Clinical investigations of gastroesophageal reflux disease with and without complications

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PhD Thesis

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4. SUMMARY

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common disease globally that can cause troublesome symptoms and have a significant impact on quality of life. Population-based studies conducted in developed, western countries suggest approximately 20 percent prevalence based on weekly appearing typical symptoms (heartburn and/or acid regurgitation) of the disease, while it remains well below 10 percent in the East. Little is known about Eastern Europe including Hungary. Unfortunately, heartburn as the key symptom of GERD is identical to the heartburn of patients with functional heartburn (FHB), making the differential diagnosis resource-intensive. According to the most recent Rome IV definition endoscopy and esophageal function tests should be performed to establish the diagnosis of FHB. In contrast, the presence of oral manifestations of GERD (such as dental erosions) is considered a cumulative long-term consequence of exposure to gastric acid and can be easily examined. The role of oral manifestations has not been studied yet in this context; however, their exploration is easy, cheap, and widely available, and could be a useful tool in the differentiation of GERD and FHB.

AIMS

The aim of our first study was to collect population-based data on the prevalence of reflux symptoms in South-East Hungary, as well as on possible risk factors, and to compare the obtained data with known Western and Eastern data.

In our second study, we sought to collect data on the occurrence of DE and PD in patients with heartburn and examine whether a difference in their frequency of occurrence can be verified between the FHB and GORB patient groups.

METHODS

In the first study, 2,002 apparently healthy blood donor volunteers were consecutively enrolled and completed detailed questionnaires related to general factors, demographic data, socioeconomic factors, and the presence and frequency of typical and atypical GERD-related symptoms.

In our other research, 116 [M/F: 51/65, mean age: 54 (17-80) years] consecutive patients with heartburn were enrolled for detailed esophageal function and orodental examinations.

RESULTS

Among 2,002 study participants, 56.5% were completely asymptomatic. The prevalence of typical GERD symptoms appearing at least monthly or weekly was 16.5% and 6.8%, respectively. Two-thirds (209/330) of the patients experienced at least monthly occurring typical GERD symptoms and also had associated atypical symptoms and this was even more pronounced when comparing subgroups with higher symptom frequencies. Significant correlations were found between monthly GERD-related complaints and height, body mass index (BMI), coffee consumption, and smoking. Positive family history was another significant factor in all the symptom-frequency categories. GERD-related symptom frequency showed a linear association with sex ($R2 = 0.75$, $P = 0.0049$). Typical and atypical GERD symptoms were significantly more common in those with chronic diseases than those without. Heartburn was observed in 12.5% and 4.4% ($P<0.05$) and acid regurgitation was seen in 6.9% and 1.8% ($P<0.05$), respectively.

In the other study, dental disorders were detected in 89% (103/116). Patients with PD + DE had significantly more often pathologic reflux (90.0% vs 27.8%; $P < 0.05$), higher esophagitis scores (1.8 vs 0.9; $P < 0.05$), and a significantly different mean impedance curve ($P = 0.04$) than those without any dental diseases. The opposite approach established that patient with GERD had a significantly higher prevalence of DE and PD, especially if both were present (28.9% vs 2.0%; $P < 0.01$), more severe PD (1.5 vs 1.0; $P < 0.01$), and longer history of heartburn (15 years vs 9 years; $P < 0.01$) than those with FHB.

CONCLUSIONS

In conclusion, the prevalence of GERD-related symptoms among South-East Hungarian blood donor volunteers was significantly lower than in the Western countries and closer to the Eastern values. In otherwise healthy, non-obese individuals, the prevalence of at least weekly occurring GERD-related symptoms was <5%. The presence of mild, non-exclusionary chronic diseases significantly increased the prevalence of GERD-related symptoms, as well as positive family history, coffee consumption, smoking, shorter height, and increased BMI.

Dental examination of patients with heartburn seems to be useful in the differential diagnosis of GERD and FHB. The co-occurrence of dental erosions and periodontal diseases was associated with reflux disease, while their absence was associated with functional heartburn. Neither DE nor PD (especially its mild forms) alone were predictive of the examined pathologies.

5. INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal diseases worldwide. It is a chronic condition in which frequent regurgitation of the gastric acid into the esophagus, mouth, and/or respiratory system causes typical (heartburn, regurgitation) and atypical (chronic cough, other respiratory symptoms, chest pain, dysphagia, globus sensation, nausea, vomiting) symptoms and/or esophageal/extraesophageal complications. These symptoms are common in the general population and have an impact on quality of life; however, only a few people consult a doctor about them [1-7]. There are different phenotypes of GERD: non-erosive reflux disease is the most common one with its 60-70% of prevalence followed by erosive esophagitis and Barrett's esophagus seen in 30% and 6-12% of patients with GERD, respectively. [8-10].

Heartburn is the mostly considered typical symptom of gastroesophageal reflux disease (GERD) and has a global prevalence of 11.9%. However, it cannot be diagnosed without performing detailed esophageal function tests based on the symptoms of patients with functional heartburn (FHB) [11].

The prevalence of GERD has been determined according to the presence of the abovementioned typical GERD symptoms in many epidemiological studies, although symptom-oriented diagnosis of GERD has at least two issues. First, these "typical symptoms" are also present in patients with functional esophageal disorders (e.g., functional heartburn), which cannot be subjectively distinguished from those caused by acidic reflux. This is supported by the recommendation of the Rome Foundation, as the presence of symptoms alone is not sufficient to diagnose functional esophageal disorders, and a more detailed evaluation is required [12, 13]. Second, many patients do not have typical symptoms of GERD (mostly in Barrett's esophagus or asthma), therefore a symptom-oriented diagnosis cannot be carried out at all, and a detailed clinical evaluation is needed [14, 15].

With the exception of these limitations, large epidemiological studies have shown that the prevalence of symptomatic GERD is around 20% to 25% in the Western world and 10% in Eastern countries [16-18].

Little, if anything, is known about the prevalence in Central Europe, which is located between the west and east, and is where a substantial part of the population lives outside of the larger cities.

According to the Montreal definition, GERD may be associated with supraesophageal manifestations, including oropharyngeal symptoms [19]. Among various oropharyngeal symptoms (salivation, mouth burning, and tongue burning), dental erosion (DE) is considered to have a proven correlation with GERD. The association between DE and GERD was apparently first reported in 1933[20]. By definition, DE is a progressive loss of tough tissues of the teeth due to the action of extrinsic or intrinsic acids. Its median prevalence has been reported to be 24% in all patients with GERD and 32.5% in adult patients with GERD [21]. However, DE can be accompanied by other disorders, such as bulimia, rumination, and the consumption of acidic foods or drinks.

