Epidemiology of Peptic Ulcer Disease: Endoscopic Results of a Systematic Investigation in Iran

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ABSTRACT

BACKGROUND

Peptic ulcer disease is a multifactorial health problem affecting almost all populations worldwide. Large scale population-based studies are crucial to understanding its scope and specifications in various nations. We aimed to explore environmental risk factors of peptic ulcer disease in the first population based study in Ardabil, Northwest Iran.

METHODS

This study was a part of a larger survey on upper gastrointestinal tract health conducted in Ardabil and Meshkinshahr with a total catchment area population of 600,000 persons during 2000-01. Using a random sampling proportional to place of residence, 1122 persons aged 40 or elder were selected. 1011 (90.1%) accepted participation and underwent a comprehensive medical examination and a systematic upper gastrointestinal endoscopy. Point prevalence of peptic ulcers was correlated to various life style risk factors.

RESULTS

Gastric and duodenal ulcers were identified in 33 (3.26%) and 50 (4.94%) participants, making an overall prevalence of 8.20%. Based on multivariable logistic regression analyses, *H.pylori* infection (OR 3.1, 95% CI: 2.1-4.7), Smoking (OR 1.8, 95% CI: 1.1-6.8), and chronic intake of NSAIDs (OR 2.8, 95% CI: 1.3-4.4) were main risk factors of gastric ulcer. For duodenal ulcer, in addition to *H.pylori* infection (OR 5.6, 95% CI: 1.9-8.8) and Smoking (OR 2.3, 95% CI: 1.4-6.5), male gender (OR 3.6, 95% CI: 1.2-5.8) and living in an urban area (OR 1.9, 95% CI: 1.1-5.2) were among significant risk factors.

CONCLUSION

This is the first population-based endoscopic study in North West of Iran reporting accurate point prevalence of peptic ulcer disease. The rate of 3.3% for gastric ulcer and 4.9% for duodenal ulcers are substantially lower than the estimates reported in Asian population-based endoscopic studies but higher than European reports.

KEYWORDS

H.pylori; Peptic ulcer disease; Epidemiology.

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INTRODUCTION

Clinical symptoms are not enough for accurate diagnosis of peptic ulcer disease (PUD) and endoscopic assays are necessary for confirmation of diagnosis.[1-3] Despite previous studies in Europe and East Asia,[4-6] there were no population-based endoscopic study for evaluation of prevalence of PUD in Iran. Previous studies were based on patients

self-reports during referrals, following appearance of gastrointestinal symptoms in patients. Subsequently, conducting an epidemiological PUD survey was very important in our study area, particularly due to high prevalence of PUD complications.[7] The complications of PUD impose substantial economic and morbidity burden on the health system and the society. We did not have comprehensive economical studies in our area, but according to literature, the total costs of PUD in USA (both direct and indirect due to loss of work output) has been estimated to reach 6.46 billion USD per year.[8-9] On the other hand, gastric cancer in Northern Iranian provinces is quite common, while it is known that gastric ulcers might later lead to gastric cancers.[10-12]

In a series of collaborations between the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences and Ardabil University of Medical Sciences aiming to formulate a preventive strategy for gastric cancer in Ardabil, we sought to endeavor an endoscopy-based exploratory study to determine the PUD prevalence and risk factors in residents of two major districts of Ardabil Province. We assessed the prevalence of Helicobacter pylori (*H. Pylori*) and its relation with the aforementioned factors as well.

MATERIALS AND METHODS

Study participants

First part of the study was conducted between January and September 2000 in the district of Ardabil, North-West of Iran with a catchment area population of 435,487 persons. The second part was conducted in Meshkinshahr district, with catchment area population of 164,007 persons between July and September 2001. Selected regions of each district were included 17 villages in Ardabil and 19 villages in Meshkinshahr. The professional local health experts interviewed with all family members of the participants who were above 40 years old to achieve a sample size of 1122. After thorough explanation of the purpose and the procedure of the study, one individual within the target age, was randomly selected from each family. Our exclusion criteria were no inclination to participate at any stage of the study for any reason, inability to tolerate the upper gastrointestinal (GI) endoscopy for any reason, quoted during the interview or within the procedural time. The current or previous medical history of GI problem and any known benign or malignant upper GI disease was asked from the participants. All of the willing participants were transferred to the study site on the appointed day.

The purpose of our study, including the risks and benefits were thoroughly explained on the appointed day and written consent form was obtained from all participants. The study protocol, physical examinations, diagnostic techniques and consent form were approved by DDRC ethics committee of Tehran University of Medical Sciences.

