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• *RAPID COMMUNICATION* •

Retinol-binding protein, acute phase reactants and *Helicobacter pylori* infection in patients with gastric adenocarcinoma

Nicolas Tsavaris, Christos Kosmas, Petros Kopterides, Dimitrios Tsikalakis, Hlias Skopelitis, Fotini Sakelaridi, Nikitas Papadoniou, Michalis Tzivras, Vasilios Balatsos, Christos Koufos, Athanasios Archimandritis

Nicolas Tsavaris, Petros Kopterides, Hlias Skopelitis, Christos Koufos, Department of Pathophysiology, Oncology Unit, "Laiko" University Hospital, University of Athens, School of Medicine, Athens 11527, Greece
Fotini Sakelaridi, Department of Pathophysiology, Biochemistry Laboratory, "Laiko" University Hospital, University of Athens, School of Medicine, Athens 11527, Greece
Michalis Tzivras, Athanasios Archimandritis, Department of Pathophysiology, Gastroenterology Unit, "Laiko" University Hospital, University of Athens, School of Medicine, Athens 11527, Greece
Christos Kosmas, 2nd Department of Oncology, "Metaxa" Hospital, Piraeus 185 37, Greece
Dimitrios Tsikalakis, Biochemistry Laboratory, "Metaxa" Hospital, Piraeus 185 37, Greece
Nikitas Papadoniou, Department of Gastroenterology, "A. Papandreou" General Hospital of Rhodes, Rhodes 85100, Greece
Vasilios Balatsos, Department of Gastroenterology, "A. Papandreou" General Hospital of Athens, Mesogion 154, Athens 11527, Greece
Correspondence to: Dr Petros Kopterides, 28-30 Korai Street, Nea Ionia - Athens 14233, Greece. petkop@ath.forthnet.gr
Telephone: +30-210-2759863 Fax: +30-210-2855476
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Abstract

AIM: To determine the serum levels of c-reactive protein (CRP), transferrin (TRF), a2-macroglobulin (A2M), ceruloplasmin (CER), a1-acid glycoprotein (AAG), pre-albumin (P-ALB) and retinol-binding protein (RBP) in gastric carcinoma patients and to explore their possible correlation with underlying *Helicobacter pylori* (*H pylori*) infection.

METHODS: We measured the serum levels of CRP, TRF, A2M, CER, AAG, P-ALB, and RBP in 153 preoperative patients (93 males; mean age: 63.1±11.3 years) with non-cardia gastric adenocarcinoma and 19 healthy subjects.

RESULTS: The levels of CRP, CER, RBP, and AAG in cancer patients were significantly higher than those in healthy controls (P<0.0001), while no difference was found regarding the TRF, P-ALB, and A2M levels. Cancer patients with *H pylori* infection had significantly lower RBP values compared to non-infected ones (P<0.0001) and also higher values of CRP and AAG (P = 0.09 and P = 0.08, respectively).

CONCLUSION: High serum levels of CRP, CER and AAG in cancer patients do not seem to be related to *H pylori* infection. Retinol-binding protein seems to discriminate between infected and non-infected patients with gastric carcinoma. Further studies are needed to explore if it is directly involved in the pathogenesis of the disease or is merely an epiphenomenon.

Key words: Gastric cancer; *Helicobacter pylori*; Acute phase reactants; A1-acid glycoprotein; Transferrin; A2-macroglobulin; Ceruloplasmin; Retinol-binding protein; Pre-albumin; c-reactive protein

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INTRODUCTION

Though the incidence of gastric adenocarcinoma has decreased during the last 50 years, it still remains one of the most common cancers worldwide. Even though the exact molecular mechanisms leading to gastric carcinogenesis are incompletely understood, the current school of thought accepts a multifactorial model in which various dietary and non-dietary factors (i.e. *Helicobacter pylori* infection) operate at different steps in the process.

Epidemiological studies in the early 1990s demonstrated an up to sixfold increased risk of developing gastric adenocarcinoma in patients infected with *H pylori*[1-4]. More than 10 years ago, *H pylori* was classified as a type I carcinogen for human beings by the World Health Organization, being recognized in this way as a crucial player in the gastric carcinogenesis. Increased epithelial cell proliferation and oxidative damage of the gastric mucosa are the two main mechanisms that seem to operate as a result of *H pylori* infection[5].

Table 1 Characteristics of studied populations and demographic data

Group	Number of subjects	Sex (M/F)	Mean age(yr)	Tumor location (antrum/body)
Gastric cancer	153	93/60	63.1	125/28
Infected	82	46/36	64.2	64/18
Non-infected	71	42/29	62.4	56/15
Healthy controls	19	10/9	62.2	

M, male; F, female.

