Upregulation of COX-2/PGE2 and NF-κB in Colorectal Disease: Associations with *H.pylori* Seropositivity and Gastrin Signaling

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Abstract

This study investigated the roles of Cyclooxygenase-2 (COX-2), Prostaglandin E2 (PGE2), Nuclear Factor Kappa B (NF-κB), and gastrin hormone in colorectal cancer pathogenesis and their potential associations with *H. pylori* infection. In a cross-sectional study of 40 patients with colorectal symptoms, serum gastrin and PGE2 levels were measured by the ELISA technique, H. *pylori* seropositivity was evaluated, and evaluated COX-2/NF-κB expression via immunohistochemistry. The results found: High median of gastrin (118 pg/mL) and PGE2 (174.5 pg/mL) and a high COX-2 expression of 47.5% and NF-kB levels of 27.5% and no association between H. pylori status and gastrin/PGE2 levels ($p>0.05$). Histologically, adenocarcinoma (27.5) and inflammatory conditions (15) prevailed. These findings indicate that COX-2/PGE2 and NF-kB signaling is increased in colorectal disease without considering the H. pylori, and NF-kB signaling is associated with inflammatory biomarkers and gastrin receptor expression. The results show possible disease stratification and therapeutic targeting of biomarker patterns.

Keywords: Colorectal disease, COX-2, PGE2, NF-κB, gastrin, *Helicobacter pylori*

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1. Introduction

1.1 Helicobacter pylori and Its Potential Role in Colorectal Disease

Helicobacter pylori (H. pylori) is a Gram-negative, microaerophilic bacterium that colonizes the gastric mucosa and is a well-established etiological agent for chronic gastritis, peptic ulcers, and gastric malignancies, including adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [1]. H. pylori infection is geographically uneven, with more cases being reported in developing countries like the Middle East, in which seropositivity has been reported to be as high as 70 percent in certain groups [2]. Virulence factors that contribute to the pathogenicity of the bacterium include cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), which cause chronic inflammation, damage to epithelia, and imbalanced cellular multiplication [3]. Although the gastric effects of the infection caused by H. pylori are sufficiently described, there is recent evidence to indicate a possible linkage between H. pylori and extra-gastric diseases such as colorectal cancer (CRC) and inflammatory bowel disease (IBD) [4].

The mechanisms put forward to relate H. pylori to colorectal pathology are multifactorial. One of the hypotheses is the hypergastrinemia, which is caused by the gastric hypochlorhydria of the H. pylori. The atrophic gastritis may also be a result of chronic infection, which causes a decrease in acid secretion, and this is compensated for by the gastrin release of G-cells [5]. Gastrin is a trophic hormone that stimulates the proliferation of the mucosa of the gastrointestinal tract, making it prone to neoplastic transformation in the colon [6]. It has been experimentally shown that gastrin stimulates the growth of colorectal epithelial cells through cholecystokinin-2 receptor (CCK2BR), and triggers mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways [7]. Moreover, H. pylori can have a systemic effect on the induction of pro-inflammatory cytokines (e.g., interleukin-1β, tumor necrosis factor-α) and reactive oxygen species, which can cause damage to DNA and carcinogenesis [8].

Contradictory results have been obtained in epidemiological studies on the correlation between H. pylori and CRC. A meta-analysis has also noted a

significant yet small effect of H pylori on CRC risk (odds ratio [OR] = 1.39, 95 percent confidence interval [CI]: 1.18164), especially in CagA-positive strains [9]. On the other hand, the rest of the literature did not see a significant association, which implies that the association is possibly confounded by other factors like geographic variation, host genetics and comorbidities [10]. The role of H. pylori in colorectal disease is not well documented in Iraq, where it is endemic as a result of H. pylori infection. The purpose of the present research is to fill this gap by considering H. pylori seropositivity and the correlation of seropositivity with molecular markers of colorectal pathogenesis in an Iraqi cohort.

