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The relationship between severity of gastric inflammation due to Helicobacter pylori and colorectal malignancies

Helikobakter piloriye bağlı gastrik inflamasyon şiddetinin kolorektal malignansilerle ilişkisi

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SUMMARY

Objective: Several factors play role in colorectal carcinogenesis. Among these factors, helicobacter pylori infection is supposed to be one of the causative factors. Previous studies were focused on investigation of the relationship between helicobacter pylori existence and colon carcinomas by particular serological diagnostic tests. The aim of our study was to determine the effect of the helicobacter pylori infection and the severity of inflammation related to this infection on the colon carcinomas and non carcinoma colon mass lesions(tubular adenoma, tubulovillous adenoma, hyperplastic polyp).

Method: A retrospective study was conducted at Kecioren Teaching - Research Hospital between 2010 to 2018. The files of 657 patients who underwent colonoscopy and were diagnosed as colon benign or malign mass lesions were examined retrospectively from the hospital database. Two hundred five patients who had undergone both upper gastrointestinal endoscopy and colonoscopies were included in the study. The presence and severity of inflammation due to helicobacter pylori were evaluated by histopathological examination of biopsies taken during upper gastrointestinal endoscopy. The severity of H. pylori inflammation was graded according to the Sydney classification

Results: In the comparison of colon carcinoma with other colon mass lesions group, there was no statistical significance in terms of gender (P= 0.094) and H. pylori serology (P= 0.998). However, the degree of inflammation was significantly high in patients with colon carcinoma than other colon mass lesions (P< 0.001).

Conclusions: The fact that the severity of helicobacter pylori inflammation is higher in patients with colon carcinoma than patients with non-carcinoma colonic mass lesions suggests that inflammation due to helicobacter pylori may be more important than the presence of helicobacter pylori in the carcinogenesis of colon cancer.

Keywords: Helicobacter pylori, colon carcinoma , inflammation

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ÖZET

Amaç: Kolorektal karsinom gelişiminde çeşitli faktörler rol oynamaktadır. Helikobakter pilori infeksiyonu bu faktörlerden biri olarak öne sürülmektedir. Önceki çalışmalar, serolojik tanı testleri ile belirlenen helikobakter pilori varlığının kolorektal karsinom ile ilişkisinin araştırılmasına odaklanmıştır. Önceki çalışmalardan farklı olarak çalışmamızın amacı, helikobakter pilori infeksiyonu ve buna bağlı inflamasyon şiddetinin kolorektal karsinom ve karsinom dışı kolon kitle lezyonları üzerindeki etkisini belirlemektir.

Yöntem: Bu retrospektif çalışma 2010-2018 yılları arasında, Keçiören Eğitim Araştırma Hastanesi gastroenteroloji kliniğine başvuran ve yapılan kolonoskopi sonucunda benign veya malign lezyon saptanan 657 hastanın dosyalarının geriye yönelik taranması ile yapılmıştır. Kolonoskopi işlemi ile birlikte üst gastrointestinal sistem endoskopisi işlemi yapılmış ve helikobakter pilori seropozitifliği olan 205 hasta çalışmaya dahil edilmiştir. Helikobakter pilori varlığı ve inflamasyon şiddeti üst gastrointestinal sistem endoskopisi sırasında alınan biyopsilerin histopatolojik incelemesi sonucu belirlenmiştir. Helikobakter pilori inflamasyon şiddeti Sydney sınıflamasına gore yapılmıştır.

Bulgular: Kolon karsinomu olan hasta grubu ile kolonun karsinom dışı kitle lezyonlarına sahip hastaların karşılaştırması yapıldığında her iki grup arasında cinsiyet (P= 0.094) ve helikobakter pilori serolojisi (P= 0.998). arasında istatistiksel fark yoktu. Bununla birlikte helikobakter pilori inflamasyonunun şiddeti kolon karsinomlu hastalarda, karsinom dışı kolon kitle lezyonu olan hastalara göre anlamlı derecede yüksek saptandı (P< 0.001).

