RESEARCH ARTICLE

Helicobacter pylori Infection Impacts on Functional Dyspepsia in Thailand

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Abstract

Background: *Helicobacter pylori (H. pylori)* is a well known major cause of gastric cancer and even when asymptomatic infected patients are at elevated risk. Functional dyspepsia (FD) is also one of the most common gastrointestinal diseases, which greatly impacts the quality of life. *H. pylori* infection and psychosocial stress are frequently associated with FD but limited studies have confirmed the relationships, especially in Southeast Asian countries. Here we aimed to investigate the prevalence and impact of *H. pylori* infection, anxiety and depression on Thai FD patients. Materials and Methods: This cross-sectional study was conducted in a tertiary care center in Thailand, during February 2013-January 2014. All FD patients were diagnosed and categorized by Rome III criteria into epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) groups. The Hospital Anxiety and Depression Scale was used to evaluate psychological status. The presence of *H. pylori* was defined as positive with *H. pylori* culture, positive rapid urease test or positive histology. Results: Three hundred FD patients were included, 174 (58%) female. Overall mean age was 54.8+15.1 years. There were 192 (64%) patients with PDS and 108 (36%) with EPS. *H. pylori* infection was demonstrated in 70 (23.3%) patients. Anxiety and depression were documented in 69 (23%) and 22 (7.3%), respectively. *H. pylori* infection, anxiety and depression were significantly higher in PDS than EPS patients (27.1% *vs* 16.7%; p=0.04; OR=1.86; 95%CI=1.01-3.53 and 29.7% *vs* 11.1%; p=0.0002; OR=3.4; 95%CI=1.7-7.1 and 10.4% *vs* 1.9%; p=0.006; OR=6.2; 95%CI=1.4-38.9, respectively). Conclusions: *H. pylori* infection, anxiety and depression were commonly found in Thai FD patients and more prevalent in PDS than EPS. *H. pylori* eradication might be the key to success for the treatment of Thai FD patients and prevent the development of gastric cancer.

Keywords: *H. pylori* infection - functional dyspepsia - gastric cancer - Thailand

Asian Pac J Cancer Prev, **15 (24)**, 10887-10891

Introduction

Helicobacter pylori (*H. pylori*) remains an important cause of gastric cancer and peptic ulcer disease worldwide. Functional dyspepsia (FD) is also one of the most common functional gastrointestinal disorders (FGIDs) in the world and might be related to *H. pylori* infection but limited studies were reported from Southeast Asian countries. According to Rome III, FD can be diagnosed from at least one symptom of the followings: early satiation, postprandial fullness, epigastric pain or epigastric burning symptoms fulfilled for the last 3 months with onset at least 6 months before diagnosis (Tack et al., 2006). Roughly 25% of adults in Western countries suffer from dyspepsia annually (Talley et al., 2005) and the prevalence of dyspepsia in Eastern is around 7.7-30.4% (Mahadeva and Goh, 2006; Min et al., 2014). Moreover, FD takes nearly 5% of all primary health care consultation cases (Baron and Sonnenberg, 2008).

The pathophysiology and etiology of FD are multifactorial and still uncertain. The possible pathophysiology of FD consists of slow gastric emptying, increased sensitivity to gastric distension, impaired fundic accommodation to a meal, increased duodenal acid exposure, duodenal hypersensitivity to acid, lipids or released cholecystokinin and duodenal immune activation (Lee and Tack, 2010). The genetic factors associated with FD include the genetic variant C825T in *GNβ3* (Dai et al., 2014), the COX-1 gene polymorphism (Arisawa et al., 2008), polymorphism in codon 158 of the Catechol-O-methyltransferase (COMT) gene (Tahara et al., 2008). The other potential risk factors of FD are gender, age, smoking, psychological disturbances and *Helicobacter pylori* (*H. pylori*) infection (Li et al., 2002; Shaib and El-Serag, 2004;

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Mahadeva and Goh, 2011; Ford, 2012; Filipovic et al., 2013; Kim et al., 2013). Furthermore, those with *H. pylori* infection will get chance to develop gastric cancer between three to six times more than uninfected persons (Forman et al., 1991; Nomura et al., 1991; Parsonnet et al., 1991). Seroreactivity to the 89kDa (VacA) and 116kDa (CagA) proteins in *H. pylori* infected patients is risk indicators for cancer of stomach (Karami et al., 2013; Basiri et al., 2014). *H. pylori* eradication is not only significantly improve symptoms of FD patients (Moayyedi et al., 2006) but also decreases the gastric cancer incidence in asymptomatic infected Asian persons (Hamajima et al., 2004; Ford et al., 2014). In high prevalence area of gastric cancer, screening and treatment programs for gastric cancer are cost effective (Tsubono et al., 2000; Li et al., 2014).