Before endoscopy, a questionnaire with special sections including dietary habits, demographic information, life style, smoking history, drug abuse, alcohol consumption and medication history was filled out for all participants. Each participant was interviewed by a trained general practitioner. They were also asked about GI symptoms and upper GI malignancy alarming signs, in the first or second degree relatives. After the interview, physical examinations of selected individuals were performed. Thereafter, they underwent standard endoscopy by cardiopulmonary monitoring and local anesthesia of pharyngeal mucosa with 10% lidocaine spray and sedation with Midazolam. The endoscopic findings and a special endoscopy report form were recorded using an appropriate coding system for different lesions. Gastric biopsies for urease test were taken, from all observed lesions by trained assistant pathologist in the endoscopy room, and its result was recorded in related endoscopy form. In the next step, these samples were located immediately in a neutral buffered formalin solution and labeled by the individual's name for further pathologic assays. The species were transferred to DDRC research laboratory in the city of Tehran. After endoscopy, the participants were transferred to recovery room and if general condition was acceptable, they were discharged.

Statistical analysis

Numerical data are expressed as mean ± SD.

Pearson Chi square or Fisher's exact tests were used to examine relationships between categorical variables, where appropriate. Associations between PUD and education, age and BMI were expressed using p value for trend. We made separate multivariable logistic regression models (stepwise method) for DU and GU to determine main risk factors of PUD. P values less than 0.05 were considered significant. Data analysis was performed using SPSS statistical package version 16.0 (SPSS Inc. Chicago, Illinois, USA).

RESULTS

Study participants

Of initial 1122 selected and eligible persons, 1011 individuals (90.1%) accepted to participate in the study. Among them, 494 (48.8%) were men and 517 (51.2%) were women. The mean age was 53.25±10.38 years (ranging from 40 to 92 years). Among the participants, 539 (53.3%) were residants of Ardabil and Meshkinshahr cities and the remaining 434 (46.7%) were from rural areas. The mean body mass index (BMI) of our participants was measured to be 27±4.7kg/m^2 while most of our subjects had BMI between 25 and 30kg/m^2. Their literacy level included none (76%), secondary (16.5%), advanced (5.6%) and primary (1.9%) respectively. Most of the volunteers were from low socioeconomic groups of the society, appreciating free of charge screening, and their literacy level was lower than the average Iranian population (75% literate).

Among the participants, 302 (29.9%), 18(1.8%) and 35 (3.5%) had tobacco smoking, opium addiction and alcohol consumption, respectively. Even though there was no statistically significant difference in the prevalence of digestive complaints, 539 (52.9%) and 443 (43.8%) of the participants reported heart burn and epigastric pain, respectively.

GI symptoms of heart burn, regurgitation, GI medication use related to gastric or duodenal ulcers; and GI alarm signs such as dysphasia as symptoms of upper GI malignancy were analyzed in our patients. The frequency of these manifestations and their relationship with PUD in endoscopy is calculated and presented in table 1. The majority of patients with PUD had none of the upper gastrointestinal symptoms. In symptom defined gastroesophageal reflux disease, heart burn was significantly more common in normal adults than patients with PUD, however there was no significant association between retrosternal pain and PUD. Also vague persistent abdominal pain and dyspepsia medication use was significantly more common in PUD patients than normal subjects. Among gastrointestinal alarm symptoms, weight loss in last 12 months was more common in PUD patients.

Table 1: Symptom profile of peptic ulcer disease in cases and controls.

Symptom/History		Cases N (%)	Controls N (%)	p - value
Retrosternal Pain	Gastric Ulcer	15 (55.6)	218 (46.9)	0.380
	Duodenal Ulcer	18 (40.9)	218 (46.9)	0.448
Heartburn	Gastric Ulcer	9 (27.3)	245 (52.7)	0.005
	Duodenal Ulcer	31 (68.9)	245 (52.7)	0.037
Dysphagia to solids	Gastric Ulcer	3 (11.5)	72 (15.5)	0.782 f
	Duodenal Ulcer	8 (16.7)	72 (15.5)	0.924
Dysphagia to liquids	Gastric Ulcer	1 (3.7)	42 (9.0)	0.497 f
	Duodenal Ulcer	3 (6.4)	42 (9.0)	0.787 f
Vague persistent abdominal pain	Gastric Ulcer	22 (66.7)	118 (25.4)	<0.001
	Duodenal Ulcer	19 (40.4)	118 (25.4)	0.026
Dyspepsia medications	Gastric Ulcer	17 (63.0)	196 (42.2)	0.034
	Duodenal Ulcer	26 (57.8)	196 (42.2)	0.043
Weight loss in last 12 months	Gastric Ulcer	12 (44.4)	127 (27.3)	0.055
	Duodenal Ulcer	6 (12.8)	127 (27.3)	0.030

