Original Article

Evaluation of the relationship between serum levels of pepsinogen, gastrin-17 and anti-Helicobacter with gastric pathological alterations in dyspeptic patients over 25 years

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ABSTRACT

Introduction: One of the most common gastric complaints associated with complications is dyspepsia, and therefore, early detection of high-risk individuals by minimally invasive procedures is necessary because it is related with some gastric malignancies. Therefore, we seek to determine the association between serum levels of pepsinogen, gastrin-17 and anti-Helicobacter with pathological alterations in the stomach in patients with dyspepsia over 25 years of age in this investigation. **Methods:** After the patients were contented and demographic information were recorded, serum levels of pepsinogen, gastrin 17, and anti-helicobacter and gastric pathology, this cross-sectional study was carried-out on a statistical population consisting of 169 patients with dyspepsia. To compare the data, Chi-Square and Mann-Whitney U tests were used. **Results:** The results of the present study showed that chronic gastritis, helicobacter pylori bacilli, erosive gastritis, atrophic gastritis, dysplasia and metaplasia were seen in 67.5, 72.8, 41.4, 38.5, 6.5 and 3 percent of dyspeptic patients, respectively. It was also found that the levels of four biomarkers such as pepsinogen I and II, gastrin-17 and anti-Helicobacter increased in chronic gastritis, helicobacter pylori bacilli, and erosive gastritis. However, serum pepsinogen I levels alleviated in dysplasia, metaplasia, and atrophic gastritis, while serum gastrin-17 levels and anti-Helicobacter increased in these diseases. **Conclusion**: The reason for preventive measures in high-risk individuals and screening based on serum levels, is the high frequency of pathological findings in dyspeptic patients and the relationship of these findings with serum levels of biomarkers that are studied.

Keywords: pepsinogen, gastrin-17, anti-Helicobacter, dyspepsia.

Introduction

When a person feels episodic or permanent discomfort in the upper abdominal region (or the origin of the upper gastrointestinal tract), this condition is called dyspepsia [1]. With about 25 to 40 percent of people experiencing it during their lifetime, dyspepsia is considered one of the most common gastric complaints [2, 3]. Most of these complaints have two origins of gastro-esophageal reflux disease (GERD) in the major condition and of rarely organic [4, 5]. The occurrence of Helicobacter pylori infection (HP) and atrophic gastritis (AG), which are also closely related, are the most important clinical factors in the development of this disease [6, 7]. Several important diseases of the