Much less data are available regarding other oral symptoms, especially periodontal diseases (PD), which have recently been suggested to be associated with GERD [22]. PD, which represent a group of oral inflammatory conditions caused by oral pathogens, lead to the destruction of tooth-supporting soft tissues. DE and PD are chronic, cumulative, gradually worsening changes; therefore, they take longer to develop. Thus, their presence indicates the long-term recurring or persistent existence of the factor responsible for their triggering (e.g. GERD). It seems to be a logical assumption that this is why their occurrence is rarer in functional heartburn, where gastric acid has no pathologic role. However, no studies have been carried out in this regard so far.

6. AIMS

The aim of our first study was to collect population-based data on the prevalence of reflux symptoms in South-East Hungary, as well as on possible risk factors, and to compare the obtained data with known Western and Eastern data.

In our second study, we sought to collect data on the occurrence of DE and PD in patients with heartburn and examine whether a difference in their frequency of occurrence can be verified between the FHB and GORB patient groups.

7. PATIENTS AND METHODS

In study I, a total of 2,002 apparently healthy, health-conscious, unremunerated blood donor volunteers [1,156 (42.1) males and 846 (57.9%) females; mean age, 39 (18–65) years] were

consecutively enrolled, after given informed consent in written form. Data were collected by means of a questionnaire at the Hungarian National Blood Transfusion Service in Szeged and in the settlements of Csongrád-Csanád county. In Hungary, blood donation from healthy people who weigh >50 kg and are aged between 18 and 65 years is permitted. Volunteers are allowed to have the following diseases in initial and/or mild/well-controlled form: hypertension (at target value with antihypertensive monotherapy), diabetes mellitus (normal serum glucose and HbA1c levels with diet ± metformin), obesity, hypothyroidism/hyperthyroidism (normal thyroid gland function with therapy), hypercholesterolemia (at normal value with diet ± statin), hyperuricemia, asthma bronchial (normal respiratory function test with long and short-acting bronchodilator inhalers, and/or with other medication), allergy (intermittent antihistamine therapy), GERD, osteoporosis, tachycardia/arrhythmias, polycystic ovary syndrome, coeliac disease, eczema, Gilbert's syndrome, and some musculoskeletal disorders [23]. These conditions were confirmed by the physician of the Hungarian National Blood Transfusion Service.

Participant donors completed detailed questionnaires related to general factors [age, sex, body mass index (BMI) calculated from height and weight], demographic data (place of childhood, current place of residence, composition of the family, occupation), socioeconomic factors (smoking habits, alcohol and coffee consumption, family history of GERD, patient history of chronic diseases). The presence and frequency of typical (heartburn, acid regurgitation) and atypical GERD-related symptoms (nausea, dysphagia, globus sensation, respiratory symptoms as chronic cough, shortness of breath, hoarseness, new or worsening asthma, and chest pain) were also assessed. The following symptom-frequency categories were used: at least once a day, at least once a week, at least once a month, and less than once a month.

Subgroup analysis was performed by age, sex, height, weight, BMI, smoking habits, alcohol and coffee consumption, inheritance (GERD in the family), chronic diseases, and prevalence of symptoms. The study I received ethical approval (ethical committee approval number: WHO 3345).

For the other study, 116 consecutive patients (M/F: 51/65, mean age: 54.00 years ± 15.62 years) with heartburn were enrolled in our tertiary center for detailed esophageal function testing, including upper gastrointestinal endoscopy, high-resolution esophageal manometry [medical measurement systems (MMS) solar with a 22-channel, water-perfused catheter], and 24-h multi-

channel intra-esophageal pH-impedance monitoring (MMS Ohmega®, with a pHersaflex Z61A pH probe). Any medications with any effect on gastrointestinal motility or gastric secretion were suspended one month before the esophageal testing. For gastroscopy, Olympus GIF-Q165 endoscopes were used, and the procedure was carried out under local, topical anesthesia. The presence of esophageal manifestations was recorded. Esophagitis was classified per the Los Angeles criteria [24]. On this basis, the following scoring system (no erosion = 0, LA-A = 1, LA-B = 2, LA-C = 3, LA-D = 4) was applied for quantitative comparison of the degree of esophagitis. Esophagogastric junction outflow obstruction and other major motility disorders were excluded *via* high-resolution esophageal manometry according to the Chicago classification 3.0 [25]. During pH-impedance monitoring, the pH sensor was placed 5 cm above the lower esophageal sphincter as determined *via* manometry.

The significance of GERD was judged by the Lyon consensus [26]. The diagnosis of FHB was established according to the Rome IV criteria [27], including < 4% acid exposure time in the esophagus and the independence of symptoms of acidic and non-acidic reflux episodes. The occurrence of reflux hypersensitivity was also evaluated, but none of the studied patients fulfilled the accepted Rome IV criteria of this disease. Moreover, baseline impedance values were above 2000 Ω in this patient group [28]. We also calculated the mean 24-hour impedance in all channels, the impedance values of the six channels during the 24-hour measurement were exported to a .csv file and averaged.

Before dental examinations, general personal data, social and dental habits, and the presence, frequency, and appearance of typical and atypical reflux symptoms were assessed using standardized questionnaires that were collected by an interviewer (medical doctor and student). Among the enrolled subjects, 116 patients [M/F: 51/65, mean age: 56 (22-82) years] with heartburn were participating in further oral and dental examinations. Oral evaluations were carried out by a dentist who was blinded to the results of the esophageal function tests. The tooth wear index was evaluated and scored using the Smith and Knight's criteria, while the clinical staging of periodontitis was performed according to some studies [29, 30]. To quantitatively compare the severity of periodontitis, the following score system was used: No sign = 0, mild = 1, moderate = 2, severe = 3). The plaque index was calculated *via* the percentage of plaque area in relation to the total area.

Based on the presence of DE and/or PD, subgroups were formed.

All statistical analyses (one-way analysis of variance, chi-squared test, linear regression, and unpaired *t*-test) were performed using R and GraphPad Prism software; the significance level was set at $P = 0.05$. Data are expressed using the mean ± SD. Study II was approved by the Regional Human Research Ethics Committee of the University of Szeged (Ethical approval No. 4564).

8. RESULTS

In the first study, among the 2,002 consecutive blood donor volunteers, 56.5% (1,131/2,002) were completely asymptomatic. Among the remaining volunteers, 27.9% (559/2,002) had typical symptoms of GERD (heartburn and/or acid regurgitation). However, symptoms that appeared at least monthly or weekly were significantly less common [16.5% (330/2,002) and 6.8% (136/2,002), $P < 0.05$, respectively]. The majority of participants with typical GERD symptoms [56.4% (315/559)] also had atypical symptoms (such as abdominal pain, nausea, vomiting, dysphagia, globus sensation, cough, respiratory symptoms, and chest pain). This difference was further and significantly increased and showed a linear correlation with symptom frequency ($R^2 = 0.9748$, $P < 0.0001$) (Figure 1).