1.2 Colorectal Cancer: Molecular Pathways and Biomarkers

Colorectal cancer (CRC) has been one of the predominant causes of cancer morbidity and mortality in the world, with an estimated 1.9 million cases diagnosed each year [11]. CRC progression is a multi-step process, which implies genetic mutations (e.g., APC, KRAS, TP53), epigenetic changes, and sustained inflammation [12]. The pathogenesis of CRC is mainly divided into two major pathways: the chromosomal instability pathway, which is associated with consecutive mutations in tumor suppressor genes and the microsatellite instability pathway, which is associated with defects in the DNA mismatch repair [13]. Besides these genetic processes, inflammatory pathways also have a central role in CRC, especially in colitis-related cancer, where chronic inflammation of the mucosa promotes neoplastic progression [14].

COX-2 and prostaglandin E2 (PGE2) are some of the important inflammatory mediators that have been studied in relation to CRC. PGE2 is synthesized through the action of COX-2, an inducible enzyme that is upregulated by the stimulus of pro-inflammatory. High COX-2 expression is seen in nearly 80 percent of colorectal adenocarcinomas, and is associated with high tumor stage and low prognosis [15]. There are many ways in which PGE2 enhances tumorigenesis, and some of them are: cell proliferation, antigenic apoptosis, and angiogenesis via vascular endothelial growth factor (VEGF) [16]. It has been shown by preclinical studies that inhibition of COX-2 prevents the formation of polyps in animal models of familial adenomatous polyposis, which is evidence of the therapeutic value of targeting this pathway [17].

Another key controller of inflammation and carcinogenesis in the colon is nuclear factor-kappa B (NF-KB). NF- -B activation leads to the transcription of cell survival (e.g., Bcl-2), proliferation (e.g., cyclin D1), and inflammatory (e.g., IL-6, TNF-) genes [18]. Chronic NF-kB activation in IBD patients plays a role in chronic mucosal injury and in the risk of colitis-related CRC [19]. Moreover, NF-KB also correlates with COX-2/PGE2 signaling, which forms positive feedback that maintains the inflammation and promotes tumor proliferation. Since central pathways play a key role in the pathogenesis of CRC, risk stratification and therapeutic targeting biomarkers like COX-2, PGE2 and NF-KB have been suggested [20].

Gastrin, which is long known as gastrointestinal acid secretion, has also been implicated in the carcinogenesis of the colon. In some studies, hypergastrinemia (i.e., associated with the H. pylori infection or not) has been linked with a higher risk of CRC [21]. Gastrin achieves its actions via CCK2BR and stimulates proliferative and anti-apoptotic processes in colorectal epithelial cells [22]. The correlation between gastrin and CRC is, however, controversial since other researchers have not confirmed this relationship [23]. The present research examines the level of gastrointestinal secretion in colorectal disease and whether it is correlated with H. pylori seropositivity.

2. Materials and Methods:

2.1 Study Design and Patient Selection

This cross-sectional study consecutively enrolled 40 adult patients (mean age 50.45 ± 17.27 years, range 17-75; 45% ≤50 years, 55% >50 years) presenting with colorectal symptoms (e.g., abdominal pain, rectal bleeding, chronic diarrhea) at the Gastroenterology and Hepatology Teaching Hospital in Baghdad, Iraq. Inclusion required age ≥18 years, clinical suspicion of colorectal pathology, and willingness to provide informed consent. Exclusion criteria comprised a prior history of colorectal cancer or inflammatory bowel disease (IBD), recent antibiotic or proton pump inhibitor (PPI) use within 4 weeks, or an active gastrointestinal infection other than *H. pylori.*

2.2 Laboratory Investigations

A. Complete Blood Count (CBC):

Hemoglobin (Hb) and total leukocyte count (WBC) were measured using an automated hematology analyzer.

B. *H. pylori* Serology:

The Anti-Helicobacter Pylori IgG ELISA (ORG 917G, Morgentec Diagnostika GmbH) is a quantitative in vitro diagnostic test that detects IgG antibodies against H. pylori in human serum or plasma using antigen-coated wells (whole-cell lysate and recombinant Cag A) and an enzyme-linked reaction (HRP/TMB). The test employs barcoded Alegria® Test Strips for automated processing on the Alegria® system, with results interpreted as

negative (<20 U/mL), borderline (20–25 U/mL), or positive (>25 U/mL), demonstrating high sensitivity (96.7%) and specificity (96.2%). It includes controls, sample buffer, and enzyme conjugate, with validated precision (CV <10%) and linearity (0–200 U/mL), supporting clinical diagnosis and monitoring of H. pylori infection [24].

