# ОСОБЕННОСТИ ИММУНОЛОГИЧЕСКИХ ПРОЯВЛЕНИЙ У ПАЦИЕНТОВ С РЕВМАТОИДНЫМ АРТРИТОМ ПРИ НАЛИЧИИ ХРОНИЧЕСКОГО ИНФИЦИРОВАНИЯ ШТАММОМ *HELICOBACTER PYLORI*, КОДИРУЮЩИМ АССОЦИИРОВАННЫЙ С ЦИТОТОКСИНОМ ГЕН *A*

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**Резюме.** Цель исследования – оценить взаимосвязь между серопозитивностью по антителам к циклическому цитруллинированному пептиду и хронической инфекцией *Helicobacter pylori* (*H. pylori*) у пациентов с ревматоидным артритом (РА). В исследование были включены 92 женщины с умеренной активностью РА. В иммуноферментном анализе определяли сывороточные антитела к циклическому цитруллинированному пептиду (anti-CCP), антитела к *H. pylori* (anti-*H. pylori*-IgG), суммарные антитела к антигену CagA *H. pylori* (anti-CagA); наличие позитивного результата anti-CagA-IgG подтверждали методом иммуноблота. 68,5% больных РА показали положительный результат anti-*H. pylori*-IgG, причем среди пациентов данной группы 40% дали положительный результат на anti-CagA-IgG. Все участники исследования были распределены на группы: I – *H. pylori* серонегативные пациенты (*H. pylori*$^-$); II – *H. pylori* положительные, но CagA отрицательные (*H. pylori*$^+$/CagA$^-$); III – пациенты сероположительные и на *H. pylori*, и на CagA (CagA$^+$). Показатели anti-CCP у больных РА с CagA$^+$ (группа III) были достоверно выше не только по сравнению с группой больных, серонегативных по *H. pylori* ($p < 0,001$), но и по сравнению с пациентами из группы II (*H. pylori*$^+$/CagA$^-$) ($p < 0,041$). Изучение влияния активности РА, наличия РФ и *H. pylori* данных факторов на содержание anti-CCP продемонстрировало незначительную долю изменчивости anti-CCP при высоком удельном вкладе

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*H. pylori* (beta = 0,25). Добавление в представленную модель показателя CagA(+) (beta = 0,503) позволило описать изменчивость anti-CCP практически в 30% случаев ($R^2$ = 0,29). В группе больных РА с показателями anti-CCP, превышающими установленное пороговое значение в 20 МЕ/мл (показатель нормы), наблюдалось повышение доли больных, инфицированных *H. pylori* (p < 0,001), но не доля CagA-положительных пациентов (p = 0,06). При увеличении порогового уровня до 60 МЕ/мл (трехкратное превышение верхней границы нормы) у пациентов с достоверно высоким anti-CCP связь с позитивностью на CagA стала значимой (p = 0,005). CagA, обладая высокой иммуногенностью, способен вызывать воспалительную реакцию в организме хозяина, которая выходит за рамки действия самой *H. pylori*. Необходимы дополнительные экспериментальные исследования для изучения возможных клинических и лабораторных ассоциаций, которые могут оказать влияние на тактику лечения $CagA^+$ пациентов с РА, серопозитивных по антицитруллинированным антителам, а также оценить эффективность эрадикации *H. pylori* в данной группе.

*Ключевые слова: ревматоидный артрит, антитела к циклическому цитруллинированному пептиду, инфекция, диагностика, хеликобактер пилори, белок CagA*

# PECULIARITIES OF IMMUNOLOGICAL MANIFESTATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN THE PRESENCE OF CHRONIC INFECTION WITH *HELICOBACTER PYLORI* VARIANT ENCODING CYTOTOXIN-ASSOCIATED GENE *A*