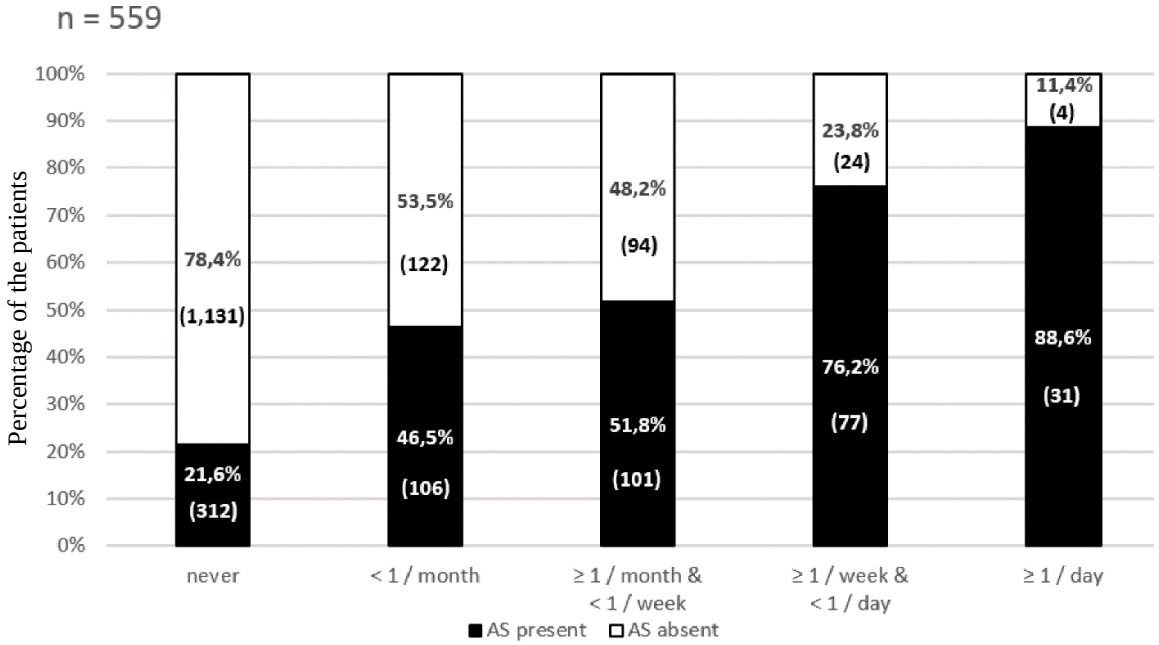

Figure 1. The occurrence of atypical symptoms in participants with typical GERD symptoms. There is a positive linear association between the frequency of the typical GERD-related symptom, and the presence of atypical symptoms (AS). ($R^2 = 0.9748$, $P < 0.0001$).

Atypical symptoms were also seen in participants who had typical GERD symptoms at least monthly [63.1% (209/330)], weekly [79.4% (108/136)], and daily [88.6% (31/35)] (Table 1).

n = 2,002						
typical GERD symptoms	**atypical GERD symptoms**	**ever**	**< 1 / month**	**≥ 1 / month & < 1 / week**	**≥ 1 / week & < 1 / day**	**≥ 1 / day**
present (n = 559)	***present***	315 *(15.7%)*	106 *(5.3%)*	101*(5.0%)*	77 *(3.8%)*	31*(1.6%)*
	absent	244 *(12.2%)*	122 *(6.1%)*	94 *(4.7%)*	24 *(1.2%)*	4 *(0.2%)*
absent (n = 1,443)	***present***	312 *(15.6%)*				
	absent	1,131 *(56.5%)*				

Table 1. The presence of the typical and/or atypical symptoms

Detailed symptom analysis showed that the prevalence of heartburn was higher than that of acid regurgitation in all symptom-frequency categories.

Among the atypical (esophageal and extraesophageal) symptoms, respiratory symptoms were the most prevalent (19%), although only 13% of the participants had respiratory symptoms at least monthly. Globus sensation occurred in 6% and other atypical symptoms were reported by <5% of the participants (Table 2).

n = 2,002	**< 1 / month**	**≥ 1 / month& < 1 / week**	**≥ 1 / week& < 1 / day**	**≥ 1 / day**
heartburn	168 *(8,4%)*	160 *(8,0%)*	93 *(4,6%)*	29 *(1,4%)*
acid regurgitation	163 *(8,1%)*	108 *(5,4%)*	44 *(2,2%)*	18 *(0,9%)*
typical symptoms during night	51 *(2,5%)*	32 *(1,6%)*	20 *(1,0%)*	5 *(0,2%)*
dysphagia	8 *(0,4%)*	12 *(0,6%)*	13 *(0,6%)*	4 *(0,2%)*
globus sensation	54 *(2,7%)*	33 *(1,6%)*	23 *(1,1%)*	9 *(0,4%)*

upper respiratory tract symptoms	121 *(6,0%)*	80 *(4,0%)*	80 *(4,0%)*	93 *(4,6%)*
dyspnea	35 *(1,7%)*	14 *(0,7%)*	16 *(0,8%)*	3 *(0,1%)*
chest pain	26 *(1,3%)*	40 *(2,0%)*	11 *(0,5%)*	4 *(0,2%)*
epigastric pain	66 *(3,3%)*	56 *(2,8%)*	60 *(3,0%)*	21 *(1,0%)*
abdominal pain	8 *(0,4%)*	19 *(0,9%)*	24 *(1,2%)*	11 *(0,5%)*
nausea, vomiting	37 *(1,8%)*	27 *(1,3%)*	20 *(1,0%)*	4 *(0,2%)*

Table 2. The prevalence and frequency of different GERD-related symptoms

Among the blood donors who had GERD-related symptoms at least monthly, significant correlations were found between the complaints and some socioeconomic factors, such as height, BMI, coffee consumption, and smoking. The correlation between the frequency of symptoms and sex of the volunteers was different. Females showed an increased frequency of GERD-related symptoms ($R^2 = 0.75$, $P = 0.0049$). This linear association was observed when both typical and all symptoms were assessed (Figure 2).

