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Case Report

The Prevalence of Intestinal Metaplasia in Dyspeptic Patients

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ABSTRACT

Gastric cancer may be asymptomatic until advanced stages so it is important to detect the precancerous lesions. One of these precancerous lesions is Intestinal Metaplasia (IM). This study aimed to find out the prevalence of IM and its related risk factors in dyspeptic patients.

In this cross-sectional study, 1650 dyspeptic patients above 15 years who were undergoing endoscopy department in two hospitals in Khorramabad, Iran, were invited to participate in the study during October 2015 to August 2016. The patients were examined in terms of erythema and inflammation, ulcers, erosions, atrophy, mass, gastric outlet obstruction during upper endoscopy. Six biopsy samples were taken and fixed in 10 percent formalin solution and then were sent to the pathology laboratory for histological examination. Data were analyzed by SPSS 21.

In total, 1016 patients were entered in this study. The overall prevalence of IM was 10.5% (107/1016). In dyspeptic patients; the prevalence of complete and incomplete IM was 12.15% and 87.85% respectively. Increasing age, smoking and peptic ulcer were significantly related to IM ($P<0.001$, $P=0.027$, $P=0.012$). There was no significant meaning between gender, level of education, place of residence, family history of gastric cancer, opium, hookah smoking and alcohol consumption with IM.

The relatively high prevalence of IM was found in dyspeptic patients. Especially incomplete subtype is a risk factor of gastric cancer and due to its relationship with smoking and increasing age, it is recommended to provide preventive procedures of gastric cancer in elderly aged and smokers.

Keywords: Dyspepsia, Prevalence, Risk Factor, Intestinal Metaplasia.

INTRODUCTION

Gastric cancer is one of the most common types of cancer (1,2). There are two types of gastric cancer including diffuse and intestinal type. In intestinal type, gastric inflammation leads to mucosal atrophy, which increases the risk of Intestinal Metaplasia (IM), dysplasia and gastric cancer (3). Precancerous lesions such as atrophic gastritis and IM increase the risk of gastric carcinoma (4). Progression rate towards gastric cancer is respectively as chronic gastritis, gastric atrophy, IM, dysplasia and carcinoma (5). In a large Iranian study the prevalence of IM have been reported about 16.1% (6). IM is defined as the replacement of the gastric epithelium by two types of similar intestinal epithelium and included three phenotypes such as: I) Complete or the small

intestine and II & III) Incomplete or colonic type (4). The progression from IM toward adenocarcinoma is related to histological subtype so that type II & III or colonic IM is associated with the most risk of gastric cancer (7). H. pylori infection is known as the most important risk factor for the gastric cancer and precancerous lesions (8). Dyspepsia is defined as an epigastric pain, early satiation and postprandial fullness with the prevalence of 7-45% in different studies around the world (9,10).

It is recommended the patients undergo Esophagogastroduodenoscopy (EGD) to differentiate organic pathology such as malignancies and peptic ulcer disease from functional dyspepsia (11). EGD is the most sensitive and specific diagnostic method for the early detection of upper gastrointestinal cancers in combination with biopsy (12).

By using the upper endoscopy of peptic ulcers, gastric and esophageal cancers are diagnosed and in addition, biopsy is taken in case of abnormalities in the gastric mucosa (atrophy, erythema, erosions) and they're examined pathologically in order to the presence of atrophy, IM and dysplasia (13,14). In this study, in addition the awareness of the prevalence of gastric cancer, IM and IM risk factors, we can modify these risk factors and do preventive measures to reduce the incidence of precancerous lesions and gastric cancer. This study aimed to find out the prevalence of IM and its related risk factors in dyspeptic patients.

MATERIAL & METHODS

This is a cross-sectional study. A total of 1650 dyspeptic patients above 15 years who were presenting to endoscopy department in ShohadaAshayer and ShahidRahimi hospitals in Khorramabad in Iran were selected and invited to participate in the study during October 2015 to August 2016. Pregnant women, people with the history of upper gastrointestinal surgeries, patients with gastric outlet obstruction, and those who did not consent to participate in the study were excluded. Prior to endoscopy, the patients were informed about the study objectives and written informed consent was obtained from all participating subjects. All subjects who provided informed consents, were asked to fill a questionnaire included questions regarding demographic data such as age, sex and risk factors including family history of gastric cancer, smoking history, hookah smoking, opium and so on; then the subjects underwent a clinical interview for upper endoscopy by a gastroenterologist.

