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Original Article

Association of Gastroesophageal Reflux Disease Symptoms and Non-alcoholic Fatty Liver Disease by Eliminating the Body Mass Index Effect

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ABSTRACT

Background:
Different studies have reported the association between gastroesophageal reflux disease (GERD) and non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of the metabolic syndrome. This association is considered either body mass index (BMI) related or independent of BMI. In the current study, we aimed to illustrate the correlation between GERD symptoms and NAFLD and to determine the role of BMI in this regard.

Materials and Methods:
This study was conducted on 332 out-patients referred to the clinics affiliated to Imam Khomeini and Imam Reza Hospitals in Kermanshah in 2015-2016 who were divided into two groups of patients with NAFLD and without NAFLD. The two groups were investigated and compared for symptoms of GERD. The confounding effect of BMI and sex were eliminated in this study by multiple logistic regression.

Results:
The prevalence of heartburn, belching, nausea and vomiting, and hypertension (HTN) was higher in patients with NAFLD ($P<0.05$). Moreover, these four variables were still associated with NAFLD after eliminating the BMI and sex confounding effect by multiple logistic regression model.

Conclusion:
Some GERD symptoms are related to NAFLD regardless of BMI effect.

Keywords: Non-alcoholic fatty liver disease, Gastroesophageal reflux disease, Body mass index, Symptom

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as the regurgitation of acidic contents of the stomach and damaging the esophageal tissue. This disease can cause symptoms like dysphagia, regurgitation, belching, and heartburn (1). The prevalence of GERD is different worldwide, considering the differences in genetic backgrounds, *helicobacter pylori* (*H-pylori*) prevalence, and lifestyle as probable reasons. In this line, the reported prevalence of GERD in the west of Asia is 12.5-27.6 (2). Non-alcoholic fatty liver disease (NAFLD) is one of the factors influenced by lifestyle

differences that would affect reflux disease. Evidence suggests that NAFLD is accompanied by symptoms of reflux disease. Obesity and higher body mass index (BMI) are two risk factors that exacerbate the symptoms of reflux disease in patients with NAFLD (3,4). Associations between endoscopic signs of reflux disease and Barrett's esophagus with abdominal obesity in patients with NAFLD have been reported (5). Considering the approximate 30% prevalence of NAFLD (3), high prevalence of GERD, and the association between these diseases reported in previous studies (6), the aim of this study was to evaluate and compare the typical and atypical symptoms of GERD in patients with NAFLD and healthy people. Also, this study intends to eliminate the effect of BMI on the relationship between GERD and NAFLD.

MATERIALS AND METHODS

This study was conducted on 332 out-patients who were referred to the clinics affiliated to Imam Khomeini and Imam Reza Hospitals in Kermanshah in 2015-2016. Patients were divided into two groups based on the results of liver ultrasonography: patients with NAFLD and those without NAFLD. Clinical information regarding medical history, alcohol consumption, smoking, and medications was recorded. To confirm the diagnosis of NAFLD, required laboratory parameters that exclude other causes of the fatty liver, such as autoimmune and viral diseases, were examined. Demographic characteristics and symptoms of reflux disease were recorded by interviewing patients. Symptoms were counted as GERD if the patients complained about one of the symptoms of reflux disease more than three times a week in the former month.

Finally, a total of 332 subjects (calculated four times for more confidence as the groups were not matched) were eventually enrolled. Typical reflux symptoms including heartburn, regurgitation, and belching; and atypical symptoms, including nausea, vomiting, globus sensation, hoarseness, sialorrhea, chronic cough, dysphagia, epigastric pain, and chest pain were compared between the two groups. SPSS software version 16 was used to enter and analyze the data. Chi-square test was applied to synchronize qualitative variables of the two groups. Leven's and independent-sample t-test and Mann-Whitney U test were used for comparing quantitative variables between the two groups with and without normal distribution, respectively. Kolmogorov–Smirnov (KS) test was used to check normality for quantitative variables. p values < 0.05 were considered statistically significant. Multiple logistic regression analysis was used to control BMI and other confounding variables.