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**Abstract.** The study aimed to evaluate the association between cyclic citrullinated peptide antibody seropositivity and chronic *Helicobacter pylori* (*H. pylori*) infection in patients with rheumatoid arthritis (RA). We examined 92 women with moderate RA activity. Serum antibodies to cyclic citrullinated peptide (anti-CCP), antibodies to *H. pylori* (anti-*H. pylori*-IgG), and total antibodies to *H. pylori* CagA antigen (anti-CagA) were determined by enzyme immunoassay; the presence of anti-CagA-IgG positivity was confirmed by immunoblot. 68.5% of RA patients were positive for anti-*H. pylori*-IgG, and 44.4% of patients in this group were positive for anti-CagA-IgG. All the study participants were divided into three groups: I – *H. pylori* seronegative (*H. pylori*$^-$); II – *H. pylori* positive, CagA negative (*H. pylori*$^+$/CagA$^-$); III – *H. pylori* positive and CagA positive ($CagA^+$). The anti-CCP values in RA patients with $CagA^+$ (group III) were significantly higher not only in comparison with patients seronegative for *H. pylori* (p < 0.001), but also in comparison with patients from group II (*H. pylori*$^+$/CagA$^-$) (p = 0.041). A study of the influence of the RA activity, the presence of RF and *H. pylori* on anti-CCP content demonstrated a small proportion of anti-CCP variability (R2 = 0.09), with a high contribution of *H. pylori* (beta = 0.25). The addition of the CagA(+) index (beta = 0.503) to the presented model allowed us to describe the variability of anti-CCP in almost 30% of cases (R2 = 0.29). In the group of RA patients with anti-CCP values exceeding the established threshold value of 20 U/mL (normal index), there was an increase in the proportion of patients infected with *H. pylori* (p < 0.001), but not the proportion of CagA-positive patients (p = 0.06). When the threshold level was increased to 60 U/mL (three times the upper limit of normal) in patients with significantly high anti-CCP, the association with positivity for CagA became significant (p = 0.005). CagA is highly immunogenic and is capable of inducing an inflammatory response in the host that goes beyond the effect of *H. pylori* itself. Additional experimental studies are needed to investigate possible clinical and laboratory associations that may influence the treatment tactics of $CagA^+$ patients with RA who are seropositive for anti-citrullinated antibodies, as well as to evaluate the possible effects of therapeutic intervention aimed at the eradication of *H. pylori* in this group.

*Keywords: rheumatoid arthritis, antibodies to cyclic citrullinated peptide, infection, diagnostics, Helicobacter pylori, CagA protein*

## Introduction

In recent years, the association of *Helicobacter pylori* (*H. pylori*) infection with the spread of autoimmune pathology has attracted much attention because *H. pylori* can participate in the etiopathogenesis of a number of autoimmune diseases and persist chronic inflammation by stimulating the immune overall response [13]. Various mechanisms associated with *H. pylori* can cause loss of cellular tolerance and the production of various autoantibodies (IgM-rheumatoid factor, antinuclear and antiphospholipid antibodies, etc.) [4]. According to statistical analysis, infection with a more virulent variant of *H. pylori* encoding cytotoxin-associated gene *A* (CagA) can significantly increase the risk of autoimmune diseases [14]. This strain of *H. pylori* has an increased ability to stimulate the secretion of pro-inflammatory cytokines, which ultimately leads to modulation of the patient's immune responses [2].

The results of the many studies suggest a possible pathogenetic role of *H. pylori* infection in the progression of non-digestive diseases [3], such as chronic autoimmune rheumatic diseases, including rheumatoid arthritis (RA). Although a number of studies do not support a significant association between *H. pylori* infection and RA [1, 14], there is evidence of significant improvement in both clinical and laboratory parameters after successful eradication of *H. pylori* infection in patients with RA [2].

It should be stated that the relationship between *H. pylori* infection and RA is understudied nowadays [4].

***The study aimed*** to evaluate the association between cyclic citrullinated peptide antibody seropositivity and chronic *H. pylori* infection in patients with RA.

## Materials and methods

We examined 92 women (mean age, 55.5±9.6 years old; mean disease duration, 8.5 (7.0-9.5) years; body mass index, 29.1 (24.8-32.9) points) with moderate ($3.2 < DAS28 \leq 5.1$) RA activity. The mean value of the DAS28-ESR index was 3.83 (3.47-4.38) points. Rheumatoid factor (RF) seropositivity was found in 56 (61%) people. Rheumatoid arthritis diagnosis was based on the diagnostic criteria defined by the "American College of Rheumatology/European League Against Rheumatism Collaborative initiative" (2010).