The patients were examined in terms of erythema and inflammation, ulcers, erosions, atrophy, mass, gastric outlet obstruction during upper endoscopy. Six biopsy samples were taken and fixed in 10 percent formalin solution and then were sent to the pathology laboratory. Biopsy samples were analyzed by an expert pathologist in terms of chronic gastritis and its severity, atrophic gastritis and its severity, IM and its types, dysplasia and its severity, presence of H. pylori and malignancy. Data were analyzed by SPSS 21.

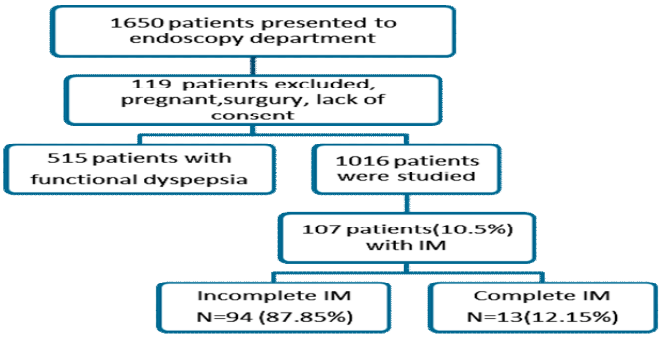
To analyze the results and the relationship between IM and its risk factors, descriptive statistics (Means, standard deviation, and frequency) and chi-square statistics were used and the significance level was considered less than 0.05.

RESULTS

A total of 1650 dyspeptic patients were surveyed. 119 of them were excluded due to pregnancy, history of upper gastrointestinal surgeries and gastric outlet obstruction or lack of consent to participate in the study; so 1531 patients remaining were selected and underwent endoscopy. 33.6% (515/1531) had normal endoscopy, or in other words they had functional dyspepsia.

Finally 1016 of them who had biopsy samples were included in the study in order to analyze the prevalence of IM.

Diagram 1- The patients entered the study



From 1016 patients, 54.2% (551/1016) were female and 45.8% (465/1016) were male. The mean age of them was 47±16 years. The majority of cases (38.3%) were under 40 years. most of them (76.7%) were under graduated. Family history of gastric cancer, smoking, hookah smoking, opium and alcohol consumption was reported in 16.2% 15.2%, 9.3%, 6.8% and 1.4% respectively (Table 1).

Table 1- Demographic data of patients

Risk Factors		Frequency	Percent
Age (Year)	>40	389	38.3
	49-40	185	18.2
	59-50	190	18.7
	≤60	252	24.8
Sex	Male	465	45.8
	Female	551	54.2
Educational Level	Under Graduated	779	76.7
	Graduated	237	23.3
BMI	BMI >25 kg/m2	502	49.4
	BMI <25 kg/m2	514	50.6
Place Of Residence	Urban	736	72.4
	Village	280	27.6
Family History of Gastric Cancer	No	852	83.8
	Yes	164	16.2
Smoking	No	862	84.8
	Yes	154	15.2
Hookah Smoking	No	921	90.7
	Yes	95	9.3
Opium	No	947	93.2
	Yes	69	6.8
Alcohol Consumption	No	1002	98.6
	Yes	14	1.4

The most common endoscopic findings included mild erythema 70.3% (714/1016) and erosions 53.8% (547/1016). The most common anatomic site for abnormal findings on endoscopy was antrum (Table 2).

Table 2- Frequency of endoscopic lesions in 1016 dyspeptic patients

Endoscopic Lesions	Cardia N (%)	Body N (%)	Antrum N (%)	Total N (%)
Erosions	1 (0.2)	199 (36.4)	347 (63.4)	547 (100)
Mild erythm	33 (4.6)	275 (38.5)	406 (56.9)	714 (100)
Severe erythm	1 (0.3)	166 (47.8)	180 (51.9)	347 (100)
Ulcer	17 (11.9)	28 (19.6)	98 (68.5)	143 (100)
Mild atrophy	11 (13.1)	15 (17.9)	58 (69)	84 (100)
Severe atrophy	5 (5.6)	37 (41.6)	47 (52.8)	89 (100)
Nodularity	6 (2.5)	126 (53.4)	104 (44.1)	236 (100)
Total*	74 (3.4)	846 (39.2)	1240 (57.4)	2160 (100)

*Due to the presence of more than one lesion in some patients, the total is not equal to the number of samples.