RESULTS

A total of 332 subjects were enrolled, out of whom 165 (49.7%) subjects diagnosed as having NAFLD were classified as cases, and 167 (50.4%) subjects with normal ultrasonography were classified as non-NAFLD. Of the total patients, 170 subjects were women, and 162 subjects were men. Characteristics of the two groups were compared. Women were more likely to have NAFLD than men ($p < 0.001$). KS test indicated that BMI ($p < 0.001$, KS = 0.112) and age ($p < 0.001$, KS = 0.080) did not have a normal distribution. Minimum and maximum BMI values were 20 and 38 kg/m2. The average BMI values in subjects with NAFLD (27.34 ± 2.68) was significantly higher than in the non-NAFLD group (24.56 ± 2.02) ($p < 0.001$). Also, BMI value > 30 was higher in the group of cases (p <0.001). The two groups had no significant difference in the mean age (table 1).

Also, the results showed that the prevalence of heartburn (47.9% vs. 29.9%, $p < 0.001$), belching (52.1% vs. 30.5%, $p < 0.001$), nausea and vomiting (26.7% vs. 10.8%, $p < 0.001$), HTN (46.7 vs. 28.8, p <0.001) were higher in NAFLD group compared with the non-NAFLD group. However, the prevalence of other GERD symptoms including regurgitation (38.8 vs. 29.9, $p > 0.05$), dysphagia (26.7% vs. 18.6, $p > 0.05$), sialorrhea (13.9 vs. 13.2, $p > 0.05$), non-cardiac chest pain (6.7 vs. 8.6, $p > 0.05$), chronic cough (12.7 vs. 20.4, $p > 0.05$), hoarseness (14.5 vs. 10.7, $p > 0.05$), and epigastric pain (27.2 vs. 33.5, $p > 0.05$) did not have statistically significant differences in NAFLD and non-NAFLD groups (table 2). Since the two groups were not matched for BMI, in the end, using multiple logistic regression analysis, the BMI and the other variables were enrolled in the model with controlled BMI.

To eliminate the confounding BMI effect, we entered 14 variables in the multiple logistic regression model. In the first step, the BMI was entered into

Table 1: Comparison of clinical profiles frequency (percent) between NAFLD and non-NAFLD groups

Variables		Groups			Test Statistic	*p* value
		NAFLD	Non-NAFLD	Total		
Sex	Female	101(61.2)	69(41.3)	170(51.2)	CS = 13.148	< 0.001
	Male	64(38.8)	98(58.7)	162(48.8)		
BMI (kg/m^2)		27.34 ± 2.68	24.56 ± 2.01	25.94 ± 2.74	UMW = 5368.5	0.001
Age (year)		50.8 ± 11.3	48.3 ± 13.9	49.6 ± 12.7	UMW = 12097.0	0.054
HTN (percent)		77(46.7)	48 (28.8)	125(37.6)	CS = 26.089	< 0.001
BMI Groups	20-25	80(47.9)	26(15.8)	106(31.9)	CS = 52.829	< 0.001
	25-30	84(50.3)	109(66.1)	193(58.1)		
	>30	30(18.2)	3(1.8)	33(9.9)		
Total		165(100)	167(100)	332(100)		

Chi-Square test, UMW=Mann-Whitney U test, BMI: body mass index, HTN: hypertension

Table 2: Comparison of GERD symptoms frequency (percent) between NAFLD and non-NAFLD groups

Variables	Groups			Test statistic	*p* value
	NAFLED	non-NAFLD	Total		
Heart burn	79 (47.9)	50 (29.9)	129 (38.9)	11.242	0.001
Regurgitation	64 (38.8)	50 (29.9)	114 (34.3)	2.882	0.090
Belching	86 (52.1)	51 (30.5)	137 (41.3)	15.951	< 0.001
Nausea and vomiting	18 (10.8)	44 (26.7)	62 (18.7)	13.795	< 0.001
Dysphagia	31 (18.6)	44 (26.7)	75 (22.6)	3.117	0.077
Sialorrhea	22 (13.2)	23 (13.9)	45 (13.6)		0.483
Non-cardiac chest pain	14 (8.4)	11 (6.7)	25 (7.5)	0.351	0.553
Chronic cough	34 (20.4)	21 (12.7)	55 (16.6)	3.498	0.061
Hoarseness	24 (14.5)	18 (10.7)	42 (12.6)		0.303
Epigastric pain	45 (27.2)	56 (33.5)	104 (31.3)		0.114
Total	165 (100)	167 (100)	332 (100)		

