Prevalence of *Helicobacter Pylori*-Negative, Non-Steroidal Anti-Inflammatory Drug Related Peptic Ulcer Disease in Patients Referred to Afzalipour Hospital

Seyed Mahdi Seyed Mirzaei[1], Mohammad Javad Zahedi[1], Sara Shafiei pour[1,2*]

1. Gastroenterology and Hepatology Research Center, Kerman University of Medical Sciences, Kerman, Iran
2. Institute of Basic and Clinical Physiology sciences, Kerman University of Medical Sciences, Kerman, Iran

ABSTRACT

BACKGROUND

Although *Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) are the main causes of peptic ulcers disease (PUD), recently the prevalence of idiopathic peptic ulcer (IPU) is increasing in most parts of the world. The aim of this study was to assess the prevalence of IPU in Kerman, the center of largest province in south-east Iran.

METHODS

We included 215 patients with peptic ulcer in our study. Combined methods rapid urease test (RUT), histology, and real time polymerase chain reaction (PCR) was performed on endoscopic samples of peptic ulcers. NSAID use was determined by medical history. SPSS software version 16 was used for data analysis. p value<0.05 was considered as statistically significant.

RESULTS

Of 215 consecutive patients with peptic ulcer, four (1.8%) had *H.pylori*-negative and NSAID-negative PUD. There were not significant differences between patients with IPU and patients with peptic ulcer associated with *H.pylori* or NSAIDs regarding the sex, age, cigarette smoking, and opioid abuse.

CONCLUSION

Our study showed that in contrast to other reports from western and some Asian countries, the prevalence of IPU is low in Kerman and *H.pylori* infection is still the major cause of PUD. We recommend a large and multi-central study to determine the prevalence of IPU in Iran.

KEYWORDS
Peptic ulcer; Prevalence; *Helicobacter pylori*; Non-steroidal anti-inflammatory drugs; Iran

Please cite this paper as:
Seyed Mirzaei SM, Zahedi MJ, Shafiei pour S. Prevalence of *Helicobacter Pylori*-Negative, Non-Steroidal Anti-Inflammatory Drug Related Peptic Ulcer Disease in Patients Referred to Afzalipour Hospital. *Middle East J Dig Dis* 2015;7:242-5.

* **Corresponding Author:**
Sara Shafiei pour, MD
Afzalipour Hospital, Kerman, Iran
Tel: + 98 34 33312156
Fax: +98 34 33215667
Email: sarashafieipour@yahoo.com
Received: 10 May 2015
Accepted: 18 Jul. 2015

INTRODUCTION

After the discovery of *Helicobacter pylori* (*H.pylori*), the possibility of its association with pathogenesis of peptic ulcers disease (PUD) was discussed by Warren and Marshall in 1983.[1,2] *H.pylori* may be an important cause in 90-95% of duodenal and 70-90% of gastric ulcers.[3] In addition to *H.pylori*, non-steroidal anti-inflammatory drugs (NSAIDs) are the other most common causes of PUD.[4] Zollinger-Ellison syn-

drome, smoking, Crohn's disease, and viral infections are the other less common causes of PUD.[5] However, recently some studies show an increase in the prevalence of idiopathic peptic ulcer (IPU), which is defined as gastric or duodenal ulcers without these known risk factors. In a study by Xia and colleagues the prevalence of IPU was 40% in Australia.[6] Also, Goenka and co-workers reported a similar result in India in 2011.[7] But a few studies from Italy and Japan show that the frequency of IPU is still low in these societies.[8,9] IPU in contrast to other well known PUD has higher recurrence, more complications, and difficult management.[10,11]

The prevalence of IPU in 61 patients with PUD that were complicated with gastrointestinal bleeding was reported about 13% by Rajabalinia in Taleghani Hospital (a medical center in the capital of Iran) in 2011.[12]

The aim of this study was to assess the prevalence of IPU in Kerman, the center of the largest province in south-east Iran. To the best of our knowledge up to now no study has been performed for estimation of the prevalence of IPU in south-east Iran.

MATERIALS AND METHODS

Patients

From January 2012 to December 2013, we included 215 consecutive patients with an endoscopically defined active peptic ulcer in our study. The diagnosis of PUD was made by loss of mucosal integrity ≥5 mm. According to its location, PUD was classified as gastric, duodenal, or coexistent. Patients were defined as NSAID users if they had any history of taking NSAIDs (including low doses of aspirin) within 30 days before endoscopy.