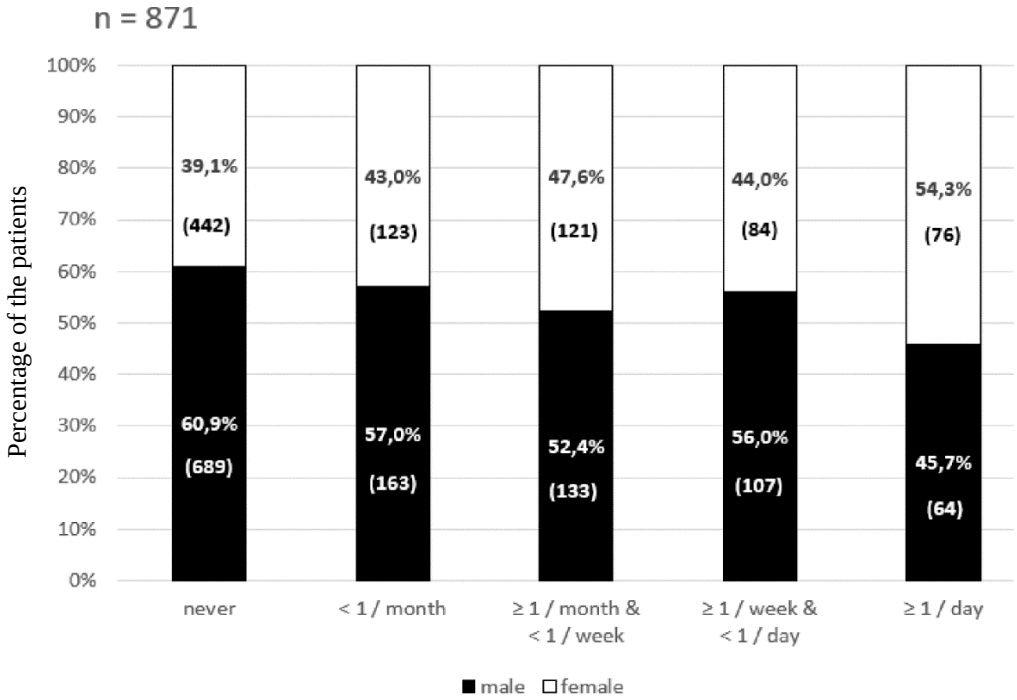

Figure 2. The frequency of GERD-related symptoms is positively associated to female sex ($R^2 = 0.75$, $P = 0.0049$). Similar association was found if only the typical symptoms were assessed.

The remaining parameters (occupation, household population, current, and childhood residence) showed no correlation. Positive family history was a significant predictive factor in all studied symptom-frequency categories (Table 3a).

	Asymptomatic ***(n = 1,131)***	**Any GERD-related symptoms (typical / atypical)** ***(n = 871)***			
		< 1 / month ***(n = 286)***	**≥ 1 / month& < 1 / week** ***(n = 254)***	**≥ 1 / week& < 1 / day** ***(n = 191)***	**≥ 1 / day** ***(n = 140)***
Sex					
Male	689 (60.9%)	163 (57.0%)	133 (52.4%)	107 (56.0%)	64 (45.7%)
Female	442 (39.1%)	123 (43.0%)	121 (47.6%) *	84 (44.0%)	76 (54.3%) **
Age (years)	39 ± 12.4 (17-66)	39 ± 12.7 (17-65)	38 ± 13.3 (18-65)	38 ± 12.3 (18-64)	41 ± 12.2 (18-64)
Weight (kg)	81 ± 15.8 (50-140)	81 ± 16.7 (52-135)	80 ± 17.2 (51-180)	81 ± 17.0 (52-130)	79 ± 16.9 (50-140)
Height (cm)	174 ± 9.2 (150-197)	173 ± 8.9 (155-198)	172 ± 9.5 (150-197) **	173 ± 9.1 (150-196)	171 ± 9.9 (150-200) **
BMI (kg/m^2)	26.6 ± 4.5 (16.9-52.7)	27.0 ± 4.8 (18.9-45.2)	27.0 ± 5.2 (17.7-52.6)	27.0 ± 4.8 (18-43.9)	26.9 ± 4.9 (17.0-45.2)
BMI categories					
1 – underweight	3 (0.3%)	0 (0.0%)	3 (1.0%)	2 (1.0%)	1 (0.7%)
2 – normal weight	444 (39.3%)	112 (39.2%)	96 (37.8%)	71 (37.2%)	57 (40.7%)
3 – overweight	455 (40.2%)	109 (38.1%)	99 (39.0%)	73 (38.2%)	43 (30.7%)
4 – obesity	169 (14.9%)	45 (15.7%)	39 (15.4%)	36 (18.8.%)	32 (22.9%)
5 – extreme obesity	60 (5.3%)	20 (7.0%)	17 (6.7%)	9 (4.7%)	7 (5.0%) *
Smoking					
recent / previous	368 (32.5%)	102 (35.7%)	106 (41.7%) **	84 (44.0%) **	72 (51.4%) **
never	763 (67.5%)	184 (64.3%)	148 (58.3%)	107 (56.0%)	8 (48.6%)
Coffee					
yes	756 (66.8%)	195 (68.2%)	187 (73.6%)	132 (69.1%)	110 (78.6%)
no	375 (33.2%)	91 (31.8%)	67 (26.4%) *	59 (30.9%)	30(21.4%)**

Alcohol					
regular	30 (2.7%)	8 (2.8%)	10 (3.9%)	9 (4.7%)	9 (6.4%)
never / occasional	1101 (97.3%)	278 (97.2%)	244 (96.1%)	182 (95.3%)	131 (93.6%)
GERD in the family					
yes	147 (13.0%)	54(18.9%)**	63(24.8%)**	54(28.3%)**	39(27.9%)**
no	825 (72.9%)	176 (61.5%)	154 (60.6%)	110 (57.6%)	77 (55.0%)
unknown	159 (14.1%)	56 (19.6%)	37 (14.6%)	27 (14.1%)	24 (17.1%)

Table 3a. Socioeconomic factors of blood donor volunteers with any GERD-related symptoms (typical and/or atypical). Age, weight, height, and BMI are presented with mean ± SD and range.

(: p < 0.05, compared to the asymptomatic subjects; **: p < 0.01, compared to the asymptomatic subjects)*

Analysis of typical GERD-related symptoms only showed the tendency was the same as in blood donors with any GERD-related symptoms (Table 3b).