Sonuç: Kolon karsinomu olan hastalarda helikobakter pilori inflamasyon şiddetinin karsinom dışı kolon kitle lezyonlarından daha yüksek bulunması kolon kanseri karsinogenezinde helikobakter pilori varlığından ziyade helikobakter piloriye bağlı oluşan inflamasyonun daha önemli olabileceğini düşündürmektedir.

Anahtar sözcükler: Helikobakter pilori, kolon kanseri, inflamasyon

INTRODUCTION

There is an association between helicobacter pylori *(H. pylori)* infection and malignancies. Although carcinogenesis and pathogenesis in *H. pylori* infection are not fully understood, several mechanisms such as chronic inflammation, genetic mutations, and virulence factors are proposed to explain the role of *H. pylori* in different carcinomas [1]. Gastric carcinoma is the most common cancer associated with *H. pylori* [2] . *H. pylori* is also related to mucosa-associated lymphomas (MALT lymphomas), pancreatic cancer, and biliary tract cancers. [3-5]

Colorectal cancer (CRC) ranks third in the ranking of cancers and second in the ranking of cancer-related mortalities in both sexes and all ages worldwide.[6] Among different etiologies in CRC carcinogenesis, epidemiological analyses have shown a relationship between colorectal adenomas and/or adenocarcinomas with *H. pylori* [7, 8]

Studies conducted to date have investigated this relationship on the basis of *H. pylori* existence with particular serological diagnostic tests.

Unlike other studies, the aim of our study was to determine the effect of the helicobacter pylori infection and the severity of inflammation related to this infection on the colon carcinomas and mass lesions of colon other than carcinomas.

MATERIAL AND METHODS

This retrospective study was conducted at Kecioren Teaching and Research hospital's Department of Internal Medicine. Between 2010 to 2018, the files of 657 patients, who underwent colonoscopy and were diagnosed with colon benign or malign lesions, were examined retrospectively from the hospital database. A total of 205 patients who underwent both upper gastrointestinal endoscopy and colonoscopy were analyzed. The colonic lesions that were diagnosed histopathologically were classified as carcinoma and mass lesions other than carcinoma. The presence and the severity of inflammation due to *H. pylori* were evaluated by histopathological examination of biopsies taken from at least two sites including antrum and corpus at upper gastrointestinal endoscopy. Severity of *H. pylori* inflammation was graded according to the Sydney classification system. In 205 patients colon carcinoma and other colonic mass lesions were detected by pathologic assessment **.**Shapiro Wilk test, Mann Whitney U test, Kruskal Wallis and Dunn multiple comparison tests were used in the statistical comparisons. Chi-square test was applied in order to investigate the relationship between 2 categorical variables. Statistical analysis was performed with SPSS for Windows version 22.0 (IBM Corporation, United States) and a P value < 0.05 was accepted as statistically significant.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The

protocol of this study was reviewed and approved by the local ethics committee **(Date: 26/09/2018, no: 1758).** Written informed consent was obtained.

RESULTS

A total of 205 patients [87 (42.4%) female; 118 (57.6%) male] were included in the study. The average age of the patients was 68 years ± standard deviation, SD (interquartile range, IQR: 59 – 78). Demographic data, presence of upper endoscopic evaluation and histopathological findings of patients are demonstrated in (**Table 1).**

Table 1: Characteristics of patients

		n	**%**
Gender	Female	261	39.70
	Male	396	60.30
Groups	Colon carcinoma	278	42.30
	Non carcinoma colon mass lesions		
	I. Tubuler adenoma	136	20.70
	II. Tubulovillous adenoma	37	5.60
	III. Hyperplastic polyp	206	31.40
Endoscopy	Present	205	31.20
	Absent	452	68.80
H pylori	Positive	104	50.70
	Negative	101	49.30

When colon carcinoma group was compared with non carcinoma colon mass lesions group (tubular adenoma, tubulovillous adenoma, hyperplastic polyp*),* there was no statistical significance in terms of gender (P = 0.094), family history of colorectal carcinoma(P>0.05) and *H. pylori* presence (P = 0.998). However, there was statistically significant difference in termes of smoking status (P<0.05), alcohol consumption (P<0.05), BMI(body mass index) (P<0.05) and age (P < 0.001) between colon carcinoma and non carcinoma colon mass lesions. Additionally intense of inflammation was significantly higher in patients with colon carcinoma than non carcinoma colon mass lesions (P < 0.001), **Table 2.**