Among the subjects, 4.3% (44/1016) had normal pathology completely. The prevalence of H. pylori infection was 53.4% (543/1016). The most common pathologic findings were: moderate gastritis 41.4% (421/1016) and mild gastritis 13.6% (138/1016). The prevalence of IM was 10.5% (107/1016). Of the 107 patients with IM, 87.85% (94/107) had incomplete IM and 12.15% (13/107) had complete IM. Pathological lesions and their distribution are shown in Table 3.

Table 3- Pathological lesions in 1016 dyspeptic patients

Pathological Lesions	Cardia N (%)	Body N (%)	Antrum N (%)	Total N (%)
Mild Gastritis	2 (1.4)	24 (17.4)	112 (81.2)	138 (100)
Moderate Gastritis	11 (2.6)	59 (14)	351 (83.4)	421 (100)
Severe Gastritis	2 (4.2)	8 (16.7)	38 (79.1)	48 (100)
Mild Atrophy	11 (16.2)	18 (26.5)	39 (57.3)	68 (100)
Moderate Atrophy	5 (12.5)	13 (3.25)	22 (55)	40 (100)
Severe Atrophy	5 (31.25)	6 (37.5)	5 (31.25)	16 (100)
Incomplete Intestinal Metaplasia (IIM)	6 (6.4)	5 (5.3)	83 (88.3)	94 (100)
Complete Intestinal Metaplasia (CIM)	1 (7.7)	2 (15.4)	10 (76.9)	13 (100)
Low-Grade Dysplasia (LGD)	0 (0)	0 (0)	11 (100)	11 (100)
High-Grade Dysplasia (HGD)	0 (0)	0 (0)	2 (100)	2 (100)
Helicobacter Pylori Infection	8 (1.5)	66 (12.1)	469 (86.4)	543 (100)
Polyps	10 (45.5)	3 (13.6)	9 (40.9)	22 (100)
Malignancy	11 (52.4)	4 (19)	6 (28.6)	21 (100)
Total *	72 (5)	208 (14.5)	1157 (80.5)	1437 (100)

*Due to the presence of more than one lesions in some patients, the total is not equal to the number of samples.

Of the 107 patients with IM, 57% (61/107) were female and 43% (46/107) were male. The mean age of these patients was 58.3 ± 15. 47.7% (51/107) of IM patients were older than 60 years and 85 patients (79.4%) were under graduated. Family history of gastric cancer, smoking, hookah smoking, opium and alcohol consumption were reported in 16.8% (18/107), 22.4% (24/107), 13.1% (14/107), 7.4% (8/107) and 2.8% (3/107) respectively. The peptic ulcer was observed in 22.4% with IM and 13.1% in those without IM. Statistical analysis showed a significant relationship between IM with peptic ulcer, increasing age and smoking (P=0.012, P<0.001 and P=0.027), while there was no significant relationship between IM with gender, BMI, place of residence, educational level, family history of gastric cancer, hookah smoking, opium and alcohol consumption. The prevalence of H. pylori infection in patients with IM, was 60.7%, and in patients without IM was about 52.6%. Although the prevalence of this infection was higher in patients with IM, but this difference was not statistically significant (P=0.067) (Table 4).

Table 4- The relationship of IM and its risk factors

Risk Factors		With IM N (%)	Without IM N (%)	P-value
Age	>40	15(14)	374(41.2)	<0.001
	40-49	9(8.4)	176(19.3)	
	50-59	32(29.9)	158(17.4)	
	≥60	51(47.7)	201(22.1)	
Sex	Male	46(43)	419(46.1)	0.542
	Female	61(57)	490(53.9)	
BMI	BMI >25 kg/m2	47(43.9)	455(50)	0.261
	BMI <25 kg/m2	60(56.1)	454(50)	
Place of Residence	Urban Area	74(69.2)	662(72.8)	0.422
	Rural Area	33(30.8)	247(27.2)	
Educational Level	Under Graduated	85(79.4)	694(76.3)	0.474