		GERD-related typical symptoms *(n = 559)*			
	Asymptomatic *(n = 1,131)*	**< 1 / month *(n = 229)***	**≥ 1 / month & < 1 / week *(n = 194)***	**≥ 1 / week & < 1 / day *(n = 101)***	**≥ 1 / day *(n = 35)***
Sex					
Male	689 (60.9%)	145 (63.3%)	100 (51.5%) **	54 (53.5%)	16 (45.7%)
Female	442 (39.1%)	84 (36.7%)	94 (48.5%) **	47 (46.5%)	19 (54.3%)
Age (years)	39 ± 12.4 (17-66)	39 ± 12.5 (18-65)	39 ± 12.9 (18-64)	41 ± 11.6 (18-64)	39 ± 10.9 (21-58)
Weight (kg)	81 ± 15.8 (50-140)	83 ± 16.7 (51-135)	83 ± 18.3 (51-180)	82 ± 15.7 (54-130)	82 ± 20.9 (50-140)
Height (cm)	174 ± 9.2 (150-197)	174 ± 9.4 (153-198)	172 ± 9.7 (150-200) **	172 ± 8.7 (150-190) *	172 ± 9.0 (153-187)
BMI (kg/m^2)	26.6 ± 4.5 (16.9-52.7)	27.2 ± 5.0 (17.7-45.2)			27.6 ± 5.7 (20.1-45.2)

			27.9 ± 5.4 (18.3-52.6) **	27.7 ± 4.5 (18.8-39.7) *	
BMI categories					
1 – underweight	3 (0.3%)	3 (1.3%)	1 (0.5%)	0 (0%)	0 (0%)
2 – normal weight	444 (39.3%)	84 (36.7%)	66 (34.0%)	33 (32.7%)	11 (31.4%)
3 – overweight	455 (40.2%)	84 (36.7%)	73 (37.6%)	39 (38.6%)	14 (40.0%)
4 – obesity	169 (14.9%)	40 (17.5%)	36 (18.6%)	26 (25.7%)	7 (20.0%)
5 – extreme obesity	60 (5.3%)	18 (7.9%) *	18 (9.3%)	3 (3.0%)	3 (8.6%)
Smoking					
recently/previously	368 (32.5%)	80 (34.9%)	77 (39.7%)	44 (43.6%)	14 (40.0%)
never	763 (67.5%)	149 (65.1%)	117 (60.3%) *	57 (56.4%) *	21 (60.0%)
Coffee					
yes	756 (66.8%)	151 (65.9%)	145 (74.7%)	77 (76.2%)	25 (71.4%)
no	375 (33.2%)	78 (34.1%)	49 (25.3%) *	24 (23.8%) *	10 (28.6%)
Alcohol					
regularly	30 (2.7%)	6 (2.6%)	9 (4.6%)	6 (5.9%)	2 (5.7%)
never/occasionally	1101 (97.3%)	223 (97.4%)	185 (95.4%)	95 (94.1%)	33 (94.3%)
GERD in the family					
yes	147 (13.0%)	52 (22.7%)	49 (25.3%)	43 (42.6%)	13 (37.1%)
no	825 (72.9%)	133 (58.1%)	107 (55.2%)	47 (46.5%)	17 (48.6%)
unknown	159 (14.1%)	44 (19.2%) **	38 (19.6%) **	11 (10.9%) **	5 (14.3%) **

Table 3b. Socioeconomic factors of blood donor volunteers with any GERD-related typical symptoms. Age, weight, height, and BMI are presented with mean ± SD and range.

(: $p < 0.05$, compared to the asymptomatic subjects; **: $p < 0.01$, compared to the asymptomatic subjects)*

Associations between different chronic diseases and GERD-related symptoms were examined. Due to the rules of eligibility to donate blood, volunteers with mild, well-controlled, chronic diseases were not excluded. Therefore, 390 participants with non-exclusionary diseases were also enrolled. Among these, 93.3% (364/390) had only one disorder, whereas 6.7% (26/390) had two different chronic conditions.

Among blood donors with non-exclusionary chronic diseases (e.g., hypertension, hyperthyroidism/hypothyroidism, diabetes), those with typical GERD symptoms appearing at least weekly were significantly more common compared with those without non-exclusionary chronic diseases. Heartburn and acid regurgitation were reported by 12.5% and 6.9% of participants with chronic diseases, in contrast to 4.4% and 1.8% of completely healthy participants, respectively (for all categories $P < 0.05$).

Overweight or obesity without any further chronic diseases were detected in 925/2,002 (46.2%) participants and showed no relevant effects on the prevalence of GERD-related typical symptoms (Table 4).

	with chronic diseases *(n = 390)*				**without chronic diseases**							
					BMI < 25 kg/m² *(n = 687)*				**BMI > 25 kg/m²** *(n = 925)*			
	< 1 / month	**≥ 1 / month & < 1 / week**	**≥ 1 / week& < 1 / day**	**≥ 1 / day**	**< 1 / month**	**≥ 1 / month & < 1 / week**	**≥ 1 / week& < 1 / day**	**≥ 1 / day**	**< 1 / month**	**≥ 1 / month & < 1 / week**	**≥ 1 / week& < 1 / day**	**≥ 1 / day**
heartburn	39 *(10.0%)*	33 *(8.5%)*	38 *(9.7%)* **	11 *(2.8%)* *	47 *(6.8%)*	47 *(6.8%)*	22 *(3.2%)*	8 *(1.2%)*	82 *(8.9%)*	80 *(8.6%)*	33 *(3.6%)*	10 *(1.1%)*
acid regurgitation	42 *(10.8%)* *	34 *(8.7%)* **	16 *(4.1%)* *	11 *(2.8%)* **	40 *(5.8%)*	28 *(4.1%)*	12 *(1.7%)*	1 *(0.1%)*	81 *(8.8%)*	46 *(5.0%)*	16 *(1.7%)*	6 *(0.6%)*
typical symptoms during night	18 *(4.6%)* **	8 *(2.1%)*	8 *(2.1%)* *	3 *(0.8%)*	5 *(0.7%)*	9 *(1.3%)*	4 *(0.6%)*	1 *(0.1%)*	28 *(3.0%)*	15 *(1.6%)*	8 *(0.9%)*	1 *(0.1%)*

dysphagia	4 *(1.0%)*	5 *(1.3%)*	7 *(1.8%)* *	2 *(0.5%)*	1 *(0.1%)*	4 *(0.6%)*	3 *(0.4%)*	1 *(0.1%)*	3 *(0.3%)*	3 *(0.3%)*	3 *(0.3%)*	1 *(0.1%)*
globus sensation	16 *(4.1%)* *	9 *(2.3%)*	7 *(1.8%)*	6 *(1.5%)* **	21 *(3.1%)*	15 *(2.2%)*	7 *(1.0%)*	3 *(0.4%)*	17 *(1.8%)*	9 *(1.0%)*	9 *(1.0%)*	0 *(0%)*
upper respiratory tract symptoms	28 *(7.2%)*	20 *(5.1%)*	20 *(5.1%)*	33 *(8.5%)* **	46 *(6.7%)*	24 *(3.5%)*	30 *(4.4%)*	23 *(3.3%)*	47 *(5.1%)*	36 *(3.9%)*	30 *(3.2%)*	37 *(4.0%)*
dyspnea	17 *(4.4%)* **	8 *(2.1%)* **	7 *(1.8%)* *	3 *(0.8%)* **	5 *(0.7%)*	2 *(0.3%)*	5 *(0.7%)*	0 *(0%)*	13 *(1.4%)*	4 *(0.4%)*	4 *(0.4%)*	0 *(0%)*
chest pain	11 *(2.8%)* *	14 *(3.6%)* *	3 *(0.8%)* *	3 *(0.8%)* *	7 *(1.0%)*	13 *(1.9%)*	7 *(1.0%)* *	1 *(0.1%)*	8 *(0.9%)*	13 *(1.4%)*	1 *(0.1%)*	0 *(0%)*
epigastric pain	21 *(5.4%)* *	11 *(2.8%)*	25 *(6.4%)* **	11 *(2.8%)* **	16 *(2.3%)*	22 *(3.2%)*	14 *(2.0%)*	3 *(0.4%)*	29 *(3.1%)*	23 *(2.5%)*	21 *(2.3%)*	7 *(0.8%)*
abdominal pain	2 *(0.5%)*	5 *(1.3%)*	10 *(2.6%)* **	6 *(1.5%)* *	5 *(0.7%)*	7 *(1.0%)*	9 *(1.3%)*	2 *(0.3%)*	1 *(0.1%)*	7 *(0.8%)*	5 *(0.5%)*	3 *(0.3%)*
nausea & vomiting	12 *(3.1%)*	8 *(2.1%)*	10 *(2.6%)* **	2 *(0.5%)*	11 *(1.6%)*	12 *(1.7%)*	4 *(0.6%)*	2 *(0.3%)*	14 *(1.5%)*	7 *(0.8%)*	6 *(0.6%)*	0 *(0%)*