FD was reported to be associated with anxiety and depression (Li et al., 2002; Mahadeva and Goh, 2011; Filipovic et al., 2013). In addition, patients with baseline functional gastrointestinal disorder (FGID) will greatly develop psychological distress either anxiety or depression in the future. Patients with depression had tendency to develop FD as well (Koloski et al., 2012). However, the prevalence and relationship between *H. pylori* infection and depression or anxiety especially in subgroup of FD is limited and remains unclear. This study aimed at investigating the prevalence and impact of *H. pylori* infection, anxiety and depression in subgroup of FD patients in Thailand.

Materials and Methods

Subjects

Patients who underwent gastroscopic examination at Thammasat University Hospital, Thailand for dyspeptic symptoms between February 2013 and January 2014 were eligible for inclusion in this study. The entry criteria were any patient age over 18 years with a diagnosis of FD after endoscopy. The diagnosis of FD was established in subject with a normal endoscopic finding or mild gastritis. Exclusion criteria were: (1) those received *H. pylori* eradication or proton pump inhibitor, histamine H2-receptor antagonists, bismuth or antibiotics in the prior one month, (2) receiving anticoagulants or non-steroid anti-inflammatory drugs, (3) had previously undergone gastric surgery, (4) other significant clinical diseases, (5) drug or alcohol abuser, (6) breast-feeding woman, and (7) who had been diagnosed with psychiatric disorders or were taking psychiatric medication. Signed informed consent was obtained before participating in this study. All included patients were subdivided into epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) predominance according to the Rome III criteria. During endoscopy, 3 biopsy samples from gastric antrum were obtained for rapid urease test, culture and histology. The presence of *H. pylori* was defined as: positive *H. pylori* culture or positive rapid urease test or positive histology. Anxiety and depression status were evaluated in all patients by the Hospital Anxiety and Depression Scale (HADS). This scale ranges from 0-21 in each subscale (anxiety and depression), and is classified as follows: normal (0-7), mild (8-10), moderate (11-14), severe (15-21) (Zigmond and Snaith, 1983). This study was conducted according to the good clinical practice guideline as well as the Declaration of Helsinki, and was approved by our local ethical committee.

Statistical methods

The data were expressed as frequency or mean ± standard deviation (SD) when appropriate. Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were compared using the two-tailed Student's t-test. p value<0.05 was taken as statistical significance. All statistic analyses were performed using SPSS for Windows Version 19.0 (IBM Corp., Armonk, NY).

Results

A total of 300 FD patients with a mean age of 54.8±15.1 years were included. Of which, 174 (58%) patients were female. By using the Rome III criteria, 108 (36%) and 192 (64%) patients were classified as EPS and PDS, respectively. *H. pylori* infection was demonstrated in 70 (23.3%) patients. By using the HADS questionnaire, 69 (23%) patients and 22 (7.3%) patients were diagnosed with anxiety and depression, respectively.

As demonstrated in Table 1, the demographic information between EPS and PDS patients including age, sex and underlying diseases were not different. Interestingly, *H. pylori* infection, anxiety and depression