Note: Pearson's Chi square test has been used for all rows except for items marked with "f" which indicates Fisher's exact test

Prevalence of PUD

Endoscopy results showed that gastric ulcers were present in 33 individuals (3.26%) while duodenal ulcer was detected in 50 subjects (4.94%). Therefore, the overall prevalence of PUD was 8.2% (83 out of 1011). The mean age of patients with (54.5± 10.12) and without gastric ulcers (53.29±10.4) was not significantly different. The mean age of patients with (51.52±9.83) and without duodenal ulcers (53.41±10.41) was not significantly different either.

The characteristics of participants with and without the gastric ulcers are presented in table 2. As shown in this table, gastric ulcer was more common in

men than women and most of subjects with gastric ulcer were married and lived in rural areas. There were not statistically significant differences in gender (p=0.17), age (p=0.51), area of living (p=0.57), literacy level (p=0.75), and marital status (p=0.07) between participants with or without gastric ulcers. Gastric ulcer was associated with smoking and chronic NSAIDS use (>3 months vs. non or short term use).

As for duodenal ulcers (Table 3), they were similarly more common in men and married individuals with low literacy level, while most of them were living in urban areas. The association between some of these variables (gender, region, literacy, marital and smoking statues) with duodenal ulcers was significant (p <0.05).

In analyzing the association between BMI and PUD, a very large amount of data was missing; therefore, we had to analyze the BMI data for about 15% of participant. Still, our results were significant. As shown in Tables 4-5, duodenal ulcers are associated with increased BMI and gastric ulcers with relatively decreased BMI.

Table 2: **Demographic and life style characteristics of individuals with gastric ulcer and their controls.**

Factor		With GU N (%)	Without GU N (%)	Statistical Test p - value
Gender	Men	20 (60.6)	474 (48.5)	0.170
	Women	13 (39.4)	504 (51.5)	
Age (year)	40-49	11 (33.3)	445 (45.5)	0.516
	50-59	9 (27.3)	245 (25.1)	p - value for trend= 0.183
	60-69	10 (30.3)	211 (21.6)	
	≥ 70	3 (9.1)	77 (7.9)	
Residence	Urban	16 (48.5)	523 (53.4)	0.576
	Rural	17 (51.5)	456 (46.6)	
Education	Non	24 (75.0)	736 (76.0)	0.752
	Primary	2 (6.3)	75 (7.7)	p- value for trend = 0.950
	Secondary	5 (15.6)	102 (10.5)	
	Graduate/ postgraduate	1 (3.1)	55 (5.7)	
Marital Status	Married	32 (97.0)	836 (85.8)	0.073 (Fisher's exact test)
	Single/Divorced/widow	1 (3.0)	138 (14.2)	
Tobacco	Current smoker	18 (54.5)	260 (27.1)	0.001
	Non smoker	15 (45.5)	700 (72.9)	
BMI	<18.5	1 (3.2)	11 (1.4)	0.004
	18.5 – 24.9	21 (67.7)	293 (36.9)	
	25.0 – 29.9	6 (19.4)	314 (39.6)	
	≥ 30	3 (9.7)	175 (22.1)	

Endoscopic findings

The overall prevalence of atrophic gastritis (based on histological studies) was %2.5. About 30.12% of individuals with PUD had some forms of atrophic gastritis. However, atrophic gastritis was also present in 40.28% of those without PUD. Thus, patients with PUD did not face a significantly increased risk of atrophic gastritis compared with those without PUD. Moreover, antral intestinal metaplasia (IM) (13.25%) was found in individuals with PUD more commonly, than those without PUD (8.84%); it was also more prevalent among individuals with duodenal ulcers than gastric ulcers.

The prevalence of reflux esophagitis was 36.7%. The accompanying endoscopic findings included: GERD type A in 145 (28.8%) and GERD type B in 40 subjects (7.9%) according to LA classification. The prevalence of reflux esophagitis in individuals with (83/1011) and without PUD (928/1011) was not significantly different (data not shown).