Serum samples were obtained after centrifugation (5 mL of whole blood at 3000 rpm for 5 minutes), then samples were kept at -20°C until testing. Serum antibodies to cyclic citrullinated peptide (anti-CCP) were determined by enzyme immunoassay (Anti-CCP hs kit, Cat. No. 416-6010, Orgentec Diagnostika, Germany). The presence of helicobacteriosis was established using the Anti-*Helicobacter pylori* ELISA (IgG) ELISA test (EI2080-9601G, Euroimmun, Germany) designed for semi-quantitative/quantitative determination of human IgG antibodies to *Helicobacter pylori* (anti-*H. pylori*-IgG) in blood serum and plasma. All serum samples from RA patients were also analyzed for the presence of total antibodies to *Helicobacter pylori* CagA antigen (anti-CagA) (Vector-Best, Russia). The threshold values were determined at the levels recommended in the manufacturer's instructions. The immunoblot method and the recomLine Helicobacter IgG 2.0 kit (Cat. No. 4774, Mikrogen, Germany) were additionally used to confirm *Helicobacter pylori* CagA-IgG associated infection.

**Statistical analysis**

The results were statistically analyzed using Microsoft Excel 2011 and Statistica 10.0 (Stat Soft Inc., USA).

Data were displayed as median and lower/upper quartile Me ($Q_{0.25}$-$Q_{0.75}$) for variables with asymmetric distribution, and as mean ± standard deviation (M±SD) for variables with normal distribution. The test of variance analysis (ANOVA) and Kruskal–Wallis H test (as appropriate) were used in intergroup comparisons. Categorical variables were presented as percentages (%). Correlation analysis was performed using Spearman's coefficient ($r_s$). We used the $\chi^2$ criterion to analyze differences in the frequencies of the variables between the groups. Differences were considered statistically significant at $p < 0.05$.

## Results and discussion

In determining anti-CCP, the mean interquartile range was 63.4 (9.49-312) U/mL. About half of the patients (47.8%) had a significantly high level of anti-CCP (> 60 U/mL; three times the upper limit of normal). In 18.5% of the patients the index was in the range of 20 U/mL to 60 IU/mL (moderate increase).

68.5% of RA patients (n = 63) were positive for anti-*H. pylori*-IgG, and 44.4% (n = 28) of patients in this group were positive for anti-CagA-IgG.

All the study participants were divided into three groups: group I (n = 29; *H. pylori*$^-$) – *H. pylori* seronegative (no anti-*H. pylori*-IgG); group II (n = 35; *H. pylori*$^+$/CagA$^-$) – *H. pylori* positive, CagA negative (positive anti-*H. pylori*-IgG, but no anti-CagA-IgG); group III (n = 28; CagA$^+$) – *H. pylori* positive and CagA positive (positive anti-*H. pylori*-IgG and anti-CagA-IgG).

There were no intergroup differences in determining C-reactive protein (CRP) and rheumatoid factor class IgM (IgM-RF) ($p > 0.05$), except for group 3 patients, whose IgM-RF levels were significantly

**TABLE 1. LEVELS OF LABORATORY MARKERS OF RHEUMATOID ARTHRITIS IN GROUPS OF PATIENTS WITH CHRONIC *H. PYLORI* INFECTION**

| | Group I | Group II | Group III |
|---|---|---|---|
| **CRP, mg/L** | 17.0 (9.4-19) | 12.5 (4.8-17.7) | 13.3 (9.4-19.7) |
| **IgM-RF, IU/mL** | $13.5\pm10.9^{I-III}$ | 20.6±17.7 | 23.2±19.9 |
| **anti-CCP, U/mL** | $9.07\ (3.77\text{-}32.4)^{I-II,\ I-III}$ | $63.7\ (14.6\text{-}149.0)^{II-III}$ | 788 (74.3-1392.0) |

Note. CRP, C-reactive protein; IgM-RF, rheumatoid factor class IgM; anti-CCP, antibodies against cyclic citrullinated peptide; the upper register indicates intergroup differences at $p < 0.05$.

higher ($p = 0.026$) than those of *H. pylori* seronegative patients (group I) (Table 1).

