RESEARCH LETTER

Nonerosive reflux disease is more common in patients with chronic thyroid disease: preliminary results

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Introduction According to the Montreal definition, gastroesophageal reflux disease (GERD) is a condition presenting with persistent symptoms and complications that result from the reflux of stomach contents into the esophagus.[1] The etiopathogenesis of GERD includes impaired gastric emptying, impaired esophageal clearance, and dysfunction of the lower esophageal sphincter.[2] Numerous studies have demonstrated an association between the intensity of GERD symptoms and abdominal obesity, considered to be a risk factor for Barrett esophagus and esophageal adenocarcinoma.[2-4] Esophageal acid exposure time and the number of refluxes correlate positively with body mass index (BMI).[5] Some studies have indicated that GERD complications are associated with arterial hypertension, insulin resistance, and lipid abnormalities, while the intensity of reflux symptoms may be affected by metabolic syndrome or diabetes.[6-9]

Few studies have evaluated whether thyroid diseases affect the clinical manifestations of GERD. We evaluated differences in the clinical course and endoscopic images of GERD between patients with and without thyroid disease.

Patients and methods The study included 60 patients from the Department of Gastroenterology and Hepatology, University Hospital in Kraków, and from the Department of Internal Medicine and Gastroenterology, 5th Military Hospital in Kraków. Patients were recruited from September 2017 to September 2018.

The inclusion criteria were as follows: age above 18 years and newly diagnosed GERD based on the frequency scale for the symptoms of GERD (FSSG) criteria.[10] The exclusion criteria were pregnancy, acute diseases (such as infections, myocardial infarction, stroke, pulmonary embolism), and chronic diseases (such as liver cirrhosis, severe heart or lung failure, diabetes, or malignancy). None of the subjects had used a proton pump inhibitor or prokinetic therapy prior to enrollment. Some individuals used alkalizing agents or H_2 inhibitors on demand, but not during the 7 days before the study. Informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of Jagiellonian University Medical College, Kraków, Poland.

The study groups consisted of 24 patients with GERD and thyroid disease (GERD-Th) and 36 patients with GERD without an endocrine disorder, who constituted the control group. The GERD-Th group consisted of 19 patients with hypothyroidism (79.17%), 4 patients with hyperthyroidism (16.67%), and 1 patient with multinodular goiter (4.17%). All GERD-Th patients were treated for thyroid diseases and remained euthyroid.

Each participant completed the FSSG questionnaire, and BMI and waist-to-hip ratio were calculated. Blood cell count, fasting glucose, lipids, thyrotropin, free thyroxine (FT_4), and free triiodothyronine were measured. Esophagitis severity was assessed according to the Los Angeles scale, and the patients were classified into nonerosive reflux disease (NERD) or erosive reflux disease groups.

Statistical analysis Continuous variables were presented as arithmetic means and standard deviations or as medians and interquartile ranges (Q1–Q3). The Shapiro–Wilk test was used to test the normality of the variable distribution. The *t* test or Mann–Whitney test was used to assess the differences in continuous variables between control and GERD-Th groups. Categorical variables were reported as numbers (percentages) and were analyzed using the χ^2 test or Fisher exact test, as appropriate. Statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago,

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TABLE 1 Characteristics of patients with gastroesophageal reflux disease and thyroid disease (GERD-Th) and controls

Parameter	GERD-Th (n = 24)	Controls (n = 36)	*P* value
Age, y, mean (SD)	62.4 (12)	57.33 (15.78)	0.24[a]
Sex, female, n (%)	23 (95.8)	17 (47.2)	<0.001[c]
BMI, kg/m^2, mean (SD)	26.47 (4.8)	26.16 (4.56)	0.92[a]
WHR, mean (SD)	0.84 (0.07)	0.9 (0.07)	<0.001[a]
Hemoglobin, g/dl, mean (SD)	13.68 (1.13)	13.7 (1.56)	0.56[a]
FG, mmol/l, median (Q1–Q3)	5.29 (4.8–5.57)	5.2 (4.8–5.6)	0.93[b]
TC, mmol/l, mean (SD)	5.4 (1.0)	5.3 (1.6)	0.19[a]
HDL-C, mmol/l, mean (SD)	1.6 (0.35)	1.4 (0.3)	0.04[a]
LDL-C, mmol/l, mean (SD)	3.2 (1.0)	3.4 (1.3)	0.12[a]
Triglycerides, mg/dl, median (Q1–Q3)	113 (86–143)	93 (73–122)	0.16[b]
Thyrotropin, ulU/ml, median (Q1–Q3)	1.7 (0.7–2.88)	1.25 (0.94–1.91)	0.43[b]
FT_3, pmol/l, mean (SD)	4.26 (0.5 8)	4.61 (0.64)	0.008[a]
FT_4, pmol/l, mean (SD)	17.63 (2.76)	14.88 (2.21)	<0.001
FSSG score, mean (SD)	20.38 (7.37)	16.58 (6.58)	0.04[a]
NERD, n (%)	20 (83.3)	22 (61.1)	0.04[c]
Comorbidities			
Hypertension[a], n (%)	10 (41.67)	13 (36.1)	0.48[c]
Lipid disorders[b], n (%)	6 (25)	13 (36.1)	0.50[c]
Medications			
LT_4 substitution, n (%)	19 (79.17)	0 (0)	
Antithyroid therapy, n (%)	4 (16.67)	0 (0)	

a *t* test, **b** Mann–Whitney test, **c** χ^2 test, **d** Hypertension defined as use of antihypertensive drugs, **e** Lipid disorders defined as use of lipid-lowering drugs

SI conversion factors: to convert hemoglobin to g/l, multiply by 10; triglycerides to mmol/l, by 0.0113.