Table 4. The effect of coexisting, chronic diseases (including obesity) on the prevalence of GERD-related symptoms.

(: $p < 0.05$, compared to the respective group of subjects without chronic diseases; **: $p < 0.01$, compared to the respective group of subjects without chronic diseases*

On the contrary, blood donors with any GERD-related symptoms were more obese than asymptomatic participants and a linear correlation was observed between these two parameters ($R^2 = 0.63$, $P = 0.0497$) (Table 3a-3b, Figure 3).

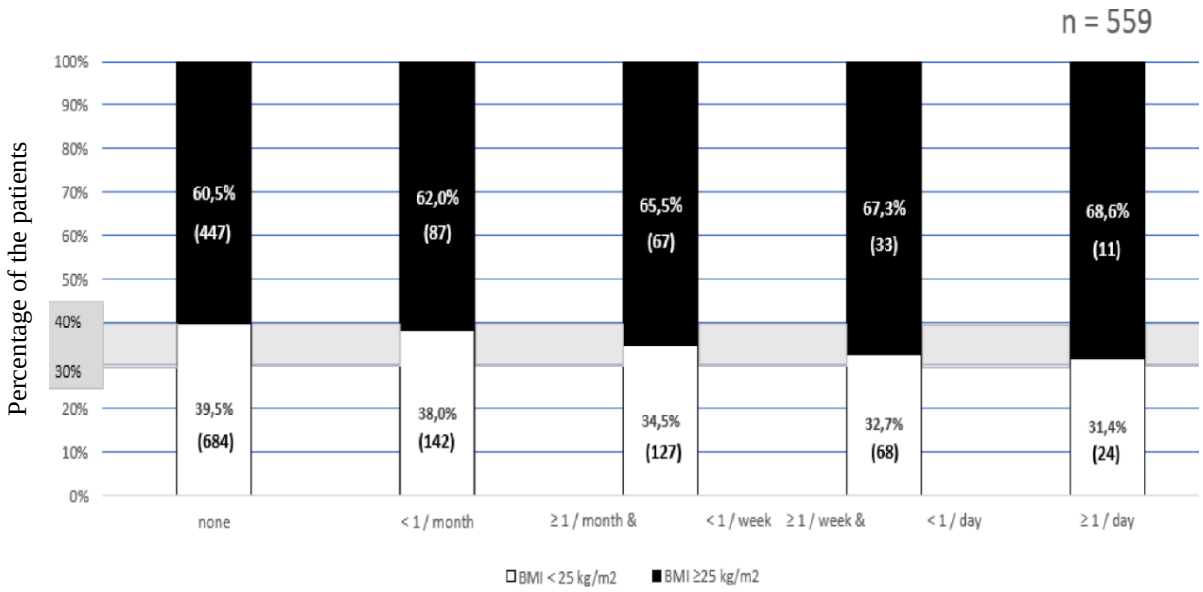

Figure 3. The frequency of GERD-related typical symptoms is positively associated to the presence of overweight ($R^2 = 0.63$, $P = 0.0497$). Similar association was found if all (typical + atypical) reflux related symptoms were assessed.

In participants with hypertension (173/2,002, 8.6%), heartburn (45/173, 26%, $P = 0.0313$), acid regurgitation (35/173, 20.2%, $P = 0.0055$), nocturnal typical symptoms (14/173, 8.1%, $P = 0.009$), and respiratory symptoms (42/173, 24.3%, $P = 0.0385$) were the most common complaints and were also significantly more prevalent compared with participants without chronic non-exclusionary disorders.

All typical and atypical symptoms were significantly more common in participants with known minor respiratory diseases [44/2,002 (2.2%); $P < 0.05$]. The low number of cases did not allow for statistical confirmation of the association with a positive family history of GERD (10/44, 22.7% vs. 27/44, 61.4%).

Globus sensation was the only considerable symptom (4/23, 17.4% *vs* 5.7%, $P = 0.0434$) among participants with thyroid disorders (23/2,002, 1.2%). Any type of cardiac disease (58/2,002, 2.9%) was associated with nausea, vomiting, and chest pain ($P < 0.05$).

Patients with non-exclusionary chronic diseases were older than completely healthy participants (Table 5). However, age showed no correlation with the prevalence of GERD-related symptoms (Table 2).

	with chronic diseases *(n = 390)*	without chronic diseases	
		BMI < 25 kg/m^2 *(n = 687)*	**BMI > 25 kg/m^2** *(n = 925)*
Sex			
Male	205 (52.6%)	333 (48.5%)	618 (66.8%) **
Female	185 (47.4%)	354 (51.5%)	307 (33.2%)
Age (years)	45 ± 11.8 (18-66) **	34 ± 12.0 (18-65)	40 ± 12.0 (17-65)
Weight (kg)	85 ± 17.0 (52-134)	68 ± 9.1 (50-92)	89 ± 14.0 (58-180)
Height (cm)	172 ± 9.4 (150-198)	173 ± 8.9 (153-197)	174 ± 9.3 (150-200)
BMI (kg/m^2)	28.7 ± 4.9 (17.0-45.2)	22.5 ± 1.7 (16.9-24.9)	29.2 ± 3.8 (25.0-52.7)
BMI categories			
1 – underweight	2 (0.5%)	7 (1.0%)	0
2 – normal weight	100 (25.6%)	680 (99.0%)	0
3 – overweight	141 (36.2%)	0	638 (69.0%)
4 – obesity	110 (28.2%)	0	211 (22.8%)
5 – extreme obesity	37 (9.5%)	0	76 (8.2%)
Smoking			
recently / previously	139 (35.6%)	248 (36.1%)	345 (37.3%)
never	251 (64.4%)	439 (63.9%)	579 (62.6%)
Coffee			
yes	285(73.1%) *	457 (66.5%)	638 (69.1%)
no	105 (26.9%)	230 (33.5%)	286 (30.9%)

Alcohol			
regularly	15 (3.8%)	16 (2.3%)	35 (3.8%)
never / occasionally	375 (96.2%)	671 (97.7%)	889 (96.2%)
GERD in the family			
yes	87 (22.3%) *	119 (17.3%)	151 (16.3%)
no	244 (62.6%)	475 (69.1%)	623 (67.4%)
unknown	59 (15.1%)	93 (13.6%)	150 (16.3%)

Table 5. Socioeconomic factors of blood donor volunteers according to the presence of coexisting, chronic diseases. Age, weight, height, and BMI are presented with mean ± SD and range.