The anti-CCP values in RA patients with CagA(+) (group III) were significantly higher, not only in comparison with patients seronegative for *H. pylori* (group I), but also in comparison with patients from group II (*H. pylori*$^+$/CagA$^-$) ($p < 0.001$ and $p = 0.041$, respectively) (Table 1).

Previous studies have noted the correlation between *H. pylori* infestation, confirmed by histological method and the immunological manifestations of RA [5]. The research on laboratory parameters in RA patients with the presence of *H. pylori* demonstrates an increase in inflammatory markers and various autoantibodies [13].

Mechanisms of *H. pylori* evasion of the humoral immune response remain unclear. The persistence of *H. pylori* in the human body is accompanied, as a rule, by a successive change in the pronounced immune response at the introduction of the bacterium to the further development of immune tolerance [10].

The immune response to the soluble protein CagA present in highly virulent strains of *H. pylori* is often accompanied by increased levels of RF, ESR, CRP, and anti-mutant citrullinated vimentin (anti-MCV) [2]. CagA is highly immunogenic, has a direct effect on cancer-promoting signaling pathways, and causes an inflammatory response in the host body that goes beyond the action of *H. pylori* itself [9]. And if in our study the absence of correlation between CagA(+) and the studied markers of inflammatory reaction (CRP, CRP) can be explained by the homogeneity of RA patients by sex, age, activity and duration of the disease (the association with Helicobacter infection was previously established for all parameters), the presence of close association of anticitrullinated proteins and CagA(+) is most indicative.

Anti-CCP levels correlated with the RA activity index DAS28 ($r_s = 0.19$), the presence of RF ($r_s = 0.29$), and *H. pylori* ($r_s = 0.45$). The study of the influence of these factors on anti-CCP content demonstrated a small proportion of anti-CCP variability ($R^2 = 0.09$), with a high contribution of *H. pylori* (beta = 0.25). The addition of the CagA(+) index (beta = 0.503) to the presented model allowed us to describe the variability of anti-CCP in almost 30% of cases ($R^2 = 0.29$).

In the group of RA patients with anti-CCP values exceeding the established threshold value of 20 IU/mL (normal index), there was an increase in the proportion of patients infected with *H. pylori* (Chi-square = 13.5; $p < 0.001$), but not the proportion of CagA-positive patients (Yates Chi-square = 3.55; $p = 0.06$). When the threshold level was increased to 60 IU/mL (three times the upper limit of normal) in patients with significantly high anti-CCP (n = 44), the association with positivity for CagA became significant (Yates Chi-square = 7.67; $p = 0.005$).

The high level of *H. pylori* infection is apparently associated with impaired immune system formation in RA patients due to pronounced immune disorders and the influence of immunosuppressive therapy. Autoreactive B cells actively producing antibodies to citrullinated proteins in RA are exposed to *H. pylori*. Using modeling techniques to detect specific physiological free amino acids as biomarkers of *H. pylori*-related peptic ulcer disease, citrulline has been identified as one of the key traits [6]. It has been argued that citrullination processes could potentially play a role in bacterial and viral sepsis because high levels of circulating citrullinated histone H3 have been found in patients with sepsis and coronavirus [11, 12]. According to Kastbom et al., decreased mucosal immunity to citrullinated proteins/peptides and recruitment of new B-cells are important characteristics of the response to antirheumatic therapy in patients with early RA [8].

Based on the results of our study, we can conclude that chronic infection with *Helicobacter pylori* strain encoding cytotoxin-associated gene *A* (CagA) and immunological processes occurring in anti-CCP-

positive patients, regardless of the activity and duration of rheumatoid arthritis, are closely associated.

## Conclusion

The role of *H. pylori* infection in the induction and maintenance of autoimmunity remains unclear. Clarification of the mechanisms of the influence of chronic H. pylori infection on the course of immunological processes in RA, especially in $CagA^+$ patients, is of clinical significance due to the fact that an infection with CagA-positive strains leads to increased resistance to antibiotics [7] used in eradication therapy.

Additional experimental studies are needed to investigate possible clinical and laboratory associations that may influence the treatment tactics of $CagA^+$ patients with RA who are seropositive for anti-citrullinated antibodies, as well as evaluate the possible effects of therapeutic intervention aimed at the eradication of *H. pylori* in this group.

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