Exclusion criteria were: patients with histopathology consistent with malignant changes such as adenocarcinoma, lymphoma, Gastro Intestinal Stromal Tumors (GIST), metastasis, and Crohn's disease or presence of liver , kidney, and coagulation disorders.

Diagnostic Methods for *H. Pylori* Infection

During the upper GI endoscopy, four biopsy samples were taken from the body and antrum of gastric mucosa and rapid urease test (RUT) was done for two of the samples and if negative other specimens were sent for histological assessment (hematoxylin and eosin staining). Real time polymerase chain reaction (PCR) was performed for the samples that had negative results in two previous tests. Patients were considered infected if any of the three diagnostic tests had a positive result.

Statistical analysis

Frequency and percentage were used for categorized qualitative variables in addition to mean and standard deviation for quantitative variables. Pearson's Chi squared test and also Fisher's exact test were used to compare demographic variable between patients with IPU and patients with *H.pylori* or NSAIDs associated PUD. SPSS software version 16 was used for data analysis. p value<0.05 was considered as statistically significant.

Ethics

All patients with PUD who were referred for upper gastrointestinal endoscopy consented to participate and the Ethical Review Committee of the Faculty of Medicine, Kerman University of Medical Sciences approved the protocol of this survey.

RESULTS

215 patients with PUD were enrolled in this study. NSAID use during the previous 30 days was observed in 46 of the patients with PUD (21.4%). Locations of ulcer and demographic variables of the patients are summarized in table 1.

RUT was positive in 197 (91%) patients and 11 patients with negative RUT had histological assessment consistent to *H.pylori* infection (61.1%). Real time PCR was performed in all patients with negative RUT and histological resalts 7(3.2%). *H.pylori* was not to detect in these patients by PCR.

Subsequently, of the 215 patients with PUD, 7 patients had negative *H.pylori* results (3.2%).

Drug history of NSAIDS use was positive in 43 (39.1%) patients with positive *H.pylori* tests. Only four patients with negative *H.pylori* tests had also no history of recent NSAIDS use. so, the preva-

Table 1: Clinical and demographic features of the patients with PUD

Characteristic		Frequency n (%)
Total number of patients		215(100)
men		134(62.3)
women		81(37.7)
Age (mean)		62 ± 15.2
NSAID/aspirin use		46 (21.4)
Smoking		34(15.8)
Opioid Abusers		34 (15.8)
Ulcer location	DU	135(62.7)
	GU	65(30.2)
	DU + GU	15(6.9)

NSAID, non-steroidal anti-inflammatory drug; DU, duodenal ulcer; GU, gastric ulcer.

Table 2: Comparison between patients with idiopathic peptic ulcer and peptic ulcer associated with *H. pylori* or NSAIDs use (univariate analysis)

	Idiopathic peptic ulcer (n=4)	*H. pylori* or NSAIDs-positive (n=211)	*p* value
Male No.(%)	(50)2	(62.5) 132	0.3
Age(mean±SE)	15±61	15.4 ±63	0.1
Smoking No.(%)	(25) 1	(15.6) 33	0.5
Opioid Abusers No.(%)	(25) 1	(15.6) 33	0.5

lence of *H.pylori* and NSAIDS negative PUD was 1.8% (figure 1).

There were not significant differences between patients with IPU and patients with peptic ulcer associated with *H.pylori* or NSAIDs in regarding the sex, age, cigarette smoking, and opioid abuse (table 2).

DISCUSSION

The prevalence of IPU in our study was 1.8%. Up to now numerous studies have been published for estimating the prevalence of IPU in Asia. From 1999 to 2003 the prevalence of IPU was estimated as 1.3-4.1% in five studies in different parts of Asia but recent studies show that this prevalence has increased to 10-30%. So the prevalence of IPU is increasing in most parts of the world.[5-13]

The main reason that may explain the low prevalence of IPU in our study was the high prevalence of *H.pylori* in Iranian population especially