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gastric and duodenal mucosa originate from HP [6-10], which was classified in 1994 as a grade 1 human carcinogen [11]. Superficial gastritis occurs only with the effect of this bacterial infection (which usually occurs in childhood) on the antral mucosa. This infection can lead to mucosal atrophy if it persists and progresses to chronic conditions as well as gastritis by dominance in body-gastritis or pan-gastritis [12, 13]. Based on the studies, it is concluded that the contributing factor to HP in GC progression is the key effect of AG, although the exact mechanism of HP infection in gastric cancer (GC) has not been established before [13, 14]. For distal GC, the most powerful dependent risk factor is AG. [7, 15-17]. Due to the fact that many patients show only a short period of symptoms before GC diagnosis and no signs of dyspepsia are reported in more than 40% [18], there is no appropriate test for GC screening, which is itself is a fundamental problem [19]. According to this investigation, the following two options are considered for the diagnosis of AG and pre-malignant lesions, as well as the discrimination between normal and diseased gastric mucosa: The first is upper gastrointestinal (UGI) endoscopy and histological examination of endoscopic biopsy. Non-invasive assessment of serum bio-markers such as pepsinogen I and II, gastrin 17 and anti-Helicobacter is the second one [20]. If the terminal mucosa of the stomach is destroyed, the first three biomarkers are produced, and if the gastric mucosa reacts to the presence of an external pathogen, an anti-Helicobacter pylori will emerge [21]. Concentrations of both types of pepsinogen increase due to inflammation, whereas progression to atrophic gastritis decreases the pepsinogen I concentration and in this situation, the concentration of pepsinogen II remains high. Based on this, it can be said that the morphological condition of the gastric mucosa is subject to alterations in pepsinogen levels [22]. The gold standard for the diagnosis of HP infection is mucosal atrophy, intestinal metaplasia or dysplasia, endoscopy with biopsy [7, 13]. The need to use a reliable, inexpensive, fast, and non-invasive diagnostic test for screening and monitoring of patients with dyspepsia symptoms is felt because endoscopy is an invasive, oppressive, and costly procedure [18, 19, 23]. To assess the risk of gastric cancer using five biologic indicators specific to the stomach, Hookang To et al. conducted a cross-sectional study called serological biopsy on a statistical population consisting of 12,112 patients and in this study, they showed that the risk of developing GC was associated with a reduction in pepsinogen I and II ratio and high gastrin levels [24]. Mansour-Ghanaei et al., using pepsinogen, gastrin 17, anti-Helicobacter pylori, and anticancer antibodies in dyspeptic patients over 50 years of age in Gilan province in northern Iran, performed a study in 2014 called screening for gastric precancerous lesions. The results of this study showed that in precancerous lesions, the ratio of pepsinogen-type I to type II was significantly reduced, but between the two groups of patients and normal, the frequency of anti- Helicobacter was significantly different and its concentration in patients with precancerous lesions increased significantly [25]. While evaluating the screening process in patients hospitalized to Kazakhstan, Valerie Benbrin et al., in 2013 in their study sought to investigate the prevalence of HP and AG infection among dyspeptic and symptomatic adults. The normal range of pepsinogen I was confirmed in HP and antral AG cases and normal cases, but the concentration of this biomarker was significantly reduced in other cases of body-gastritis and pan-gastritis. In HP-dependent cases without AG and in pan-gastritis, the highest and lowest levels of pepsinogen II were observed, respectively. In AG associated with body- gastritis, in cases of antral involvement and in other cases, gastrin 17 levels were high, low, and normal, respectively. In people with a normal gastric mucosa, low levels of anti-Helicobacter and high levels of which were seen in other cases [26]. To improve the diagnostic methods of the pathological conditions of the gastrointestinal tract, it is necessary to replace the non-invasive and cheap methods, because the current method, endoscopy, is invasive and expensive. Previously, during the evaluation of different pathological conditions of the gastrointestinal tract and measurement of serum concentrations of different biomarkers, contradictory results have been created and there is no study that simultaneously measures the levels of all these biomarkers, so the present study intends to examine the association between serum levels of pepsinogen , gastrin 17 and anti-Helicobacter with gastric pathological alterations in dyspeptic patients with over 25 years of age referring to Ali Ibn Abitaleb hospital in Zahedan.

Materials and Methods

The statistical population of this descriptive-analytical study consisted of 169 dyspeptic patients referring to Ali Ibn Abitaleb hospital in 2019 in Zahedan, southeastern Iran, who had endoscopic indications according to the opinion of gastroenterologist. Patients over 25 years of age with any complaints of pain or irritation or feeling of epigastric discomfort are the inclusion criteria for into the study and previous gastritis surgery, long-term treatment (over one year) HP, kidney failure, liver failure, celiac disease, GI cancer, hemorrhage of the upper gastrointestinal tract were considered the exclusion criteria. The method of patient selection was easy and accessible sampling and also by considering the inclusion criteria. After confirming this study in the ethics committee of Zahedan University of Medical Sciences (code: IR.zums.1399.024) and observing all the principles of Helsinki, patients were tested for research purposes. A questionnaire consisting of two sections, the first containing demographic information and the second containing questions about the patient's diet, was distributed to collect data among the participants. Then, in patients who used anesthesia and venipuncture during endoscopy, blood samples were collected through angiocatheter and venipuncture, respectively. On the other hand, during endoscopy by a gastroenterologist, antrum and body of the stomach biopsy were performed. Using the questionnaire, the data were collected after coordination with the hospital's diagnostic unit, and blood samples and then antrum and body biopsy of the patients were obtained with their conscious consent, after providing an explanation about the plan