(: $p < 0.05$, compared to the respective group of subjects without chronic diseases; **: $p < 0.01$, compared to the respective group of subjects without chronic diseases)*

In our other study, 116 patients were enrolled. Among them, detailed esophageal testing identified 66 patients with GERD (56.9%) and 50 patients with FHB (43.1%). Dental disorders were detected in 89% (103/116) of the enrolled patients with heartburn. The global prevalence of DE among the enrolled patients was 23.3%. In the group of subjects with GERD, the mean DeMeester score (DMS) was 29.84 ± 27.06. In contrast, in the other group, the mean DMS was 3.34 ± 2.94. Fourteen subjects were diagnosed with Barrett's esophagus. Among patients with GERD, LA-A in 12 (18.2%), LA-B in 15 (22.7%), LA-C in 20 (30.3%), and LA-D in 4 cases (6.1%) were detected, and 15 (22.7%) of them had no sign of esophagitis. In the group with FHB, there was no esophagitis on gastroscopy. Based on the results of pH-impedance monitoring, proximal reflux was found in 41 cases. Dental erosions were significantly more common among patients with GERD (66/116) than among those with FHB (21/66, 31.8% *vs* 6/50, 12.0%; $P = 0.0312$). The mean body mass index (BMI) in the GERD group was 27.8 kg/m^2 ± 4.45 kg/m^2 while that in the FHB group was 26.2 kg/m^2 ± 4.53 kg/m^2 ($P = 0.0192$). Eleven patients were toothless. Furthermore, we established significantly more severe periodontal problems in patients with GERD ($P = 0.0253$). However, instead of the fact that neither only DE nor only PD was significantly more common in any of the study groups, PD and DE together were significantly more prevalent among patients with GERD ($P = 0.00008$). DEs alone were less common among patients with GERD (3/8, 37.5%) than among those with FHB (5/8, 62.5%). Moreover, more patients were toothless in the GERD group (8/11, 72.7%). However, the most prominent difference is the presence of DE and PD together: 19/20

(95%) in the group of patients with GERD and 1/20 (5%) in the control group. The mean plaque index was 52 (0-100) in both groups. Fewer teeth were detected in the GERD group; however, the difference was not statistically significant (18 *vs* 21; $P = 0.098$). Patients with GERD had a longer history of symptoms than those with FHB (15 years *vs* 9 years, $P = 0.0041$) (Table 6).

		GERD (*n* = 66)	**FHB (*n* = 50)**	***P* value**
Gender (male/ female)		32(48.5%)/ 34(51.5%)	19(38%)/ 31 (62%)	NS
Age, yr (min-max)		57 (22-82)	51 (25-79)	NS
BMI, kg/m^2 (min-max)		28 (16-37)	26 (17-39)	< 0.05
Mean DMS		29.84	3.34	< 0.0001
Mean impedance ± SD		2175 ± 650	2489 ± 731	< 0.05
Number of teeth (min-max)		18.3 (0-32)	20.7 (0-32)	NS
Toothless		8 (12.1%)	3 (6%)	NS
DE all		22 (33.3%)	6 (12%)	< 0.01
DE only		3 (4.5%)	5 (10%)	NS
PD all		52 (78.8%)	32 (64%)	NS
PD only		33 (50%)	31 (62%)	NS
DE and PD		19 (28.9%)	1 (2%)	< 0.01
Neither DE, nor PD		3 (4.5%)	10 (20%)	< 0.01
Periodontal scores (mean ± SD)		1.45 ± 0.85	0.97 ± 0.84	< 0.01
Drinking carbonated drinks	Nowadays	8 (12.2%)	10 (20%)	NS
	Previously	22 (33.3%)	15 (30%)	
	Never	36 (54.5%)	25 (50%)	
Eating sour foods	Nowadays	15 (22.7%)	9 (18%)	NS
	Previously	13 (19.7%)	9 (18%)	
	Never	38 (57.6%)	32 (64%)	
Bruxism/teeth grinding		9 (13.6%)	8 (16%)	NS
Total duration of heartburn, mean years (range)		15 (0-64)	9 (0-35)	< 0.01

Duration of heartburn until diagnosis, mean years (range)	5.3 (0-49)	2.9 (0-30)	NS

Table 6. Comparison of parameters between patients with gastroesophageal reflux disease and those with functional heartburn

GERD: Gastroesophageal reflux disease; FHB: Functional heartburn; BMI: Body mass index; DMS: DeMeester score; PD: Periodontal disease; DE: Dental erosion; DE all: All the patients who had DE, and some of them have associated PD as well; DE only: Such patients have only DE and have not PD; PD all: All the patients who had PD, and some of them have associated DE as well; PD only: Such patients have only PD and have not DE; SD: Standard deviation; NS: Not significant.

Mean impedance values were compared between the two study groups and found to be significantly lower among patients with GERD than among those with FHB, and a characteristic tendency of GERD was detected (Figure 4).