The other environmental factor that has been shown to play a significant role in gastric carcinogenesis is diet. Diets with low intake of fruits, vegetables and milk and high intake of smoked or salted foods, dried fish, cooking oil, and complex carbohydrates have been shown to increase the risk for gastric cancer[6,7]. Contrary to that, intake of antioxidants has been associated with decreased risk of gastric cancer[8].

The search for useful biomarkers that can help in the diagnosis of cancer and add prognostic information to that already provided by the tumor staging is a field of active research. Even though numerous studies have been published, no single substance has been found to be clinically useful in the management of patients with gastric carcinoma. Immunohistochemical analysis of gastric tumors has shown that they contain protease inhibitors such as a2-macroglobulin[9,10] or a1-acid glycoprotein[11-13] and suggests that they may serve as markers of tumor aggressiveness. Some data also suggest that the acute phase reactants CRP and AAG may have prognostic value[13,14]. Stored sera from patients that later develop gastric cancer contain lower values of ferritin, while transferrin values were not different[15]. Ceruloplasmin has been shown to be useful in some studies[16] but not in others[15-17]. Serum interleukin-6 (IL-6) level correlates with the disease status of gastric cancer, suggesting that it may be used as a new tumor marker for monitoring the response to treatment[18]. Other studies even suggested that IL-6 might have a direct role in the pathogenesis[19,20]. A recent study[21] confirmed that IL-6 is a useful parameter for the diagnosis and grading of gastric cancer, but also suggested a role for malonyldialdehyde (MDA), nitric oxide (NO) and, especially vascular endothelial growth factor (VEGF). Finally, inconclusive data surround the usefulness of the so-called negative acute phase reactants, pre-albumin, and retinol-binding protein, in the assessment of cancer patients[22-26]. Retinol-binding protein was also included in our analysis because retinol and its ligand has been associated with lower risk of gastric cancer in some studies[27] but not in others[28].

The aim of this prospective, observational study was to measure the serum levels of the acute phase reactants a1-acid glycoprotein, transferrin, a2-macroglobulin, ceruloplasmin, retinol-binding protein, pre-albumin, and c-reactive protein in patients with gastric adenocarcinoma and to explore their correlation with *H pylori* infection.

MATERIALS AND METHODS

Patients

One hundred and fifty-three patients (93 men, 60 women) with a mean age of 63.1±11.3 years and histologically confirmed non-cardia gastric cancer were included in the study. In each case we recorded the location of the tumor, the histological type and the lymph node involvement. One hundred and twenty-five malignant tumors were located in the antrum and 28 in the body of the stomach. None of the patients had any gross metastatic disease as determined by chest and abdomen CT scans and received chemotherapy or radiation therapy prior to surgery. The histological diagnosis was based on morphologic examination of hematoxylin/eosin-stained specimens. Table 1 summarizes the demographic data and characteristics of the studied populations. Nineteen healthy volunteers (10 men, 9 women) with a mean age of 62.2±13.1 years were used as controls. We defined "healthy" status as the absence of a cardiovascular disorder, malignancy, gastrointestinal pathology, and *H pylori* infection. Neither patients nor controls had any evidence of infection or received antibiotics for at least 2 mo prior to serum collection with only the use of antacids. Sera from 48 patients were prospectively collected, the rest of the sera were collected in the previous 17 mo and kept frozen at -70 ℃.

The study was approved by the Institutional Review Boards of the participating hospitals and all study individuals gave their informed consent.

Determination of H pylori serology

All enrolled subjects (cancer patients and controls) underwent an enzyme-linked immunosorbent assay (ELISA) IgG serologic test for *H pylori* (Allergy Immunotechnologies Inc., Newport Beach, CA, USA) in accordance with the manufacturer's instructions. The specificity and sensitivity of the serology test validated in our local population were 95% and 90%, respectively. *H pylori* antibody titers higher than 155 mU/L were considered positive and lower than 155 mU/L negative.

Determination of acute phase proteins

Concentrations of the specific acute-phase proteins (c-reactive protein, a1-acid glycoprotein, ceruloplasmin, transferrin, a2-macroglobulin, prealbumin, and retinol-binding protein) were measured by nephelometric method on a Dade Behring nephelometer BNII (Dade Behring, USA), using Dade Behring antibodies and standard reagents. The intra- and inter-assay coefficients of variation were in the range of 2% and 5%, respectively.