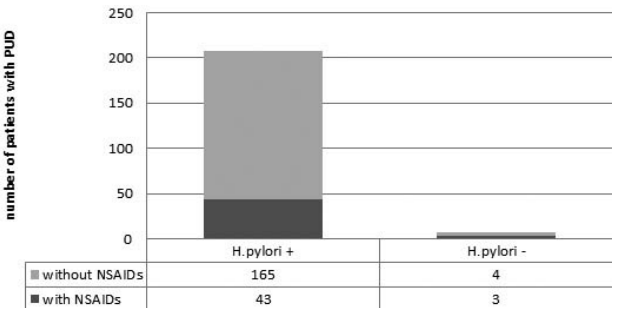

Fig. 1: Frequency of PUD and *Helicobacter pylori* status. Of the 215 patients who were found to have PUD 96.7% were *H.pylori* positive and only 4 patients (1.8%) were negative for both *H.pylori* and NSAIDs.

in southern Iran[14-16]. The *H.pylori* infection rate in the Iranian population was reported as 57-91%. Besides, the prevalence of *H.pylori* i infection is very high in southern Iran.[17-18] In Shiraz, a city in the south of Iran, 98% of 2-year-old children have positive *H.pylori* stool antigen.[19] Barazandeh and colleagues in a large endoscopic systematic investigation in north west of Iran in 2012 detected *H.pylori* in 93.9% of gastric and 100% of duodenal ulcers.[20]Low socioeconomic status and poor hygiene have been described as risk factors of *H.pylori* infection.[14-21]

The strength of our study was using the real time PCR for all patients whose *H.pylori* infection was not detected by RUT and histological examinations. In spite of the presence of several diagnostic tests to determine *H.pylori* infection status, the best method to be used as "gold standard" is uncertain.[22-24] Combining the results of two or more tests at the same time similar to what we did in our study may be one solution. PCR with the sensitivity and specificity of 75-100% and 84-100%, respectively, may be slightly superior than the other diagnostic tests, especially in detecting low bacterial loads.[23-25]

The major limitation of our study was that diagnosis of Aspirin and other NSAIDs users was according to only medical history. In many countries Aspirin and other NSAIDs are available as over the counter drugs and some users deny their consumptions.[5]. In a study by Hirschowitz and colleagues about 50% of patients with refractory PUD and negative medical history of NSAIDs use had high blood level for salicylic acid.[26]