Table 1. Demographic Data of All Patients

	PDS (N=192)	EPS (N=108)	p value	OR (95%CI)
Age (mean ± SD)	57±14	50.8 ± 16.1	0.3	0.9 (0.7-1.55)
Sex (% male)	84 (43.8)	42 (38.9)	0.4	0.8 (0.49-1.36)
H. pylori infection	52 (27.1%)	18 (16.7%)	0.04	1.9 (1.01-3.53)
Anxiety	57 (29.7%)	12 (11.1%)	0.0002	3.4 (1.65-7.04)
Depression	20 (10.4%)	2 (1.9%)	0.006	6.2 (1.35-38.96)
Smoking	24 (12.5%)	13 (12.0%)	0.91	1.0 (0.5-2.3)
Alcohol drinking	51 (26.6%)	25 (23.1%)	0.51	1.2 (0.7-2.2)
Underlying diseases				
Hypertension	68 (35.4%)	29 (26.9%)	0.13	1.5 (0.9-2.6)
Dyslipidemia	62 (32.3%)	30 (27.8%)	0.42	1.2 (0.7-2.2)
Ischemic heart disease	9 (4.7%)	3 (2.8%)	0.42	1.7 (0.4-8.2)
Arthritis	12 (6.3%)	7 (6.5%)	0.94	1.0 (0.3-2.8)
Irritable bowel syndrome	5 (2.6%)	2 (1.9%)	0.68	1.4 (0.2-10.7)

Table 2. Degree of Anxiety and Depression in Each Subgroup of FD Patients

	PDS (N=192)	EPS (N=108)	p value	OR (95%CI)
Anxiety				
Overall	57 (29.7%)	12 (11.1%)	0.0002	3.4 (1.7-7.0)
Mild	42 (21.9%)	9 (8.3%)	0.001	3.3 (1.5-7.7)
Moderate	13 (6.8%)	3 (2.8%)	0.07	3.1 (0.8-14.0)
Severe	2 (1.0%)	0	0.23	-
Depression				
Overall	20 (10.4%)	2 (1.9%)	0.006	6.2 (1.4-39.0)
Mild	16 (8.3%)	1 (0.9%)	0.007	9.9 (1.4-202.3)
Moderate	3 (1.6%)	1 (0.9%)	0.59	1.9 (0.2-46.7)
Severe	1 (0.5%)	0	0.43	-

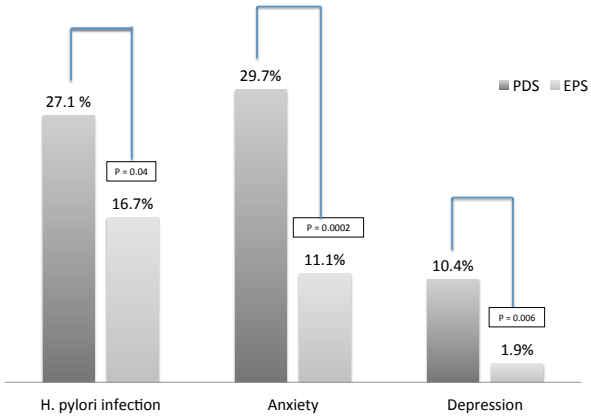

Figure 1. *H. Pylori* Infection, Anxiety and Depression in PDS and EPS subgroups of FD

were significantly higher in PDS than EPS patients (27.1% *vs* 16.7%; p=0.04; OR=1.86; 95%CI=1.01-3.53 and 29.7% *vs* 11.1%; p=0.0002; OR=3.4; 95%CI=1.7-7.1 and 10.4% *vs* 1.9%; p=0.006; OR=6.2; 95%CI=1.4-38.9, respectively) as shown in Figure 1.

As shown in Table 2, in those with anxiety or depression, only mild anxiety and depression were significantly higher in FD patients with PDS predominance (21.9% *vs* 8.3%, p=0.001: OR=3.3; 95%CI=1.5-7.7 and 8.3% *vs* 0.9% p=0.007: OR=9.9; 95%CI=1.4-202.3, respectively).