Examined parameters

Serum levels of the acute phase reactants were recorded from healthy controls and patients suffering from gastric cancer. These patients were grouped according to whether they were infected with *H pylori* or not. Normal values for the examined parameters were as follows: c-reactive protein (CRP) <50 mg/L, A1-acid glycoprotein (AAG) <1

Table 2 Mean levels of TRF, A2M, AAG, CER, RBP, P-ALB, and CRP in cancer patients and controls

Parameter (mg/dL)	Cancer patients (n = 153)	Controls (n = 19)	P
TRF	265,43	274,95	NS
A2M	263,25	233,11	NS
AAG	245,48	94,79b	<0.001
CER	53,26	41,74b	<0.001
RBP	23,78	3,77b	<0.001
P-ALB	23,04	17,74	NS
CRP	9,32	2,92b	<0.001

[b]P<0.001 *vs* controls, NS: not significant.

Table 3 Mean levels of TRF, A2M, AAG, CER, RBP, P-ALB, and CRP between infected and non-infected cancer patients

Parameter (mg/dL)	Non-infected (n = 71)	Infected (n = 82)	P
TRF	276.46	255.88	NS
A2M	281.49	247.46	NS
AAG	238.21	251.77	NS
CER	52.03	54.32	NS
RBP	31.89	16.75[b]	<0.001
P-ALB	22.35	23.64	NS
CRP	7.99	10.47	NS

[b]P<0.001 *vs* infected, NS: not significant.

200 mg/L, ceruloplasmin (CER) <550 mg/L, transferrin (TRF) <4 300 mg/L, A2-macroglobulin (A2M) <3 200 mg/L, pre-albumin (P-ALB) <450 mg/L and retinol-binding protein (RBP) <60 mg/L.

Statistical analysis

The nonparametric Mann-Whitney *U*-test was employed to study the differences in values between cancer patients and controls and to compare the significance of values' differences between infected and non-infected patients. P<0.05 was considered statistically significant. All analyses were completed using the Statistical Package for Social Sciences (SPSS 11.5).

RESULTS

The assessed parameters found between cancer patients and healthy controls and between infection and non-infection groups of cancer patients are shown in Tables 2 and 3, respectively. Out of a total of 153 cancer patients participating in the study, 82 (53.6%) were infected with *H pylori*. The levels of CRP, CER, RBP, and AAG in cancer patients were significantly higher than those in healthy controls (P<0.0001), while no difference was found regarding the TRF, P-ALB, and A2M levels. Cancer patients with *H pylori* infection had significantly lower RBP (P<0.0001) and higher CRP and AAG (P = 0.09 and P = 0.08, respectively) than those without *H pylori* infection.

DISCUSSION

In the current study, we have measured the serum levels of a group of acute phase reactants in patients with adenocarcinoma localized in the non-cardia part of the stomach. We separated these patients to either antibody-positive or antibody-negative to *H pylori*. From the examined acute phase reactants, we found that the levels of c-reactive protein, ceruloplasmin, a1-acid glycoprotein and retinol-binding protein in cancer patients were significantly higher than those in healthy controls, while no difference was found regarding the transferrin, prealbumin and a2-macroglobulin levels. However, only retinol-binding protein was significantly related to *H pylori* infection as its values were significantly lower in infected patients than in non-infected ones. The etiology of these biochemical aberrations is probably multifactorial.

Numerous studies have shown that gastric cancer patients have significantly higher levels of CRP[14,21] than healthy controls. A previous study[13] has even showed that elevated CRP levels have a prognostic significance and a recent study suggested that CRP levels contribute to the diagnosis of infection in cancer patients[21]. Our data confirm that CRP is elevated in cancer patients, but we cannot comment on its usefulness in the diagnosis of infection in cancer patients, as this was not the aim of our study. Though it was not different between infected and non-infected patients with *H pylori* (P = 0.09), one possible explanation is that chronic *H pylori* infection did not cause the elevation of CRP with acute infections as pneumonia or bacteremia. The other explanation is that our study did not have the statistical power to detect any difference.

Immunohistochemical analysis of the tumor epithelium showed that the protease inhibitor a2-macroglobulin is related to the invasive growth of gastric cancers[9,10]. Similar preliminary data exist for a1-acid glycoprotein[11-13]. Our data do not support routine measurement of A2M, but confirmed that AAG is a potentially useful marker as it was consistently higher in cancer patients and showed a trend to reach statistical significance in *H pylori*-infected patients (P = 0.08).

The role of iron-carrying protein transferrin is undetermined. Studies showed that there is no difference in the mean TRF values between controls and patients while ferritin values are significantly different[15,29], suggesting that TRF may not be a prognostic factor for future gastric carcinogenesis but its role remains uncertain. In accordance with previous studies, our data did not require measuring transferrin in gastric cancer patients whether they were infected with *H pylori* or not.