In summary, our study showed that in contrast to other studies from western and some Asian countries, the prevalence of IPU is low in Kerman, and *H.pylori* infection is still the major cause of PUD. We recommend a large and multi-central study to determine the prevalence of IPU in Iran.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Aruin LI. Helicobacter (Campylobacter) pylori in the etiology and pathogenesis of gastritis and peptic ulcer. *Arkh Patol* 1990;**52**:3-8.
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patientswith gastritis and peptic ulceration. *Lancet* 1984;**1**:1311–5.
3. Kuipers EJ, Thijs JC, Festen HP. The prevalence of Helicobacterpylori in peptic ulcer disease. *Aliment Pharmacol Ther* 1995;**9 Suppl 2**:59-69.
4. Konturek SJ, Bielański W, Płonka M, Pawlik T, Pepera J, Konturek PC, et al. Helicobacter pylori, non-steroidal anti-inflammatory drugs and smoking in risk pattern of gastroduodenal ulcers. *Scand J Gastroenterol* 2003;**38**:923-30.
5. Iijima K, Kanno T, Koike T, Shimosegawa T. Helicobacter pylori-negative, non-steroidal anti-inflammatory drug: negative idiopathic ulcers in Asia. *World J Gastroenterol* 2014;**20**:706-13.
6. Xia HH, Kalantar JS, Mitchell HM, Talley NJ. Can helicobacter pylori serology still be applied as a surrogate marker to identify peptic ulcer disease in dyspepsia? *Aliment Pharmacol Ther* 2000;**14**:615-24.
7. Goenka MK, Majumder S, Sethy PK, Chakraborty M. Helicobacter pylori negative, non-steroidal anti-inflammatory drugnegative peptic ulcers in India. *Indian J Gastroenterol* 2011;**30**:33-7.
8. Sbrozzi-Vanni A, Zullo A, Di Giulio E, Hassan C, Corleto VD, Lahner E, et al. Low prevalence of idiopathic peptic ulcer disease: an Italian endoscopic survey. *Dig Liver Dis* 2010;**42**:773-6.
9. Ootani H, Iwakiri R, Shimoda R, Nakahara S, Amemori S, Fujise T, et al. Role of Helicobacter pylori infection and non-steroidal anti inflammatory drug use in bleeding peptic ulcers in Japan. *J Gastroenterol* 2006;**41**:41-6.
10. Quan C, Talley NJ. Management of peptic ulcer disease not related to Helicobacter pylori or NSAIDs. *Am J Gastroenterol* 2002;**97**:2950-61.
11. Yoon H, Kim SG, Jung HC, Song IS. High Recurrence Rate of Idiopathic Peptic Ulcers in Long-Term Follow-up. *Gut Liver* 2013;**7**:175-81.
12. Rajabalinia H, Ghobakhlou M, Nikpour S, Dabiri R, Bahriny R, Sherafat SJ, et al. Non-Helicobacter pylori, non-NSAIDs peptic ulcers: a descriptive study on patients referred to Taleghani hospital with upper gastrointestinal bleeding. *Gastroenterol Hepatol Bed Bench* 2012;**5**:190-6.
13. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. *Aliment Pharmacol Ther* 2009;**29**:938-46.
14. Zahedi MJ, Darvish-Moghadam S, Atapoor M, Hayatbakhsh M. Relative Frequency of Helicobacter pylori Infection in the City of Kerman in 2000. *J Kerman Univ Med Sci* 2002;**9**:140-5.
15. Nassrolahei M, Khalilian A. Seropositivity of antibodies against Helicobacterpylori and hepatitis A virus in Iran. *Ann Saudi Med* 2004;**24**:61-4.
16. Malekzadeh R, Derakhshan MH, Malekzadeh Z. Gastric-cancer in Iran: epidemiology and risk factors. *Arch Iran Med* 2009;**12**:576-83.
17. Khedmat H, Karbasi-Afshar R, Agah S, Taheri S. Helicobacter pylori Infection in the general population: A Middle Eastern perspective. *Caspian J Intern Med* 2013;**4**:745-53.
18. Shokrzadeh L, Baghaei K, Yamaoka Y, Shiota S, Mirsattari D, Porhoseingholi A, Zali MR. Prevalence of Helicobacter pylori infection in dyspeptic patients in Iran. *Gastroenterology Insights* 2012;**4**:e8.
19. Alborzi A, Soltani J, Pourabbasi B, Oboodi B, Haghighat M, Hayati M, et al. Prevalence of Helicobacter pylori infection in children (south of Iran). *Diagn Microbiol Infect Dis* 2006;**54**:259-61.
20. Barazandeh F,Yazdanbod A, Pourfarzi F, Sepanlou SG, Derakhshan MH, Malekzadeh R. Epidemiology of Peptic Ulcer Disease: Endoscopic Results of a Systematic Investigation in Iran. *Middle East J Dig Dis* 2012;**4**:90-6.
21. Malaty HM, Paykov V , Bykova O. Helicobacter pylori and Socioeconomic factors in Russia. *Helicobacter* 1996;**1**:82-7.
22. Patel SK, Mishra GN, Pratap CB, Jain AK, Nath G. Helicobacter pylori is not eradicated after triple therapy: a nested PCR based study. *Biomed Res Int* 2014;**2014**:483136.
23. Wang SW, Yu FJ, Lo YC, Yang YC, Wu MT, Wu IC, et al. The clinical utility of string-PCR test in diagnosing Helicobacter pylori infection. *Hepatogastroenterology* 2003;**50**:1208-13.
24. Patel SK, Pratap CB, Jain AK, Gulati AK, Nath G. Diagnosis of Helicobacter pylori: what should be the gold standard? *World J Gastroenterol* 2014;**20**:12847-59.
25. Kalach N, Gosset P, Dehecq E, Decoster A, Spyckerelle C, Papadopolos S, et al. Usefulness of Gastric Biopsy-Based Real Time-PCR for the Diagnosis of Helicobacter Pylori Infection in Children. *J Pediatr Gastroenterol Nutr* 2015 Mar 17.
26. Hirschowitz BI, Lanas A. Intractable upper gastrointestinal ulceration due to aspirin in patients who have undergone surgery for peptic ulcer. *Gastroenterology* 1998;**114**:883-92.