C. Gastrin Quantification (ELISA):

The results of the C. Gastrin Quantification were unsatisfactory. <|human|> C. Gastrin Quantification (ELISA): Measurement of serum gastrin levels was done with the help of a competitive ELISA kit (Elabscience, E-EL-H2060). Biotinylated anti-gastrin detection antibodies were incubated on the samples and then avidin conjugated with HRP. Colorimetric detection was done by the addition of TMB substrate, and the absorbance was recorded at 450 nm. Sensitivity of the assay was 9.38 pg /mL, and the detection range was 15.63-1000 pg/mL [24] and [25].

D. Prostaglandin E2 (PGE2) Measurement (ELISA)

D. Prostaglandin E2 (PGE2) ELISA Measurement: The level of PGE2 was determined by the use of the competitive ELISA kit (Elabscience, #E-EL-0034). The samples of serum were incubated with anti-PGE2 detection antibodies that were biotinylated and competed with immobilized PGE2. HRP-conjugated avidin and TMB substrate were then put into the samples after washing, and the absorbance was determined at 450 nm. The sensitivity of the assay was 18.75 pg/mL with a range of 31.25- 2000 pg/mL[26], [27] and [28].

E. Histopathological Examination:

Establishing a diagnosis requires a thorough examination of the oral cavity along with an analysis of the findings from an MRI test.<|human|>E. Histopathological Examination: Colonoscopy biopsy samples were fixed in formalin, paraffin-embedded, sectioned and stained with hematoxylin and eosin (H&E); all the histopathological diagnoses (adenocarcinoma, adenomatous polyps and inflammation) were determined by a Specialized pathologist [29].

F. Immunohistochemistry for COX-2 and NF-κB:

Colonic tissue sections (4 μm) were prepared from formalin-fixed, paraffin-embedded samples. After deparaffinization and rehydration, antigen retrieval was performed using citrate buffer (pH 6.0). Endogenous peroxidase activity was blocked with hydrogen peroxide, followed by incubation with primary antibodies against COX-2 and NF-κB (dilution 1:100). Detection was carried out using a biotin-streptavidin-peroxidase system with DAB as the chromogen, and hematoxylin counterstaining [30]. Expression levels were scored semi-quantitatively: grade 0 (no expression), grades 1–2 (mild–moderate), and grades 3–4 (high expression).

2.3 Statistical Analysis

Demographic, laboratory, and biomarker data were summarized with the help of descriptive statistics. Mean +- standard deviation (SD) was used to display normally distributed variables and medians and ranges were employed to display non-normally distributed data like gastrin and PGE2. The frequency and percentages were used as tools to describe categorical data. The nature of the variables (age, hemoglobin, leukocyte count) exhibited a non-normal distribution, which resulted in the use of Spearman's rank correlation in order to evaluate the relationship between biomarkers (gastrin, PGE2, COX-2, NF-kB, CCK2BR) and clinical variables. The p-value less than 0.05 was deemed to be statistically significant [29].

2.4 Ethical Considerations

Samples of patients have been approved and analyzed using the data without the names in order to ensure that the privacy of the patients is preserved. This research was undertaken under the permission of the College of Medicine/ University of Anbar, as well as in line with the principle of ethical considerations of the Declaration of the ethical committee of the College (Ref: 58, Date:17/4/2024).

3. Results

The study included 40 patients with a mean age of 50.45 ± 17.27 years (range: 17–75 years); 45% were ≤50 years and 55% were >50 years. Serological testing revealed that 47.5% (n=19) of patients were positive for H. pylori Ab-IgG, while 52.5% (n=21) were negative as shown in Fig. 1. Histologically, adenocarcinoma was the most frequent diagnosis (27.5%), followed by inflammation (15%), ulcerative colitis (12.5%), adenomatous polyps (12.5%), juvenile polyps (10%), and rectal ulcers (10%), as show in Fig. 2.