and method of implementation. Unaware of the patient's characteristics and symptoms, two separate pathologists examined the biopsies and classified the samples into three groups: normal, atrophic gastritis, and Helicobacter pylori. The laboratory expert also tested blood samples to determine the levels of pepsinogen, gastrin17 and anti-Helicobacter pylori. Finally, in these three groups, normal, atrophic gastritis, and Helicobacter pylori gastritis, the levels of these biomarkers were evaluated and compared. Central and scatter indices and tables with statistical charts were used to interpret the data. The frequency and chi- Square test of SPSS software version 21 were used to analyze the data. To determine the frequency percentage of demographic variables, descriptive statistics (relative frequencies, tables and statistical diagrams) were used and the 95% confidence interval for the percentages was calculated. The relationship between atrophic gastritis and independent variables of the chi-Square test was used to analyze the data in a single-variable analysis. Also, during the data analysis, a paired T-test was used to compare the intervention group and also an independent T-test was used to evaluate the Carryover Effect.

Results

The relationship between serum levels of pepsinogen, gastrin- 17 and anti-Helicobacter with gastric pathological alterations in dyspeptic patients over 25 years of age referring to Ali Ibn Abitaleb hospital in Zahedan, was evaluated in this investigation. The statistical population of this research was 169 patients consisting of 70 males (41.4%) and 99 females (58.6%). The mean age of the participants in the present study was 41.19 ± 13.2 years. Chronic gastritis, Helicobacter pylori bacilli, erosive gastritis, atrophic gastritis, dysplasia, and metaplasia, were reported in 114 (67.5%), 123 (72.8%), 70 (41.4%), and 65 (38.5%), 11 (6.5%) and 5 (3%) of the 169 patients included in the present study. Also abnormal levels of Gastrin- 17, abnormal levels of pepsinogen I, abnormal levels of pepsinogen II, abnormal anti-Helicobacter levels were observed in 121 (71.6%), 42 (24.9%), 86 (50.9%), and 119 (70.4%) of the participants in this study, respectively. In patients over 40 years of age, the frequency of dysplasia and metaplasia increased significantly (P <0.05) compared with patients under 40 years of age, according to Table 1. Also, no statistically significant difference in sex was observed in the frequency distribution of gastric pathological alterations in dyspeptic patients (P> 0.05), (Table 1).

Table 1: Frequency distribution of gastric pathological alterations based on age, sex and weight in dyspeptic patients

variable \ pathology		Chronic gastritis		Bacilli Helicobacter		Erosive gastritis		Atrophic gastritis		dysplasia		metaplasia	
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
		Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency	Relative frequency
age	>40	37.5	62.5	29.8	70.2	54.8	45.2	60.6	39.4	97.1	2.9	100	0
	≤40	24.6	75.4	23.1	76.9	64.6	35.4	63.1	36.9	87.7	12.3	92.3	7.7
	total	32.5	67.5	27.2	72.8	58.6	41.4	61.5	38.5	93.5	6.5	97	3
	P-Value	0.082		0.339		0.208		0.745		0.023		0.008	
sex	male	32.9	67.1	30	70	58.6	41.4	65.7	34.3	92.9	7.1	97.1	2.9
	female	32.3	67.7	25.3	74.7	58.6	41.4	58.6	41.4	93.9	6.1	97	3
	total	32.5	67.5	27.2	72.8	58.6	41.4	61.5	38.5	93.5	6.5	97	3
	P-Value	0.942		0.495		0.999		0.348		0.779		0.948	
weight	>80kg	32.1	67.9	29.8	70.2	64.3	35.7	66.7	33.3	94	6	96.4	3.6
	≤80kg	32.9	67.1	24.7	75.3	52.9	47.1	56.5	43.5	92.9	7.1	97.6	2.4
	total	32.5	67.5	27.2	72.8	58.6	41.4	61.5	38.5	93.5	6.5	97	3
	P-Value	0.942		0.46		0.999		0.134		0.771		0.682	