	Graduated	22(20.6)	215(23.7)	
Family History of Gastric Cancer	Yes	18(16.8)	146(16.1)	0.84
	No	89(83.2)	763(83.9)	
Smoking	Yes	24(22.4)	130(14.3)	0.027
	No	83(77.6)	779(85.7)	
Hookah Smoking	Yes	14(13.1)	81(8.9)	0.161
	No	93(86.9)	828(91.9)	
Opium	Yes	8(7.5)	61(6.7)	0.766
	No	99(92.5)	848(93.3)	
Alcohol Consumption	Yes	3(2.8)	11(1.2)	0.181
	No	104(97.2)	898(98.8)	
H. Pylori Infection	Yes	65(60.7)	478(52.6)	0.067
	No	42(39.3)	431(47.4)	
Peptic Ulcer	Yes	24(22.4)	119(13.1)	0.012
	No	83(77.6)	790(86.9)	

DISCUSSION

This study aimed to find out the prevalence of Intestinal Metaplasia (IM) in dyspeptic patients. IM is a well-known risk factor for the development of gastric cancer (15-18). The risk of gastric cancer is closely related to the degree and extension of IM (15,19). Therefore, evaluating the prevalence and risk factors of IM may be helpful to prevent the development of gastric cancer (20,21). In this study the overall prevalence of IM was found to be 10.5%. Prevalence of IM was approximately near the different studies done in Malaysia and Hong Kong. The prevalence of IM in Yeh et.al (2009) and Yee et.al (2009) studies was 9.8% and 9.4% respectively (22,23). It was 7% in Sonnenberg et.al (2010) and 15% in Almouradi (2013) studies (24,25). The prevalence of IM in the present study is somehow similar to the studies mentioned. This is may be because of the similar population and majority, but there does not adequate information to support this issue in Iran and this is because of the few evaluating studies done in this country.

In addition the prevalence of IM was low compared to Ajdarkosh et.al (2015) study that was about 19.8% (26). Also this result is lower than previous studies that were carried out in high-prevalence areas in the northwest of Iran, reporting an overall prevalence of 46.2% for precancerous lesions (27). This discrepancy could be related to the following reasons: our study was carried out among dyspeptic patients in Khorramabad's hospitals; the number of patients included in the study could have also influenced the results of this study. In addition, environmental factors and genetic background of the patients should have also been taken into consideration.

In Western Europe, the prevalence of IM was approximately one-fourth of subjects (28). In contrast, the prevalence of IM was 28.5% in Japan (29). The prevalence rate of endoscopic IM in the Young-Eun (2013) study was 12.5%. Another reason of lower prevalence of IM in this study could be explained by the population of the participating subjects (30). It is considered that the prevalence of IM may be higher in region of the present study. This low prevalence of IM may be because of the insufficient number and inappropriate localization of biopsies.

Eriksson et al (2008) reported that the prevalence of incomplete and complete IM was 7.2% and 11% respectively (31). In SehmusOlmez (2015) study, the prevalence of incomplete type of IM (90.4%) was much higher than the complete type (8.2%). The type III IM was the highest subtype (32). Ozdil et al. (2010) reported that of 3301 consecutive dyspeptic patients 17.8% had IM. They observed that 86% had complete and 14% had incomplete IM (33). In our study the prevalence of incomplete and complete IM was 9.2% and 1.3% respectively. In other words, in our study the most patients with IM had incomplete form of IM. The incomplete form of IM has the highest risk of getting gastric cancer and this may be because of the relation of high age of patients with IM. The presence of incomplete

type IM, especially type III, significantly increases the risk of gastric cancer as compared to type I and type II (34-36). High detection of incomplete type IM, particularly type III, may shed light on the high prevalence of gastric cancer in our region. Furthermore, subtyping IM pathologically is often difficult because IM have a multifocal distribution within the stomach. Sampling errors may be unavoidable and also different subtypes of IM frequently coexist.