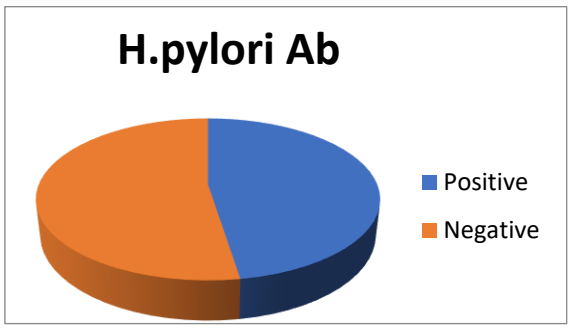

Fig. 1 Serum *H. pylori* IgG antibody detection

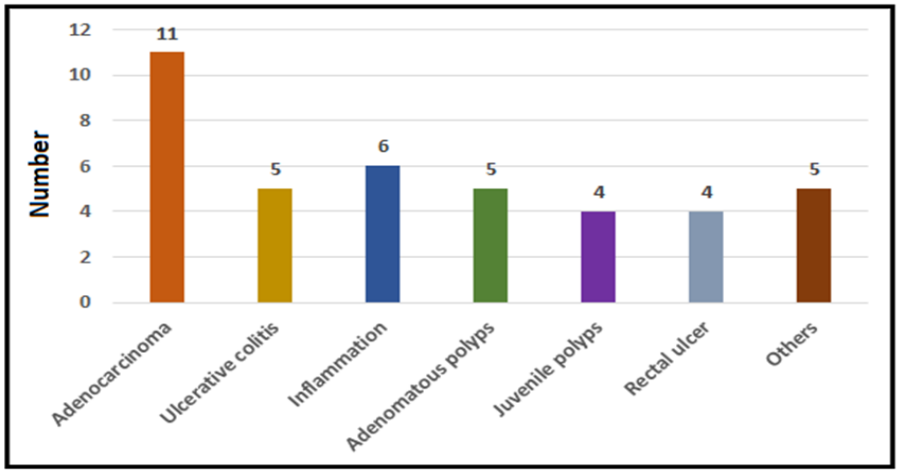

Fig. 2 Histopathological results

3.1 Laboratory Investigations:

The mean hemoglobin level was 12.0±2.41 g/dl, with a range of 6.0-16.8 g/dl. The total leukocyte count had a mean of 10.0±3.21 ×10⁹/L, ranging from 7.0 to 18 ×10⁹/L (Table 1).

Table 1: Laboratory investigations.

Variables	Mean±SD	Range
Hemoglobin, g/dl	12.0±2.41	6.0-16.8
WBC count×10^9/L	10.0±3.21	7.0-18

3.2 Serum concentration of gastrin and prostaglandin

Data regarding serum concentration of gastrin and prostaglandin were found to be non-normally distributed. According, these data were expressed as median and range. The median level of gastrin was 118 pg/ml (range 38-234 pg/ml). On the other hand, the median level of PGE2 was 174.5 pg/ml (range 61-1454 pg/ml) as shown in Table 2.

Table 2: Serum concentration of gastrin and prostaglandin.

Variables	Mean±SD	Median	Range
Gastrin, pg/ml	**122.4±63.88**	**118**	**38-234**
Prostaglandin, pg/ml	**242±295.18**	**174.5**	**61-1454**

3.3 IHC for COX-2 and NF-κB

The immunohistochemistry (IHC) results for COX-2 and NF-κB expression in colorectal disease patients revealed distinct patterns: COX-2 showed no expression in 30% of cases, mild-moderate expression (grades 1-2) in 22.5%, and high expression (grades 3-4) in 47.5%, indicating significant upregulation in nearly half the cohort. For NF-κB, 35% had no expression, 37.5% exhibited mild-moderate expression, and 27.5% demonstrated high expression, suggesting a less pronounced but still notable inflammatory response, as shown in Table 3 and Figs. 4 and 5.

Table 3: IHC for COX-2 and NF-κB

Variables	Frequency	Percentage
COX-2, grade		
None	12	30%
1-2	9	22.5%
3-4	19	47.5%
NF-κB, grade		
None	14	35%
1-2	15	37.5%
3-4	11	27.5%

3.4 Correlation of gastrin, PGE2, COX-2, NF-κB and CCK2Br with other variables

Spearman's correlation was used to explore the possible correlation of gastrin, PGE2, COX-2, NF-κB and CCK2Br with other variables. NF-κB showed a significant positive correlation with leukocyte count (r= 0.382, p= 0.015) and with CCK2BR (r= 0.532, p<0.001). Otherwise, the were no significant correlations in Table 4 and Fig. 3.