Prevalence of H.pylori infection

H.pylori in histologic studies and/or RUT test was positive in 89.2% of subjects (883/990) in whom the tests were performed . The infection was present in 97.5% and 88.7% of patients with and without PUD, respectively. There was no statistically significant difference in frequency of *H.Pylori* infection between individuals with or without PUD in simple uni-variable analysis, but in multivariable analysis (logistic regression) *H.Pylori* infection was the main correlate for both gastric and duodenal ulcers and had a much stronger association with duodenal ulcers. Individuals living in rural areas showed higher prevalence of *H.Pylori* infection than urban dwellers (Ardabil and Meshkinshar), though this difference was not significant (p=0.56; OR=1.5).

H.Pylori infection, smoking, and chronic NSAID use were the main environmental risk factors in

Table 3: Demographic and life style characteristics of individuals with duodenal ulcer and their controls.

Factor		With DU N (%)	Without DU N (%)	Statistical Test *p* -value
Gender	Men	38 (76.0)	456 (47.5)	< 0.001
	Women	12 (24.0)	505 (52.5)	
Age (year)	40-49	26 (52.0)	430 (44.7)	0.757
	50-59	12 (24.0)	242 (25.2)	*p*- value for
	60-69	9 (18.0)	212 (22.1)	trend = 0.286
	≥ 70	3 (6.0)	77 (8.0)	
Residence	Urban	37 (74.0)	502 (52.2)	0.003
	Rural	13 (26.0)	460 (47.8)	
Education	Non	27 (54.0)	773 (77.2)	0.001
	Primary	5 (10.0)	72 (7.6)	*p*- value for
	Secondary	12 (24.0)	95 (10.0)	trend < 0.001
	Graduate/ postgraduate	6 (12.0)	50 (5.3)	
Marital Status	Married	48 (98.0)	820 (85.6)	0.010
	Single/ Divorced/ widow	1 (2.0)	138 (14.4)	(Fisher's exact test)
Tobacco	Current smoker	25 (51.0)	253 (26.8)	< 0.001
	Non smoker	24 (49.0)	691 (73.2)	
BMI	< 18.5	0 (0)	12 (1.6)	0.002
	18.5 – 24.9	13 (26.0)	301 (38.9)	
	25.0 – 29.9	32 (64.0)	288 (37.2)	
	≥ 30	5 (10.0)	173 (22.4)	

Table 4: Relationship between gastric ulcer and BMI presented as quintiles.

BMI Quintiles	With GU	Without GU	Statistical Test
1st: < 22.89	10 (32.3%)	154 (19.4%)	Pearson Chi Square= 0.001
2nd: 22.89 - 25.13	12 (38.7%)	154 (19.4%)	
3rd: 25.13 - 27.39	5 (16.1%)	160 (20.2%)	*p* value for trend < 0.001
4th: 27.39 - 30.32	1 (3.2%)	164 (20.7%)	
5th: > 30.32	3 (9.7%)	162 (20.4%)	

Table 5: Relationship between duodenal ulcer and BMI presented as quintiles.

BMI Quintiles	With GU	Without GU	Statistical Test
1st: < 22.89	4 (8.0%)	160 (20.6%)	Pearson Chi Square = 0.001
2nd: 22.89 - 25.13	9 (18.0%)	157 (20.3%)	
3rd: 25.13 - 27.39	16 (32.0%)	149 (19.2%)	*p* value for trend = 0.474
4th: 27.39 - 30.32	18 (36.0%)	147 (19.0%)	
5th: > 30.32	3 (6.0%)	162(20.9%)	

patients with gastric ulcer. In patients with duodenal ulcer, risk factors included *H.Pylori* infection, smoking, male gender, and living in urban areas (Tables 6-7).

Table 6: Significant environmental risk factors for gastric ulcer in residents of Ardabil province; results of final step of multivariable logistic regression analysis.

Risk Factor		OR (95 % CI)	*p*- value
***H.pylori* infection**	positive vs. negative	3.1 (2.1 – 4.7)	0.002
Smoking	Current vs. non	1.8 (1.1 – 6.8)	0.034
Chronic NSAID intake	(> 3 months vs. non or short-term)	2.8 (1.3 – 4.4)	0.019

Nagelkerke R Square = 0.586, method: Stepwise (Backward likelihood)

Table 7: Significant environmental risk factors for duodenal ulcer in residents of Ardabil province; results of final step of multivariable logistic regression analysis.