According to Table 2, in patients with chronic gastritis compared with those without chronic gastritis, the average mean levels of pepsinogen I, II, gastrin-17, and anti-Helicobacter increased significantly (P <0.05). Also, in patients with Helicobacter pylori compared with those without Helicobacter pylori, the mean levels of pepsinogen I, II, gastrin-17, and anti-Helicobacter increased significantly (P <0.05). On the other hand, in patients with erosive gastritis compared with those without erosive gastritis, the frequency of mean pepsinogen I, II, gastrin- 17 and anti-Helicobacter significantly increased (P <0.05). According to the findings of the table above, in patients with atrophic gastritis compared with those without atrophic gastritis, the frequency of average pepsinogen I levels decreased significantly (P <0.05), but anti-Helicobacter values were significantly higher (P <0.05). Based on the findings of Table 2, in patients with dysplasia compared with those without dysplasia, the frequency of mean pepsinogen I levels decreased significantly (P <0.05), while the values of gastrin- 17 and anti-Helicobacter increased significantly (P <0.05). Finally, it was found that in patients with metaplasia compared with those without metaplasia, the frequency of mean pepsinogen I levels was significantly reduced (P <0.05), while gastrin-17 levels and anti-Helicobacter were significantly increased (P <0.05) (Table 2).

Table 2: Average and standard deviation of serum levels of biomarkers evaluated according to pathological conditions

Biomarker / variable		Pepsinogen I (µg/L)			Pepsinogen I (µg/L)			Gastrin-17 (pmol/L)			Anti-Helicobacter (ELU)		
		Mean	SD	P	Mean	SD	P	Mean	SD	P	Mean	SD	P
Chronic gastritis	No	94.55	74.045	0.003	13.74	10.35	0.006	10.34	10.972	0.002	91.61	108.845	0.006
	Yes	116.45	68.607		19.52	12.899		16.15	13.718		136.37	123.773	
Helicobacter Bacilli	No	8.11	0.002	13.612	13.22	<0.001	54.343	81.98	10.137	<0.001	48.96	42.789	<0.001
	Yes	119.55	73.863		19.29	11.544		16.56	13.429		149.05	128.911	
Erosive gastritis	No	81.22	49.155	0.001	14.49	9.831	<0.001	12.20	13.761	<0.001	94.09	80.388	0.01
	Yes	149.08	78.030		22.08	13.243		17.18	11.700		160.99	153.623	
Atrophic gastritis	No	123.00	71.0774	<0.001	17.32	10.872	0.649	14.35	12.030	0.472	106.47	118.169	0.009
	Yes	87.43	65.527		18.14	14.593		14.12	14.848		146.34	121.405	
Dysplasia	No	114.56	70.063	<0.001	17.71	12.603	0.831	13.38	12.780	0.001	116.26	117.759	0.019
	Yes	34.11	29.114		16.61	9.378		26.97	12.138		201.46	139.068	
Metaplasia	No	111.27	70.852	0.033	17.61	12.406	0.904	13.68	12.754	0.005	117.05	116.317	0.019
	Yes	45.31	41.777		18.37	13.589		33.35	12.511		277.57	169.441	