Table 4: Spearman's correlation of gastrin, PGE2, COX-2, NF-κB and CCK2Br with other variables.

Variables		Gastrin	PGE2	COX-2	NF-κB
Age	r	0.022	-0.045	-0.073	0.084
	p	0.894	0.784	0.655	0.606
Hemoglobin	r	0.271	-0.040	0.167	-0.230
	p	0.091	0.808	0.303	0.154
Leukocyte	r	0.208	0.270	-0.004	0.382
	p	0.197	0.081	0.979	0.015
PGE2	r	0.033		0.172	0.212
	p	0.841		0.290	0.189
COX-2	r	0.251			0.288
	p	0.118			0.109

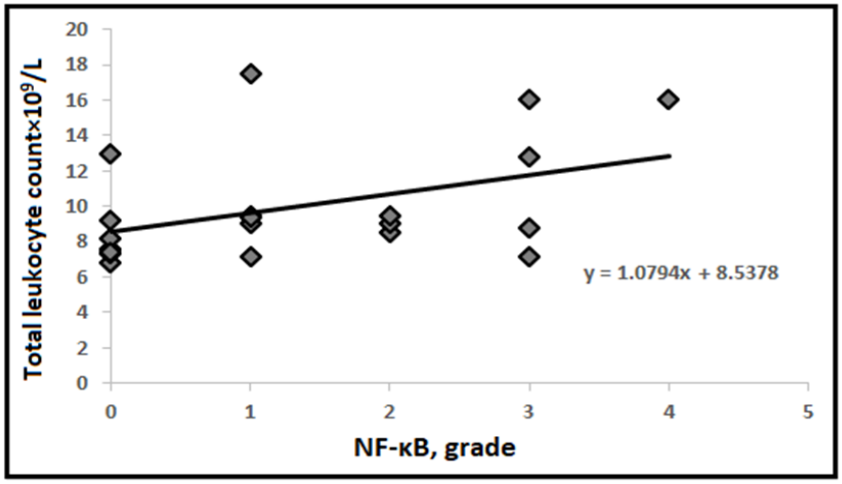

Fig. 3 Scatter plot and regression line between NF-kB and total WBC count.

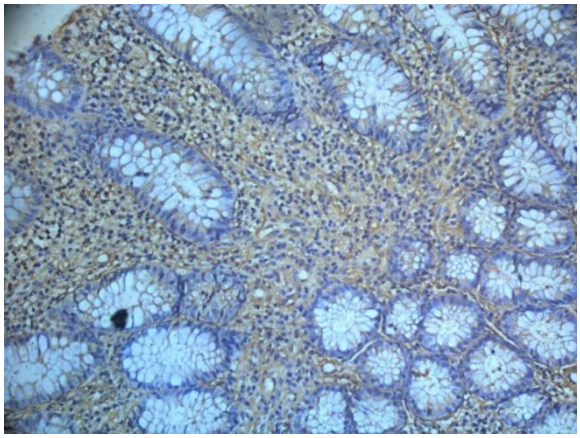

Fig. 4 Immunohistochemical staining of Cox2. Brown color refers to the positive result (Ag/Ab reaction), and purple color refers to the counterstain (hematoxylin)

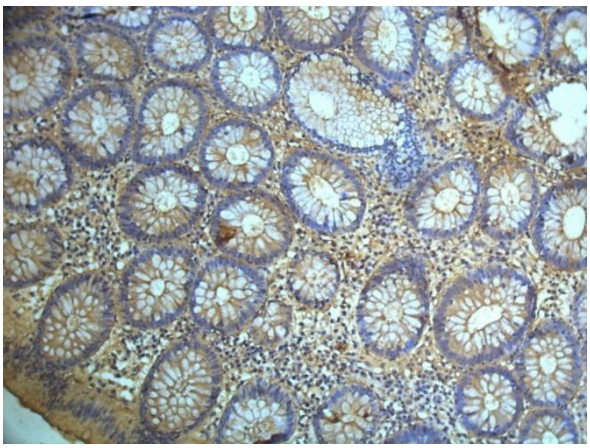

Fig. 5 Immunohistochemical staining of Nf-kB. Brown color refers to the positive result (Ag/Ab reaction), and purple color refers to the counterstain (hematoxylin)