In present study, age has been shown to be a significant risk factor for IM. As the age increases, the incidence rate of IM increases subsequently (P 0.001). But sex was not a significant risk factor for the development of IM (P=0.542). That is likely because of the men's frequently referral to the therapeutic clinics and using extensive antibiotic drugs. Yee et al (2009) concluded that with increasing age, the prevalence of IM increased, but there was no significant relationship between gender and its prevalence (22). Sonnenberg (2010) found that IM was not associated with sex, while it has a linear relationship with age and its risk increases with increasing age (25). Almouradi et al. (2013) found a significant difference between men and women in their study; so that the rate among women and men was 18.5% and 11% respectively; that is not consistent with our results (24). In a study, Watari et al. (2014) found no significant relationship between sex and IM. While there was a significant relationship between age and the prevalence of IM that is consistent with our study (4). The association between gastric IM and increasing age suggest a potential role of a chronic injury of the gastric mucosa in triggering the disease (37). In addition, the prevalence of IM in males were significantly higher than those in females in Young-Eun et al. (2013) study (30). It is generally understood that the prevalence of H. pylori infection and gastric disorders in males is more common than that in females (38,39). In Ajdarkosh (2015) study, IM showed a significant relationship with increasing age (26). In SehmusOlmez (2015) study, it was shown that gastric IM was higher in older than in younger patients. Several studies revealed that age over 50 years was an independent risk factor for IM, which is consistent with previous studies reporting that the incidence of IM increases with age (32). This discordance could be because of the low number of patients with dysplasia. The effect of age could be explained by the long duration of exposure of patients to environmental risk factors for gastric cancer such as H. pylori infection.

In the present study, in patients with IM, 60.7% (65/107) were infected with H. pylori infection, whereas in patients without IM, 52.6% had the infection. Despite the high prevalence of H. pylori infection in IM patients, there have been no statistically significant meaning between them (P=0.067). The prevalence of IM in patients with H. pylori infection was 12% and 8.9% in those without H. pylori infection. There is a high risk of IM in patients with H. pylori infection; that was 1.3 times higher than those without infection. In contrast to some studies (Zhang et al, 2012; Kim et al, 2013), we have found no a correlation between H. pylori and development of precancerous lesions (40,41). There have been no association between H. pylori infection and IM in Drasovean Silvia (2016) study (42). In Young-Eun (2013) study, the prevalence of IM increased signifi¬cantly with age and this phenomenon could be explained by H. pylori infection. H. pylori infection usually occurs in the child¬hood, but IM progress in the elderly population due to long infectious periods with H. pylori (30). In Iran, this is a very important fact as this country is categorized as an intermediate risk area, where the seroprevalence of H. pylori infection reaches to 62-90% (43-45). According to this study, the prevalence of IM in patients with H. pylori infection may be due to the existence of disease in earlier-stage of IM such as superficial and atrophic gastritis. This means that it has shown limited numbers of samples with complete and normal endoscopy in those without IM. One of the reasons for the lack of significant association between H. pylori infection and IM can be because of the relatively high prevalence of H. pylori in the general population of the present

study. The prevalence of gastric IM and atrophy in the general population is known to vary around the world, mostly depending on H. pylori status (15,46). Several studies have examined the predictor factors of atrophy and IM. Age, smoking, history of smoking, alcohol and rurality (living in rural area) are risk factors of gastric atrophy and IM reported in some studies (47,48). Others studies reported the male gender as a risk factor for gastric atrophy and IM (49). In other words, with an observation on different studies done all around the world, we could find that infected with helicobacter pylori infection doesn't related to the individuals resistance. It is also observed that the incidence rate of getting helicobacter pylori infection increases with aging. In elderly we have the high prevalence of H. pylori infection that may due to the physiological changes in their body.

In this study, there was a significant relationship between IM and peptic ulcer (P=0.012). The prevalence of IM in patients with peptic ulcer was 22.4%. Zulla et al. (2005) reported that the prevalence of IM in patients with peptic ulcer was about 32% that show the high prevalence of IM in patients with peptic ulcers and H. pylori infection (50). The prevalence of IM in patients with peptic ulcer was reported in a high range about 24% in Almuradi et al. (2013) study (24). There are limited studies evaluated the relation between IM and peptic ulcer. Here we evaluated confounding factors during analyses to reduce any imported bias. Further, we have also not taken into account a limited number of participants.

Based on the results, a high percentage of dyspeptic patients especially of those with peptic ulcer had IM. As far as most patients had shown incomplete IM type in this study, it warned that IM was diagnosed in advanced stages. Also due to its association with aging, it is recommended to consider the IM diagnostic measures in these elderly patients to provide preventive procedures of gastric cancer. Also with regard to its relationship with smoking, the occurrence of precancerous changes and cancer could be prevented as well by doing the essential activities in this field, including help to quit smoking.

CONFILCT OF INTEREST

The authors declare no conflict of interest.

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