Lek. Małgorzata Osmola

Rozprawa na stopień naukowy doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Biomarkers, Autoantibodies, and Micronutrient Deficiencies in Gastric Precancerous Lesions

Promotorzy:

Prof. dr hab. n. med. Grzegorz W. Basak

Prof. dr hab. Tamara Matysiak-Budnik

Katedra i Klinika Hematologii, Transplantologii i Chorób Wewnętrznych
Warszawskiego Uniwersytetu Medycznego

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych
Warszawskiego Uniwersytetu Medycznego

Warszawa, 2024 rok

Keywords: autoimmune gastritis, chronic atrophic gastritis, gastric precancerous lesions, pepsinogen, iron deficiency, vitamin B12 deficiency.

Słowa kluczowe: autoimmunologiczne zapalenie żołądka, niedobór witaminy B12, niedobór żelaza, pepsynogen, zanikowe zapalenie żołądka, zmiany przedrakowe żołądka.

List of publications of the doctoral dissertation:

1. Serum Pepsinogens Combined with New Biomarkers Testing Using Chemiluminescent Enzyme Immunoassay for Non-Invasive Diagnosis of Atrophic Gastritis: A Prospective, Multicenter Study.
Chapelle Nicolas, Osmola Małgorzata, Martin Jérôme, Blin Justine, Leroy Maxime, Jirka Iva, Moussata Driffa, Lamarque Dominique, Olivier Raphael, Tougeron David, Hay-Lombardie Anne, Bigot-Corbel Edith, Masson Damien, Mosnier Jean-François, Matysiak-Budnik Tamara.
Diagnostics. 2022; 12(3): 1-17

IF 3,6 MEiN 70

2. **Serum pepsinogens can help to discriminate between *H. pylori*-induced and auto-immune atrophic gastritis: Results from a prospective multicenter study.** Chapelle Nicolas, Martin Jérôme, Osmola Małgorzata, Hémont Caroline, Leroy Maxime, Vibet Marie-Anne, Tougeron David, Moussata Driffa, Lamarque Dominique, Bigot-Corbel Edith, Masson Damien, Blin Justine, Josien Regis, Mosnier Jean-François, Matysiak-Budnik Tamara.
Digestive and Liver Disease. 2023; 55 (10):1345-1351

IF 4,5 MEiN 100

3. **Atrophic Gastritis and Autoimmunity: Results from a Prospective, Multicenter Study.**
Osmola Małgorzata, Hémont Caroline, Chapelle Nicolas, Vibet Marie-Anne, Tougeron David, Moussata Driffa, Lamarque Dominique, Bigot-Corbel Edith, Masson Damien, Blin Justine, Leroy Maxime, Josien Regis, Mosnier Jean-François, Matysiak-Budnik Tamara
Diagnostics. 2023; 13(9): 1-10

IF 3,6 MEiN 70

4. **Iron and Vitamin B12 Deficiency in Patients with Autoimmune Gastritis and *Helicobacter pylori* Gastritis: Results from a Prospective Multicenter Study.**
Osmola Małgorzata, Chapelle Nicolas, Vibet Marie-Anne, Bigot-Corbel Edith, Masson Damien, Hemont Caroline, Jirka Adam, Blin Justine; Tougeron David, Moussata Driffa, Lamarque Dominique, Josien Regis, Mosnier Jean-François, Martin Jérôme, Matysiak-Budnik Tamara.
Digestive Diseases. 2024:1-9 doi: 10.1159/000535206 ahead of print

IF 2,3 MEiN 100

Impact Factor: 14
MEiN points: 340

Summary in English

Gastric cancer (GC), ranked as the fifth most prevalent cancer in the world, results in almost 800.000 deaths annually; early diagnosis is imperative to improve survival rates for patients with this cancer. Gastric precancerous lesions (GPL) precede the appearance of GC as a consequence of chronic infection with *H. pylori,* inducing non-atrophic gastritis, which may progress into chronic atrophic gastritis (CAG), intestinal metaplasia, dysplasia, and ultimately to GC. Another type of gastritis is autoimmune gastritis (AIG), which may also precede GC due to an autoimmune reaction. In this doctoral dissertation, various aspects of patients with GPL were examined, including non-invasive biomarkers, autoantibodies, and micronutrient deficiencies.