Table 2 : Comparison of groups according to gender, *H pylori* presence, and inflammation grade

Variable	Colorectal cancer	Non carcinoma colon mass lesions	**P**
Age(mean±SD)	**67,13±14,16**	**57,82±13,57**	**0.001**
Gender			
Female (n)	53	34	0,094
Male (n)	85	33	
H pylori			
H pylori (+)(n)	70	34	0,998
H pylori (-)(n)	68	33	
***H pylori* İnflammation**			
Grade 1(n)	36	32	
Grade 2(n)	22	1	**0,001**
Grade 3(n)	11	2	
Smoking status			
Smoker(n)	36	23	**0.024**
Non-Smoker (n)	102	44	
BMI (mean±SD)(kg/m^2)	26,056±**2,86**	24,775±**2,86**	**0.003**
AlcoholConsumption			
Current/Ex-drinker(n)	4	7	**0.024**
No(n)	134	60	
Family History of Colorectal carcinoma			**0.638**
Yes(n)	6	2	
No(n)	132	65	

DISCUSSION

In our study, there was no statistical significance between colon carcinoma and non carcinoma colon mass lesions group in terms of gender and H. pylori presence . However, the degree of inflammation was significantly correlated with colon carcinoma and non carcinoma colon mass lesions.

Several factors may take part in the carcinogenesis of colon malignancies.These factors are alcohol, cigarette, increased body mass index, processed meat,microbial dysbiosis, low fiber diet, inflammatory bowel disease, diabetes mellitus and genetic alterations.[7, 9]

Gut microbiota normally consists of several beneficial bacteria types such as Lactobacillus, Bifidobacterium, Clostridium spp. and Streptococcus mutants which make a barrier over colon epithelium against cellular injury [10]. A variety of disorders such as inflammatory bowel disease, obesity, and diabetes decrease the beneficial bacteria colonization and increase the colonization of harmful bacteria in colon [11, 12].This shift is termed dysbiosis. Escherichia coli, Bacteroides fragilis, Fusobacterium spp., and Peptostreptococcus spp. are the most colonized bacteria species in dysbiosis [13] .

As a result of the increased harmful bacteria species in the colon epithelium, the epithelium loses its protective barrier. Increased endotoxins, oxidants and inflammation cause DNA damage and cellular damage in the colon epithelium. [14] This micro-environment contributes to carcinogenesis in colon epithelium. [15, 16] Several mechanisms were proposed to elucidate the relationship between dysbiosis and carcinogenesis.These mechanisms include:

Chronic inflammation:Chronic inflammation occurs in colon epithelium as a consequence of dysbiosis. Chronic inflammation is one of the initiative factors in colorectal carcinogenesis 17 . Increased levels of cytokines, pro-inflammatory interleukins (IL-1-6-7-22) and TNF-alfa are associated with uncontrolled chronic inflammation. [18, 19]

Chronic inflammatory activity triggers a cascade that includes several growth factors and cytokines that disrupt apoptosis,increased oxidative stress, proliferation and angiogenesis.[20]

Other mechanisms include the activation of MSI (microsatellite instability gene) and CIMP (CpG island methylator phenotype) by fusobacterium nucleatum. Additionally,fusobacterium interacts with E-cadherin and stimulates malign transformation of the epithelial cells.[21] Furthermore, enterotoxin of Bacteroides fragilis leads to carcinogenesis by activating the Wnt/β-catenin and nuclear factor-κB. Bacterial toxins affect cell cycle by damaging DNA. [22] Dysbiosis also raises gut microbial metabolites (secondary bile acid, glucuronic acid, and acetaldehyde) that cause epithelial cell injury.[23]

Besides Escherichia coli, bacteroides fragilis, and fusobacterium,H.pylori arealso implicated in colorectal carcinogenesis.[24] Studies conducted to date have investigated the relationship between *H. pylori* and colon carcinomas and colon adenomas on the basis of *H. pylori* serology. Unlike these studies, in our study, the intensity of *H.pylori* colonization and the grade of inflammation due to *H. Pylori* infection were found to be significantly associated with colorectal cancer and other colon lesions.