Finally, we decided to include the so-called nutritional indices (prealbumin and retinol-binding protein) in our analysis to explore their relation to cancer or *H pylori* infection. In patients with colon cancer, the levels of serum prealbumin, retinol-binding protein, transferrin, and albumin were interrelated and tended to show a similar pattern of change. More specifically, in metastatic colon cancer, prealbumin was the most sensitive indicator of nutritional status and its levels and rates of change

had a prognostic significance. A rapid fall of prealbumin often occurs 2-3 mo prior to death of the patients and this preterminal phase is also frequently heralded by a progressive rise in the CRP level in the absence of any obvious infection[30]. Prealbumin concentration has a prognostic importance in women with epithelial ovarian carcinoma[24] and a general cancer population as well[23]. We cannot confirm the data on the usefulness of prealbumin testing because we did not perform any formal assessment of nutritional status in our study population.

Serum ceruloplasmin levels are higher in gastric and lung cancer[16] and our data have confirmed this finding. We did not find any correlation of *H pylori* infection with ceruloplasmin levels and cannot suggest a pathogenetic role for this copper-chelating protein apart from being a marker of systemic inflammation.

The most interesting findings of our study are the significantly higher levels of retinol-binding protein in gastric cancer patients than healthy controls, the only marker being statistically different between infected and non-infected patients with *H pylori* (it was lower in *H pylori*-infected patients). Our findings are novel and in contrast with previous studies showing decreased RBP levels in the lung[25] and colorectal cancer[17]. Retinol, the ligand of retinol-binding protein, is required to maintain immunity and epithelial turnover and is a key micronutrient needed for combating infection. Studies have shown a good correlation between RBP and retinol even in the context of infection and protein malnutrition[31]. Retinol deficiency could either directly disrupt epithelial integrity or indirectly increase susceptibility to the damaging factors contained in either tobacco smoke (in the case of lung cancer) or diet (in the case of gastric and colorectal cancer). One would expect a lower and not a higher retinol-binding protein value in gastric cancer patients.

A fundamental difference between stomach cancer and other types of cancer is the involvement of *H pylori* in the former. There is evidence that *H pylori* infection *per se* is associated with the abnormalities of the nutritional markers even in the absence of malignancy. Aguilera *et al*[32] studied the relationship between *H pylori* infection, anorexia and malnutrition in 48 peritoneal dialysis patients and found that infected patients with anorexia have lower lymphocyte counts, pre-albumin, transferrin, serum albumin, normalized equivalent of protein-nitrogen appearance and residual renal function. Eradication of *H pylori* could significantly improve the clinical syndrome and the biochemical abnormalities implying a causative role, but unfortunately retinol-binding protein was not measured in that study. The significant decrease in the activity of class IV alcohol dehydrogenase (ADH) in the antrum and corpus of stomachs of men and women infected with *H pylori* may be one of the underlying mechanisms as class IV ADH is the major isoenzyme controlling the production of retinoic acid from retinol and its supply to the human gastric mucosa[33,34]. It has been shown in animal models that the inflammatory response to infection and tissue injury is associated with low concentrations of plasma retinol and its specific transport proteins, retinol-binding protein and pre-albumin[35], suggesting that inflammation-induced hyporetinemia is attributed to a reduction in the hepatic synthesis of RBP and secretion of the retinol-RBP complex. The marked depressing effect of infections on serum retinol and retinol-binding protein has also been shown in human beings[36,37]. We speculate that *H pylori* infection in gastric carcinoma patients can lead to a decrease of retinol-binding protein by one of the above mechanisms but it remains unclear why uninfected patients with gastric cancer still have higher RBP levels than healthy controls.

The role of retinoids in gastric carcinogenesis has been studied in epidemiologic studies with conflicting results[27,28], but the molecular mechanisms that operate at either healthy or disease states have begun to be elucidated. Retinol has been shown to enhance differentiation of the gastric cell lineage in developing rabbits[38] and the reduction of retinoic acid signal has been implicated in the development and evolution of pre-malignant lesions of the human gastric mucosa[39]. The activation of the retinoic acid receptor induces cell differentiation and may antagonize cancer progression. Cellular retinol-binding protein I (CRBP-I) functions in retinol storage and its expression is lower in human cancers than in normal cells. A very recent study[40] showed that CRBP-I downregulation in human mammary epithelial cells chronically compromises retinoic acid receptor activity, leading to the loss of cell differentiation and tumor progression. The fact that class IV ADH is the major isoenzyme responsible for retinoic acid production from retinol and the more significantly decreased enzyme in the presence of *H pylori* infection associated with morphologic changes in the human gastric mucosa is intriguing. The retinoic acid pathway may be one of the missing links in the interplay of *H pylori* infection with gastric carcinogenesis.

In conclusion, gastric cancer patients with *H pylori* infection have significantly lower retinol-binding protein values than non-infected ones and both infected and non-infected groups have higher retinol-binding protein values than healthy controls. This finding may add to our understanding and management of this dreadful disease.

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