Article 1 assessed the diagnostic performance of serum pepsinogen I and II, and ratio (PGI, PGII, PG I/II ratio) measured by chemiluminescent enzyme immunoassay (CLEIA), as well as other biomarkers: interleukin-6 (IL-6), human epididymal protein 4 (HE-4), adiponectin, ferritin and Krebs von den Lungen (KL-6), for the detection of atrophic gastritis. Overall, the PG I/II ratio demonstrated 75.0% sensitivity and 92.6% specificity for the detection of moderate to severe corpus atrophic gastritis. While pepsinogens alone have limitations as biomarkers for the detection of antrum atrophic gastritis, IL-6 showed a promising sensitivity of 72.2% for this location. Combining the PG I/II ratio with HE-4 increased the sensitivity to 85.2% for detecting moderate to severe atrophic gastritis at any location. The study highlights the accuracy of pepsinogen testing for corpus atrophic gastritis. It suggests that IL-6 and HE-4 might be potential markers for antrum atrophic gastritis, offering insights into the early identification of individuals at risk for GC through serum biomarkers assessment.

Article 2 aimed to analyze the diagnostic value of pepsinogen testing for the diagnosis of atrophic gastritis by comparing two different diagnostic methods, CLEIA, and enzyme-linked immunosorbent assay (ELISA). Additionally, the article assessed the results according to the type (autoimmune *vs.* non-autoimmune) and location of atrophic gastritis. The study showed excellent diagnostic performances of PG I testing for detecting corpus CAG, with sensitivity and specificity of 92.7% and 99.1% for ELISA and 90.5% and 98.2% for CLEIA, respectively. For AIG, the corresponding values were 97.7% and 97.4% for ELISA and 95.6% and 97.1% for CLEIA. In conclusion, pepsinogens appear highly efficient for the detection of corpus-

limited CAG, especially for AIG. Subsequently, it allows to discriminate between autoimmune and non-autoimmune gastritis.

Article 3 aimed to search for the presence of autoantibodies in patients with GPL. Indeed, GC incidence has been shown to increase recently, especially in young female patients, with the underlying mechanism for this phenomenon remaining unknown but with the suggested role of autoimmunity. Since GPL precedes the development of GC, we aimed to test the possible existence of the stigmas of autoimmunity in patients with GPL. The study analyzed the prevalence of several autoantibodies in patients with GPL (AIG and *H. pylori*-related gastritis, NAIG) compared to control patients. Patients were tested for 19 autoantibodies (anti-nuclear antibodies, ANA, anti-parietal cell antibody, APCA, anti-intrinsic factor antibody, AIFA, and 16 myositis-associated antibodies). The frequency of ANA positivity was significantly higher in AIG than in NAIG or control patients (46.7%, 29%, and 27%, respectively, $p = 0.04$). Female gender was positively associated with ANA positivity (OR 0.51 (0.31–0.81), $p = 0.005$), while age and *H. pylori* infection were not. Myositis-associated antibodies were found in 8.9% of AIG, 5.5% of NAIG, and 4.4% of control patients, without significant differences among the groups ($p = 0.8$). Higher APCA and AIFA positivity was confirmed in AIG and was not associated with *H. pylori* infection, age, or gender in the multivariate analysis. Overall, the results of this study do not support an overrepresentation of common autoantibodies in patients with GPL, except ANA, which are significantly more frequent in AIG, but the clinical significance of this finding remains to be established.

Article 4 investigated micronutrient concentrations in patients with AIG, NAIG, and control patients to assess the prevalence of iron and vitamin B12 deficiencies and studied the associated factors. AIG exhibited significantly lower median vitamin B12 and ferritin concentrations than NAIG and controls. Vitamin B12 deficiency rates were 13.3%, 1.5%, and 2.8% in AIG, NAIG, and controls, respectively. Similarly, the median ferritin concentration was significantly lower in AIG than in NAIG and control patients, with iron deficiency presented in 28.9% of AIG, 12.8% of NAIG, and 12.9% of controls, respectively. Multivariate analysis demonstrated that AIG patients had a higher risk of developing vitamin B12 (OR 11.52 (2.85-57.64) $p=0.001$) and iron (OR 2.92 (1.32-6.30) $p=0.007$) deficiencies as compared to controls. Factors like age, sex, and *H. pylori* status did not affect the occurrence of micronutrient deficiencies. The study highlights the importance of screening for micronutrient deficiencies, particularly iron, in AIG patients and incorporating their management into treating patients with GPL.

In conclusion, these studies collectively contribute to understanding the diagnostic landscape of GPL, emphasizing the potential of serum markers like pepsinogens and shedding light on the associated factors, such as autoimmunity and micronutrient deficiencies.