Abbreviations: BMI, body mass index; FT_3, free triiodothyronine; FT_4, free thyroxine; FG, fasting glucose; FSSG, frequency scale for the symptoms of GERD; GERD, gastroesophageal reflux disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LT_4, levothyroxine; NERD, nonerosive reflux disease; TC, total cholesterol; WHR, waist-to-hip ratio

Illinois, United States). A *P* value of less than 0.05 was considered significant.

Results The characteristics of the study groups are presented in TABLE 1. There were significantly more women in the GERD-Th group compared with the control group. GERD-Th patients had a significantly lower waist-to-hip ratio than controls. GERD intensity as assessed by the FSSG was positively correlated with waist circumference (r = 0.45, P = 0.007) and with BMI (r = 0.43, P = 0.01) in controls. Such correlations were not found in the GERD-Th group. Thyrotropin levels did not differ between the groups. The highest mean FT_4 level was noted in the GERD-Th group rather than in the control group (P <0.001). None of the thyroid hormone parameters were significantly associated with the FSSG score. The GERD-Th group demonstrated a significantly higher FSSG score, by an average of 3.8 points, compared with controls. GERD-Th patients more commonly reported a burning sensation in the throat and heartburn while bending than controls (P = 0.02 and P = 0.01, respectively). NERD was significantly more in GERD-Th patients than in controls (TABLE 1).

Discussion Our study is among the few studies in which the GERD diagnosis was established based on a validated and clinically useful scale. Moreover, all patients underwent gastroscopy, which allowed for a detailed assessment of the esophageal mucosa. Our study is also one of the few studies to evaluate the effect of thyroid disease on the clinical picture of GERD.

Gastrointestinal symptoms may occasionally be the first sign of thyroid disease and a delayed diagnosis evokes negative consequences.[6] Extraesophageal GERD symptoms associated with irritation of the posterior throat wall are manifested as in a thyroid disease and include hoarseness, coughing, dysphonia, and dysphagia.[11] Savina et al[12] suggested that GERD symptoms in patients with hypothyroidism are associated with disorders of gastrointestinal tract motility rather than esophageal exposure to acid.

To date, the association between GERD and thyroid dysfunction has been assessed mostly in the context of anatomically close organs, such as the esophagus and thyroid, and possible thyroid surgery complications. Only Nomura et al[6] attempted to find associations between endocrine

disorders and GERD. Our study is the first to assess clinical symptoms and endoscopic images in patients with GERD and thyroid disease in comparison with patients without a concomitant hormonal disorder.

Nomura et al[6] reported a group of 111 subjects with adrenal cortex and thyroid disorders, acromegaly, obesity, and hormonally inactive adrenal tumors. The authors demonstrated that obesity and triglyceride levels were positively correlated, while high-density lipoprotein cholesterol levels were negatively correlated with FSSG-assessed GERD symptoms, confirming an earlier report on the greater frequency of GERD in patients with metabolic syndrome.[6] In our study, GERD-Th patients showed a tendency toward abdominal obesity, compared with controls. FSSG-assessed GERD symptoms correlated positively with waist circumference and BMI only in controls. In view of recent studies demonstrating the association between intensity of GERD symptoms and obesity, and considering our study, it may be concluded that overweight and obesity in patients with thyroid disease are not the principal risk factors favoring the development of reflux symptoms.

Thyrotropin levels did not differ between the groups, but significant differences were noted in the free thyroid hormone levels. The lack of a significant difference in thyrotropin levels may be because all GERD-Th patients were on therapy and remained euthyroid. However, a significantly higher FT_4 level was demonstrated in the GERD--Th group than in controls. Hence, further studies in a larger group are necessary, particularly in subjects with uncontrolled hormonal disorders, to explain more fully their effect on GERD.

Additionally, we did not find any correlation between thyrotropin and free thyroid hormone levels and GERD symptoms as assessed by the FSSG between the groups. Nomura et al[6] reported similar results.

Contrary to the above study, all patients we examined were subjected to gastroscopy, allowing us to assess the degree of esophagitis. The vast majority of the GERD-Th group did not present with esophagitis. Interestingly, GERD-Th patients had higher FSSG scores compared with controls, which confirms the lack of correlation between severity of clinical symptoms and mucosal injury. A previous study demonstrated that diabetes in patients with GERD predisposes patients to esophagitis.[8] In contrast, thyroid diseases do not show such an association.

Our report has some limitations, such as a small number of patients with thyroid disease. Studies on a larger patient population, particularly one with uncontrolled thyroid hormonal dysfunction, would allow for a more detailed determination of the effect of such disorders on the course of GERD. The groups were not uniform with respect to sex, and no posttreatment assessment was made.

In conclusion, patients with GERD and concomitant thyroid disease complained more often of burning in the throat and less commonly presented with erosive reflux disease. The results suggest that overweight in patients with a thyroid disease is not the major risk factor favoring reflux symptom development. From the clinical point of view, it can be assumed that asking the patient about burning in the throat would be helpful in early detection of GERD in patients with thyroid disease.

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