The pathophysiologic mechanisms underlying the association between *H. pylori* infection and colorectal neoplasms are not clear. Several mechanisms have been proposed to explain *H pylori* and colon carcinogenesis [25].

It is suggested that the primary mechanism for *H. pylori* and colon carcinoma relation is probably the activation of the inflammatory response of the gastric cells.[25, 26] Gastric body mucosal inflammation increases serum gastrin levels, and increased gastrin promotes carcinogenesis through its trophic effects. [27] Our findings support this hypothesis. It is assumed that gastrin makes this effect possible via receptors that are unique to the gastrin (gastrin/cholecystokinin-type B receptor (CCKB-R) [28] Despite this conclusion, Selgrad et al.[29] found that not high gastrin levels but cytotoxin-associated gene (Cag) presence is associated with increased risk of colorectal cancer. Papastergiou et al.[30] concluded that the mechanism behind the *H. pylori*-related carcinogenesis in colon carcinoma includes inflammatory process, changes in gut microflora and delivery of toxins and/or hormonal mediators. In addition, *H. pylori* urease enzyme can also turn gastric juice urea into ammonia and elevated high ammonia level in the lumen may promote cancer activity. [31]

Studies regarding the association of *H. pylori* with with colorectal cancer and/or colon polyps are controversial. Some studies found a significant relationship between *H. pylori* and colorectal cancer while others showed no such relationship. In our study, unlike other studies, we found that rather than *H. pylori* seropositivity, *H. pylori*-related inflammation has a significant role in colon carcinogenesis. Abbass et al.[32] demonstrated that

there was no relation between colon malignancies and *H. pylori*.Soylu et al.[33] found no statistically significant relationship between *H. pylori* and both colon polyp and polyp size. Similarly, Kalkan et al.[34]. observed no relationship between *H. pylori* seropositivity and colon polyps. Contrary to these findings, Nam et al.[35] showed that there was a significant relationship between *H. pylori* presence and precancerous lesions of colon. Yang et al.[36] concluded that *H. pylori* was linked with enhanced colon carcinoma hazard. In a nationwide population- based study , Liu et al.[37] concluded that there was a statistically significant affiliation between *H. pylori* and both colorectal malignancies. In a study conducted by Nam et al.[38],similar results were found showing that *H. pylori* were an independent risk factor for colorectal adenomas. Two meta-analysis conducted by Q. Wu et al.[39] and F. Wang et al. [40] from China showed a significant association between *H. pylori* and colonic neoplasia.

CONCLUSION

The fact that the severity of helicobacter pylori inflammation is higher in patients with colon carcinoma than patients with non-carcinoma colonic mass lesions suggests that inflammation due to helicobacter pylori may be more important than the presence of helicobacter pylori in the carcinogenesis of colon cancer.Our Study have some limitations. First this study is a retrospective study. We did not able to make a search about microbial dysbiosis and genetical alterations.

Main Points:

-The severity of gastric inflammation due to H. pylori infection is important than H. pylori seropositivity in colon carcinogenesis

- There was no significant difference in the presence of H.pylori infection between patients with colon cancer and patients with non carcinoma colon mass lesions

- The intensity of H.pylori inflammation was more prominent in patients with colon cancer than patients with non carcinoma colon mass lesions.

DECLARATIONS:

- **Ethics approval and consent to participate**: This research conducted in compatible to the Declaration of Helsinki, and was accepted by Health Sciences University Keçiören Teaching and Research Hospital ethics committee(date 26.09.2018) (no:092018/1758)
- **Consent for publication:** This manuscript does not contain any individual person's data in any form (including any individual details, images or videos)
- **Availability of data and materials:** The datasets generated and/or analysed during the current study are not publicly available.Before sharing the data set ,Ministry of Health should give permission but are available from the corresponding author on reasonable request.
- **Competing interests**: The authors declare that they have no competing interests
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