *Helicobacter pylori*

As shown in Table 1, comparisons between *H. pylori*-positive and -negative patients with atrophic gastritis showed no significant difference in the atrophy grades for antrum and corpus between the groups. However, the serum PII, *H. pylori* antibody titration, gastric activity in antrum and corpus and the inflammation levels in corpus were significantly lower in *H. pylori*-negative cases, while they had a significantly higher PI level and PI/PII ratio (p<0.05).

For the *H. pylori*-positive group, initial and post-treatment serum pepsinogen levels, *H. pylori* antibody titration and histopathological comparisons are shown in Table 2. While the post-treatment serum PI levels, PI/PII ratio and *H. pylori* intensity in the antrum were unchanged, PII levels, *H. pylori* antibody titration, grade of atrophy both in corpus and antrum and gastritis activity, and the *H. pylori* intensity in the corpus remarkably decreased (p<0.05 for all).

The eradication rate was 44.4% in *H. pylori*-positive patients with atrophic gastritis. The comparison between eradicated and non-eradicated *H. pylori*-positive patients with atrophic gastritis following the treatment (Table 3) showed that only serum PII levels decreased in eradicated patients (p<0.05). After eradication therapy, *H. pylori* titration decreased remarkably in both eradicated and non-eradicated cases with initially *H. pylori*-positive atrophic gastritis (p<0.05).

DISCUSSION

It has been suggested that P levels can be used as a serological marker in determining *H. pylori* gastritis (10, 12, 16) and atrophic gastritis (11, 16, 17). PI and PII levels have been reported to increase in patients infected with *H. pylori* while the PI/PII ratio decreases (10, 18, 19), whereas the PI and PII levels decrease with the eradication of bacteria, and the ratio of PI/PII increases (10).

Table 3. Comparison of eradicated and non-eradicated cases in *Hp*-positive patients with atrophic gastritis following the treatment

	PI ng/ml	**PII ng/ml**	**PI/PII**	**Anti Hp IgG U/ml**	
Groups				**Initial**	**Post-treatment**
Eradicated n=8	6.18±1.8	7.5±3.5	1.06±0.72	114.3±52.3	76±35 ♦
Non-eradicated n=10	6.47±2.74	11.92±5.09	0.69±0.45	130±36.8	67.5±21.20 ♦
p	0.80	0.05*	0.20	0.46	0.55

Data are presented as mean and SD, A p value of <0.05 was considered statistically significant, p: Pepsinogen, *Hp*: *Helicobacter pylor*i, *There was a difference in the PII levels between the eradicated and non-eradicated groups (p<0.05), ♦ Anti *Hp* IgG levels reduced significantly in both groups after the treatment compared to the initial values (p<0.05)

Any increase in the expansion of gastritis before the development of atrophy causes replacement of chief cells by pyloric glands while PII increases or remains unchanged and PI decreases, as does the ratio of PI/PII. Those changes are an indication of the histopathological state of the gastric mucosa, particularly described as a valuable indicator of chronic corpus atrophy with a lower serum PI level (11). Once the atrophy is established, both PI and PII levels decrease. Since the decline in PI is more remarkable, PI/PII ratio decreases more (11, 16). In the present study, we suggest that remarkably higher PII in the *H. pylori*-positive atrophic group may result from the fact that the corpus gastritis activity and inflammation increased remarkably in this group. It is interesting to see that the PI levels are lower, and thus the PI/PII ratio is lower in *H. pylori*-positive versus *H. pylori*-negative atrophic patients in groups with similar atrophy grades in corpus and antrum. This result suggests that contrary to what has been reported in non-atrophic *H. pylori* gastritis patients (10, 12, 16), the *H. pylori* infection ongoing in relation with gastritis activity and inflammation as well as the atrophy destroys the functions of chief cells in the corpus. The unchanged PI levels may be associated with incomplete removal of the inflammation and failure to obtain *H. pylori* eradication in all cases. PII levels remarkably decrease after the eradication therapy, *H. pylori* intensity in corpus decreases, gastritis activity in both corpus and antrum decreases, and atrophy grades show regression.

It has been reported that most patients with atrophic gastritis become exposed to *H. pylori* at some time in their life, and *H. pylori* is a more important factor than aging in the development of atrophy (4, 5, 17). Similarly, even though anti-*H. pylori* IgG titration was remarkably lower in our *H. pylori*-negative atrophic gastritis cases and their presence could not be determined histologically, we believe that the majority of these cases are exposed to *H. pylori* at some time, thus it naturally may serve as a basis for the atrophy. No determination of anemia and the lack of any increase in the mean corpuscular volume (MCV) in these cases led us to exclude pernicious anemia. In addition, no age difference between the two groups and a mean age of around 47±12 years excluded the development of any aging-induced atrophy. In the meantime, *H. pylori* disappears when the amount of gastric acid decreases, and probably it becomes responsible from the triggering of the autoimmunity (20). *H. pylori* antibodies disappear spontaneously within 10 years in almost one fourth of patients with advanced atrophic corpus gastritis. The disappearance of *H. pylori* antibodies is accompanied by no or more than a mild improvement of the gastric mucosa (21).

Lack of any correlation between anti-*H. pylori* titration and PI levels, and presence of a positive correlation with PII levels and a negative correlation with PI/PII ratio are in compliance with the literature (10, 22, 23) and is probably associated with almost all cases being atrophic, the majority having been exposed to *H. pylori*, and continuation of *H. pylori* infection (17).

The low *H. pylori* eradication rate at 44.4% in *H. pylori*-positive atrophic gastritis patients is contrary to what is expected and may be the result of resistance to strains causing atrophy in atrophic gastritis cases, low activity of PPIs due to hypoacidity, and clarithromycin resistance. Some results of previous studies also showed lower *H. pylori* eradication rates in Turkey compared to other European countries (24, 25). A primary reason for these low rates may be the increasingly wide usage in our population of clarithromycin in *H. pylori* eradication and for other bacterial diseases such as respiratory tract infections (24).

It is already known that chronic gastritis transforms into atrophy, intestinal metaplasia and dysplasia, which are precancerous (26-28). Therefore, both histological (7, 8) and physiological (7, 14) improvements obtained via the treatment applied in *H. pylori*-positive atrophic gastritis patients are promising in the prevention of gastric cancer.

We observed a more remarkable regression in the atrophy, particularly in the corpus compared to the antrum, following the treatment. The post-treatment atrophy regression in the corpus was accompanied with a remarkable reduction in the *H. pylori* intensity. In contrast, the continuation of *H. pylori* intensity in the antrum in spite of the reduction is associated with lesser regression of the atrophy. There are some studies reporting that the atrophic gastritis is irreversible and this regression in the atrophy is a result of insufficient evaluation of the Sydney classification for atrophy (29, 30). Demonstration of regression in atrophy and intestinal metaplasia via *H. pylori* eradication in some cases in a study with a long follow-up period (five years) seems to validate the concept (31).

In conclusion, PI levels and PI/PII ratio are lower and PII levels are higher in *H. pylori*-positive compared to *H. pylori*-negative atrophic gastritis patients. Additionally, a positive correlation between anti-*H. pylori* titration and PII and a negative correlation between anti-*H. pylori* titration and PI/PII ratio support the fact that they may be markers of the presence of *H. pylori* in atrophic gastritis. Observation of a significant reduction only in PII levels and its correlation with anti-*H. pylori* titration following *H. pylori* eradication therapy indicate that PII levels are more important than PI and PI/PII in predicting *H. pylori* eradication in atrophic patients.

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