4. Discussion

The findings of this study provide valuable insights into the differential expression of gastrin and prostaglandin E2 (PGE2) in colorectal diseases, particularly in relation to *H. pylori* status and histopathological subtypes. The median serum gastrin level (118 pg/mL) and PGE2 level (174.5 pg/mL) observed in our cohort align with previous reports suggesting elevated gastrin in conditions like adenocarcinoma and inflammatory bowel disease (IBD) [15]. Notably, gastrin's role as a growth factor for gastrointestinal mucosa may explain its association with neoplastic progression, as seen in other studies where hypergastrinemia correlated with colorectal cancer risk [21]. Similarly, the elevated PGE2 levels in our patients are consistent with its known pro-inflammatory and pro-tumorigenic effects, mediated through cyclooxygenase-2 (COX-2) and nuclear factor-kappa B (NF-κB) pathways [16][31] .

The immunohistochemical analysis revealed high COX-2 expression in 47.5% of cases and high NF-κB expression in 27.5%, underscoring their involvement in colorectal pathogenesis. These results corroborate earlier findings where COX-2 overexpression was linked to adenocarcinomas and adenomatous polyps, while NF-κB activation was associated with chronic inflammation and cancer progression [32][33] . The significant positive correlation between NF-κB and leukocyte count (*r* = 0.382, *p* = 0.015) further supports the interplay between inflammation and NF-κB signaling, as demonstrated in studies linking leukocytosis to NF-κB-driven cytokine production in IBD and colorectal cancer (18,19). Additionally, the strong correlation between NF-κB and CCK2BR (*r* = 0.532, *p* < 0.001) suggests a potential feedback loop between gastrin receptors and inflammatory pathways, a phenomenon observed in gastric and colorectal malignancies [7], [22] .

Contrary to expectations, no significant correlations were found between gastrin/PGE2 and *H. pylori* status, age, or hemoglobin levels. This contrasts with some studies reporting *H. pylori*-induced hypergastrinemia due to parietal cell damage [5]. but aligns with others, suggesting that gastrin elevation may be more disease-specific than *H. pylori*-dependent [23] . The lack of association with hemoglobin could reflect the multifactorial nature of anemia in colorectal diseases, where blood loss, chronic inflammation, and nutritional deficiencies all play roles [34] .

The predominance of adenocarcinoma (27.5%) and inflammatory conditions (15%) in our histopathological spectrum mirrors global trends, reinforcing the clinical relevance of these findings (11). The absence of significant correlations between PGE2 and COX-2/NF-κB in our study contrasts with experimental models showing PGE2 as a downstream product of COX-2 (17), possibly due to the small sample size or heterogeneous disease stages. However, the trend toward higher PGE2 in inflammatory and neoplastic conditions aligns with its role in mucosal damage and tumor angiogenesis [20].

Given the crosslink between COX-2/PGE2 and NF-κB pathways, dual-targeting agents may offer superior therapeutic benefits compared to single-pathway inhibitors. Natural compounds like curcumin and resveratrol have demonstrated efficacy in suppressing both COX-2 and NF-κB in preclinical models (35,36), Additionally, synthetic drugs such as licofelone (a dual COX/LOX inhibitor) have shown promise in reducing colorectal polyp formation in clinical trials [37] . Future research should explore combination therapies targeting these interconnected pathways.

5. Conclusions

In conclusion, the study highlights the complex interplay between gastrin, PGE2, and inflammatory markers in colorectal diseases. The correlations between NF-κB, leukocytosis, and CCK2BR suggest potential therapeutic targets, such as NF-κB inhibitors or gastrin receptor antagonists, warranting further investigation. These

findings contribute to the growing body of evidence supporting the use of biomarkers like gastrin and PGE2 for risk stratification and personalized management of colorectal disorders.

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