the model. In the presence of this variable, the second to sixth variables, including belching, sex, blood pressure, nausea and vomiting, and heartburn according to their importance, were entered in the second to sixth steps, respectively. In the presence of the mentioned variables, the other variables including age, sialorrhea, heartburn, non-cardiac chest pain, regurgitation, chronic cough, dysphagia, and hoarseness were not entered in the model, which means that in the presence of the six variables, the other variables, did not have an association with the disease. Among the six variables, BMI and sex were considered confounding variables. Consequently, after controlling the two confounding variables, the other four variables were associated with the disease.

DISCUSSION

This study indicates that the typical GERD symptoms, including heartburn and belching, are accompanied by NAFLD, although it revealed no significant correlation between NAFLD and symptoms of regurgitation. Among the atypical symptoms, only nausea and vomiting were correlated with NAFLD in contrast to other atypical symptoms, including dysphagia, sialorrhea, chronic cough, hoarseness, non-cardiac chest pain, and epigastric pain. Furthermore, the prevalence of HTN was higher among the patients with NAFLD, and this finding was consistent with the study of Zhi-Chao Yao and colleagues (7).

Analysis of subgroups showed that GERD symptoms in subjects with NAFLD still had a higher

prevalence after eliminating the BMI effect. Some studies have claimed that there is a correlation between high BMI values and GERD symptoms. Some other studies have disapproved this hypothesis (6,8). It has also been reported that abdominal accumulation of fat but not BMI is a significant risk factor for NAFLD (9-11). These studies are also in agreement with our findings that GERD symptoms are associated with NAFLD. Our study also confirmed that in subgroups, NAFLD is related to GERD symptoms exclusive of BMI.

Moreover, this finding is against other studies reporting that NAFLD is related to GERD symptoms due to high BMI values (8). Different studies have declared the reason for the mentioned association as metabolic syndrome and obesity. Miele and co-workers confirmed a relation between NAFLD and GERD symptoms after eliminating the BMI effect (3). In an investigation conducted by Catanzaro and colleagues, there was a relation between GERD symptoms with higher BMI values and metabolic syndrome. Also, this assessment illustrated a strong association between NAFLD and GERD symptoms independently of coexisting metabolic syndrome status and higher BMI value. Similar to our study, these studies have found NAFLD effective in GERD as an independent risk factor (12). Studies have reported an increase in inflammatory cytokines, including IL-17, IFN γ, IL-10, IL-1β, and TNFα in NAFLD (13-14).

Furthermore, Altomare et al. declared that the levels of IL-8 and platelet-activating factor (PAF) increased in esophageal mucus in patients with reflux disease (15). Additionally, IL-6 levels were also higher in patients with NAFLD (14). In the same way, IL-6 had greater levels in patients with reflux symptoms compared with the normal group (16). Therefore, a possible immunological mechanism is assumed for this association, but further investigations need to be conducted to prove the hypothesis.

For further explanation of NAFLD and GERD correlation, other studies have explicated the role of autonomic system dysfunction in GERD development in patients with NAFLD. Newton and others have reported that patients with NAFLD experienced more fatigue and dysautonomia than the non-NAFLD group (17). Thereby, dysautonomia was observed frequently in patients with GERD in different studies (18-20). Perhaps it is feasible to contribute this association to dysautonomia, but additional studies are required to confirm the hypothesis.

Limitations

This study had some limitations. First, our tool for fatty liver analysis was ultrasonography, not a highly accurate diagnostic tool such as liver biopsy. Second, we used only BMI for obesity evaluation, whereas abdominal computed tomography and estimating abdominal fat was probably more desirable.

CONCLUSION

This study shows that typical GERD symptoms, including heartburn and belching, and atypical symptoms, including nausea and vomiting, are accompanied by NAFLD. Additionally, the prevalence of HTN was also higher in the NAFLD group. The mentioned reflux symptoms have a higher prevalence in subjects with NAFLD after eliminating the confounding BMI effect.

CONFLICT OF INTEREST

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

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