Discussion

The majority of FD patients in Asian countries were PDS subgroup (Park, 2011; Vilaichone et al., 2011; Min et al., 2014). In this study, we also demonstrated that PDS was predominantly in our population. Many factors were reported as possible pathophysiological mechanisms of FD e.g. impaired gastric accommodation, delayed gastric emptying, hypersensitivity to gastric distension, altered duodenal sensitivity to lipids or acid, lack of postprandial suppression of phasic contractility in the proximal stomach (Mimidis and Tack, 2008). However, the strong mechanisms related with PDS were impaired gastric accommodation and delayed gastric emptying (Mimidis and Tack, 2008). *H. pylori* is a microaerophilic gram negative spiral bacillus that infects the gastric mucosa in 20-80% of humans throughout the world and this bacteria was reported to be the major pathologic agent in the development of FD. Prevalence of *H. pylori* infection in FD patients varies from 30-80% (Vilaichone et al., 2011; Miwa et al., 2012). The study published in 2012 demonstrated that the DQB1*0401 genotype was related to a higher risk of *H. pylori* infection (Zhao et al., 2012). To date, the correlations of *H. pylori* infection and the pathogenesis or subgroup of FD are still inconclusive (Mimidis and Tack, 2008). A systematic review demonstrated 10% risk reduction in *H. pylori* treatment group compared to placebo, and the number needed to treat to improve one case of FD was 14 (Moayyedi et al., 2006). However, a study from the Chinese population showed that odds ratio for improvement in FD after *H. pylori* eradication was 3.6, imply that the role of *H. pylori* eradication in FD is better in Asian than Western populations (Jin and Li, 2007). More important, *H. pylori* eradication can significantly prevent gastric cancer in asymptomatic infected person, and the number needed to treat was 15 in Chinese men (Ford et al., 2014). Our previous study found that metronidazole resistant strains and *cagA 2a* gene of *H. pylori* infection was commonly found in Thai FD patients. Furthermore, PDS patients had significant more prevalence of metronidazole resistant than those of EPS (Vilaichone et al., 2011). Metronidazole resistant strains of *H. pylori* infection were highly prevalent in many parts of the world e.g. 61% in France (Raymond et al., 2010), 82.9% in Bhutan (Vilaichone et al., 2013) and 95.4% in China (Su et al., 2013).

In Thailand, metronidazole resistance was the most common antimicrobial resistance which demonstrated up to 66% (Vilaichone et al., 2011; Vilaichone et al., 2013). Relationship between PDS patients and metronidazole resistance of *H. pylori* might be responsible for higher prevalence of *H. pylori* infection in PDS than those of EPS patients. This finding may imply that *H. pylori* eradication in PDS patients should be paid more attention with avoidance of metronidazole in the treatment regimens (Vilaichone et al., 2011).

Psychological distress has been widely accepted as an important factor of FD (Haug et al., 1995; Drossman et al., 1999; Locke et al., 2004). Several studies showed that the anxiety, depression and somatoform disorders were the most common psychiatric problems found in patients with FD (Magni et al., 1987; Haug et al., 1994). Anti-depressive drugs seem to be helpful in the treatment in some cases of FD patients (Mertz et al., 1998; Otaka et al., 2005). A meta-analysis published in 2005 demonstrated that anti-anxiety or anti-depressive drugs were effective in controlling symptoms in patients with FD (Hojo et al., 2005). However, some serotonin selective reuptake

inhibitors and serotonin and norepinephrine reuptake inhibitors were not more effective than placebo (van Kerkhoven et al., 2008; Tan et al., 2012).

To date, psychological factor has been documented as a strong causative factor of FD. Nevertheless, there was only 1 study evaluated the association between this factor and the subtype of FD. In this study, early satiety symptom was associated with delayed gastric emptying and days of sickness leave. By contrast, epigastric pain and epigastric burning symptoms were correlated with gastric hypersensitivity and psychopathology or somatization (Fischler et al., 2003). Some gut hormones are known to be the cause of delayed gastric emptying e.g. cholecystokinin, glucagon-like-peptide-1 or peptide YY (Khoo et al., 2010). Moreover, there is a study published in 2012 demonstrated the increase of fasting plasma peptide YY level in depressed patients (Gimenez-Palop et al., 2012). These finding may explain our result that psychological disorder either anxiety or depression even in mild symptoms was significantly more prevalent in PDS than EPS.

In conclusion, *H. pylori* infection, anxiety and depression disorder were commonly found in FD patients in Thailand and significantly higher prevalence in PDS than EPS. PDS also found to be a predominant type of FD in this study. *H. pylori* infection, anxiety and depression should be important factors for developing FD especially in PDS subtype. The management concern to anxiety, depression and *H. pylori* eradication might be the key success for the treatment of Thai FD patients and can prevent gastric cancer as well.

Acknowledgements

This study was partially supported by Research Fund at Faculty of Medicine, Thammasat University Hospital, Thailand and the National Research University Project of Thailand Office of Higher Education Commission.

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