Risk Factor		OR (95 % CI)	*p* -value
***H.pylori* infection**	positive vs. negative	5.6 (1.9 – 8.8)	0.001
Smoking	Current vs. non	2.3 (1.4 – 6.5)	0.026
Gender	Men vs. women	3.6 (1.2 – 5.8)	0.008
Residence	Urban vs. Rural areas	1.9 (1.1 – 5.2)	0.039

Nagelkerke R Square = 0.637, method: Stepwise (Backward likelihood)

DISCUSSION

This is the first population-based endoscopic study in North West of Iran that reports PUD prevalence up to 3.3 and 4.9 percent for gastric and duodenal ulcers respectively. This rate is substantially lower than prevalence estimates reported in previous Asian population-based endoscopic studies.[13-15] As Li et al.[16] found in their systematic investigation of gastrointestinal diseases, the prevalence of PUD in China reaches 17.2% (gastric ulcer: 6.1%; duodenal ulcer: 13.3%). Also the annual global incidence rates of PUD rates have been reported around 0.1-0.19% for in physician office-diagnosed PUDs and 0.03-0.17 for hospitalization records.[17] However, our findings are more close to European endoscopic epidemiologic studies,[4,6] as they reported prevalence rates from 4.1 % (gastric ulcer: 2.0 %; duodenal ulcer: 2.1 %),[4] to 6.2 % (gastric ulcer: 2.3 %; duodenal ulcer: 3.9 %).[6]

As for microbiological studies, high prevalence of *H.pylori* infection (73.3%/10130 individuals) has been demonstrated in a Chinese study.[16] *H.pylori* infection as a major cause of PUD,[18] was found in 73-100% of the patients with duodenal ulcers and 65-100% of patients with gastric ulcer.[19-23] During a 10-year study in Korea, Jang et al.[24] found out that the prevalence of PUD and mainly that of duodenal ulcers had a decreasing trend. The incidence of duodenal ulcers in western population is steadily decreasing due to better hygiene and sanitation and administration of proper regimes for *H.pylori* eradication.[25]

In the present study, we found that nearly all individuals with PUD (93.9% for gastric ulcer and 100% for duodenal ulcer) were infected with *H.pylori*. The high prevalence of *H.pylori* infection in PUD was in accordance with Chinese endoscopic studies (92.6%),[13-16] and in contrast with European studies (33.9%, 57.7%).[4,6] It was also possible that the Chinese population may have similar prevalence of ulcerogenic strains of *H. pylori* to Iran.

In contrast to the result of the European population-based studies,[4,6] and in accord with Li et al.[16] we found no association between PUD and reflux esophagitis, although reflux esophagitis was numerically more common in individuals with PUD.

Frank et al. evaluated the prevalence of upper gastrointestinal symptoms and its relation to health care utilization and quality of care. They found that individuals suffering from GERD and ulcer had more physician visits for their symptoms.[26] Gastrointestinal reflux disease appears to be increasing,[27] according to several epidemiological symptoms, particularly due to related life style factors such as diet and obesity.[28,29] Smoking, aspirin consumption, and obesity were risk factors for 4.1% prevalence of PUD in northern Sweden.[4] Although we did not evaluate the care utilization of the patients with PUD, there was no association between heart burn and GERD. While among 50-60% of our studied PUD patients with heart burn, association between heart burn (60%) and GERD was demonstrated.

Based on the multivariate analysis, *H.Pylori* infection, current smoking, and chronic NSAID intake were the main environmental risk factors associated with gastric ulcer. On the other hand, for duodenal ulcer, *H.Pylori* infection, current smoking, male gender, and urban residence were the main risk factors.

Generally speaking, our results might actually reflect the association of high prevalence of *H.pylori* infection with PUD in Iran. Moreover, this strong association may be an explanation for extremely high prevalence of atrophic gastritis in gastric ulcers.

Concluding, there is a paradox between the prevalence of PUD and *H. pylori* infection in our study findings in comparison with those of Asian and European studies. We know that the diet of Iranians contains high amounts of saturated fat and protein, which is more similar to Europeans while on the other hand, the current level of hygiene and sanitation in regions in our study is mostly identical to those in Asian studies. In short, it seems that the first explains why our PUD prevalence is close to Europeans and the latter explains why the pattern of *H.Pylori* infection mimics Asians. If this hypothesis is assumed to be accurate, it confirms that PUD is a multi-factorial disorder and multidimensional health strategies are required to overcome it.

CONFLICT OF INTEREST

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

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