Discussion

The results of the present study revealed that all four biomarkers including pepsinogen I and II, gastrin- 17 and anti-Helicobacter were increased in chronic gastritis, bacilli of Helicobacter pylori, and erosive gastritis. However, decreased serum levels of pepsinogen I were observed in dysplasia, metaplasia, and atrophic gastritis, and serum levels of gastrin-17 and anti-Helicobacter were increased in these diseases. Also in elderly patients, the higher prevalence of dysplasia and metaplasia was proven. The results of a study by Valerie Benberin et al. (2013) on the prevalence of HP and AG infection among dyspeptic and symptomatic adults showed that the concentration of pepsinogen I in HP and antral AG cases and also normal cases was within the normal range, but the concentration of this biomarker in other conditions, such as body- and pan-gastritis, were significantly reduced. HP-dependent cases without AG and pan-gastritis showed the highest and lowest pepsinogen II levels, respectively. In AG result from body- gastritis, the involvement of antrum and in other cases, the concentration of gastrin-17 was increased, decreased, and was within the normal range, respectively. In people with a normal mucosa, low levels of anti-Helicobacter and, in other cases, high levels of which were seen [26]. The most common pathological finding in our study was HP, which in these patients the levels of pepsinogen II have been elevated. The ratio of pepsinogen- type I to type II based on the results of a study by Mansour-Ghanaei et al. in 2014 was shown to be significantly reduced in precancerous lesions, but there was a significant difference in the frequency of anti-Helicobacter between the patient and normal groups and it increased significantly in patients with precancerous lesions [25]. A study of serological biopsies to assess the risk of gastric cancer using five gastric biomarkers in a 2017 study by Hokang To et al., showed that the ratio of pepsinogen I to II decreased and gastrin-17 levels were proportionate to higher risk of GC [24]. It has also been shown that in patients with dysplasia and metaplasia who participated in our study, serum levels of pepsinogen I decreased significantly and gastrin levels also increased. Other results from our study revealed that a statistically significant difference was observed between serum levels of pepsinogen I and II in different diseases, so that pepsinogen II levels were significantly reduced in malignant diseases. Also, according to the findings of our investigation, in pre-malignant lesions, the above result is true, but there was no significant difference in serum levels of pepsinogen II in pathological lesions of dysplasia and metaplasia in the present study, contrary to the study above. Differences in demographic characteristics (the mentioned study was performed on people over 40 but in our study, people over 25 were included), the kits used, sampling and the inclusion and exclusion criteria into the study cause this slight difference. In order to eradicate the Helicobacter pylori and simultaneously study the alterations in serum levels of gastrin in such conditions, the findings of the study of Torabizadeh et al. in 2013 showed that in successful treatment conditions compared to unsuccessful treatment, gastrin levels has been significantly reduced after 8 weeks. In this successful treatment period for eradication, the rate of decrease in gastrin level, sensitivity and specificity was 31%, 5.92% and 100%, respectively. One of the most reliable indicators for evaluating the successful treatment of Helicobacter pylori eradication based on the findings of this study and other previous studies, is alteration in serum gastrin levels [27]. Pathological evaluations of the presence of Helicobacter pylori bacilli in the participants in our study showed that serum gastrin levels increased significantly, and therefore, this biomarker is considered to diagnose and response to treatment. Measurement of serum levels of target biomackers in patients with gastric cancer such as pepsinogen I, pepsinogen II and gastrin-17, in a study by Haj-sheykholeslami et al. (2008) showed that the most appropriate marker in screening for any type of gastritis with normal mucosal tissue is pepsinogen II. However, pepsinogen I, the ratio of pepsinogen I to II, and gastrin-17 cannot be used to

identify precancerous conditions in first-degree relatives (FDR) with gastric cancer [28]. Serum levels of pepsinogen I, pepsinogen II, and gastrin- 17 were measured in 132 dyspeptic patients in a 2012 study by Hosseini et al., and the results showed why these biomarkers were not used in screening patients with atrophic gastritis, was their low sensitivity (> 50%) [29].

Conclusion

Based on the results of the present study, it can be reported that serum levels of all four biomarkers of pepsinogen I and II, gastrin-17 and anti-Helicobacter pylori increased significantly in chronic gastritis, Helicobacter pylori bacilli, and erosive gastritis. However, serum levels of pepsinogen I have been significantly decreased in diseases such as dysplasia, metaplasia, and atrophic gastritis, and serum levels of gastrin- 17 and anti-Helicobacter have been significantly increased in these conditions. The prevalence of dysplasia and metaplasia was also reported in elderly patients. Therefore, preventive measures in high-risk individuals and screening based on serum levels are recommended due to the high frequency of pathological discoveries in dyspeptic patients and the association of these findings with serum levels of biomarkers studied, and if during these assessments the abnormal levels of the above biomarkers have been proven, in order to reduce malignant lesions in patients, effective treatment measures should be a priority.

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