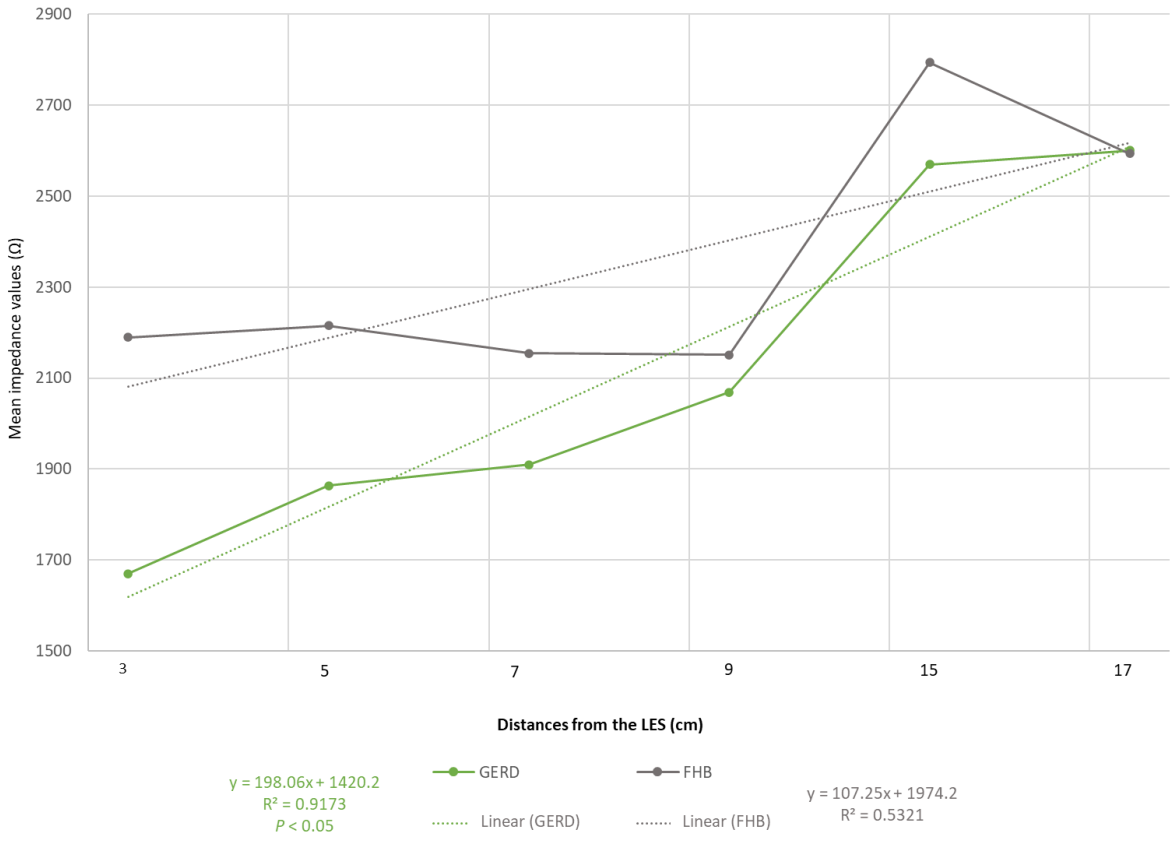

Figure 4. Mean impedance values in patients with gastroesophageal reflux disease and those with functional heartburn.

GERD: Gastroesophageal reflux disease; FHB: Functional heartburn; LES: Lower esophageal sphincter

In the entire study population, the periodontal examination was possible in only 105 patients because 11 of them were toothless. Among the examined subjects, 17/105 (16.2%) had DE alone, 24/105 (22.9%) had PD alone, 10/105 (9.5%) had both, and 54/105 (51.4%) had neither. Patients with DE alone had no more pathologic reflux than those with intact teeth (41.2% *vs* 27.8%). Among patients with both PD and DE, pathologic reflux was significantly more prevalent (27.8% and 90.0%; $P = 0.03$) than among patients without DE and PD. Furthermore, patients with PD and DE had higher esophagitis scores (1.8 *vs* 0.9; $P = 0.05$) than those without any dental diseases, and there was a tendency for more proximal reflux ($P = 0.08$). The presence of PD causing tooth loss was more common than the presence of DE or both (18 *vs* 22 and 24, $P = 0.11$) On the other hand, the mean plaque index was significantly higher among patients with PD than among patients without PD and/or DE (72 *vs* 49, $P < 0.0001$; Table 2). Other oral, atypical symptoms were not significant in the studied group, such as burning sensation of the mouth and tongue, sore throat, bad breath, sour taste, and ageusia (Table 7).

		DE (*n* = 17)	**PD (*n* = 24)**	**Both (*n* = 10)**	**Neither (*n* = 54)**	***P* value**
Gender (male/female)		7(41.2%)/ 10 (58.8%)	12(50%)/ 12 (50%)	7(70%)/ 3 (30%)	21(38.9%)/ 33 (61.1%)	NS
Age, yr (min-max)		50 (24-79)	60 (41-82)	62 (40-71)	53 (22-80)	NS
BMI, kg/m^2 (min-max)		27 (17-35)	28 (16-39)	29 (26-35)	26 (18-37)	NS
Heartburn		17 (100%)	24 (100%)	10 (100%)	54 (100%)	NS
Nausea		12 (70.6%)	9 (37.5%)	7 (70%)	23 (42.6%)	NS
Vomiting		4 (23.6%)	5 (20.8%)	5 (50%)	9 (16.7%)	NS
Dysphagia		11 (64.7%)	10(41.7%)	5 (50%)	21 (38.9%)	NS
Regurgitation		15 (88.2%)	15(62.5%)	8 (80%)	39 (72.2%)	NS
Drinking	Nowadays	2 (11.8%)	5 (20.8%)	2 (20%)	8 (14.8%)	NS
carbonated	Previously	6 (35.3%)	10(41.7%)	1 (10%)	17 (31.5%)	
drinks	Never	9 (52.9%)	9 (37.5%)	7 (70%)	29 (53.7%)	

Eating	Nowadays	5 (29.4%)	6 (25%)	0 (0%)	11 (20.4%)	NS
sour foods	Previously	2 (11.8%)	6 (25%)	4 (40%)	7 (13%)	
	Never	10 (58.8%)	12 (50%)	6 (60%)	36 (66.7%)	
Bruxism		4 (23.6%)	4 (16.7%)	2 (20%)	7 (13%)	NS
(teeth grinding)						
Number of teeth		24	18	21	22	NS
(min-max)		(13-31)	(1-30)	(13-28)	(2-32)	
Plaque Index		58	72	67	49	<0.01
(min-max)		(15-100)	(32-100)	(35-97)	(0-94)	
Esophagitis score		1.6 ± 1.4	1.5 ± 1.4	1.8 ± 1.2	0.9 ± 1.1	0.05
(mean ± SD)						
Mean DMS		23.11	17.5	26.91	13.94	NS
Mean impedance ± SD		2390 ± 878	2393 ±714	1708 ± 249	2427 ± 690	NS
Pathological reflux		7 (41.2%)	9 (37.5%)	9 (90%)	15 (27.8%)	<0.01
Any proximal reflux		8 (47.1%)	9 (37.5%)	7 (70%)	19 (35.2%)	NS
Distal reflux		11 (64.7%)	13(54.2%)	10 (100%)	21 (38.9%)	<0.01

Table 7. Comparison of parameters between patients with or without dental erosion and periodontal disease

PD: Periodontal disease; DE: Dental erosion; BMI: Body mass index; DMS: DeMeester score; SD: Standard deviation; NS: Not significant.

Evaluating the mean impedance values, the tendency in patients with DE and PD was similar to that in patients with GERD (Figure 5).

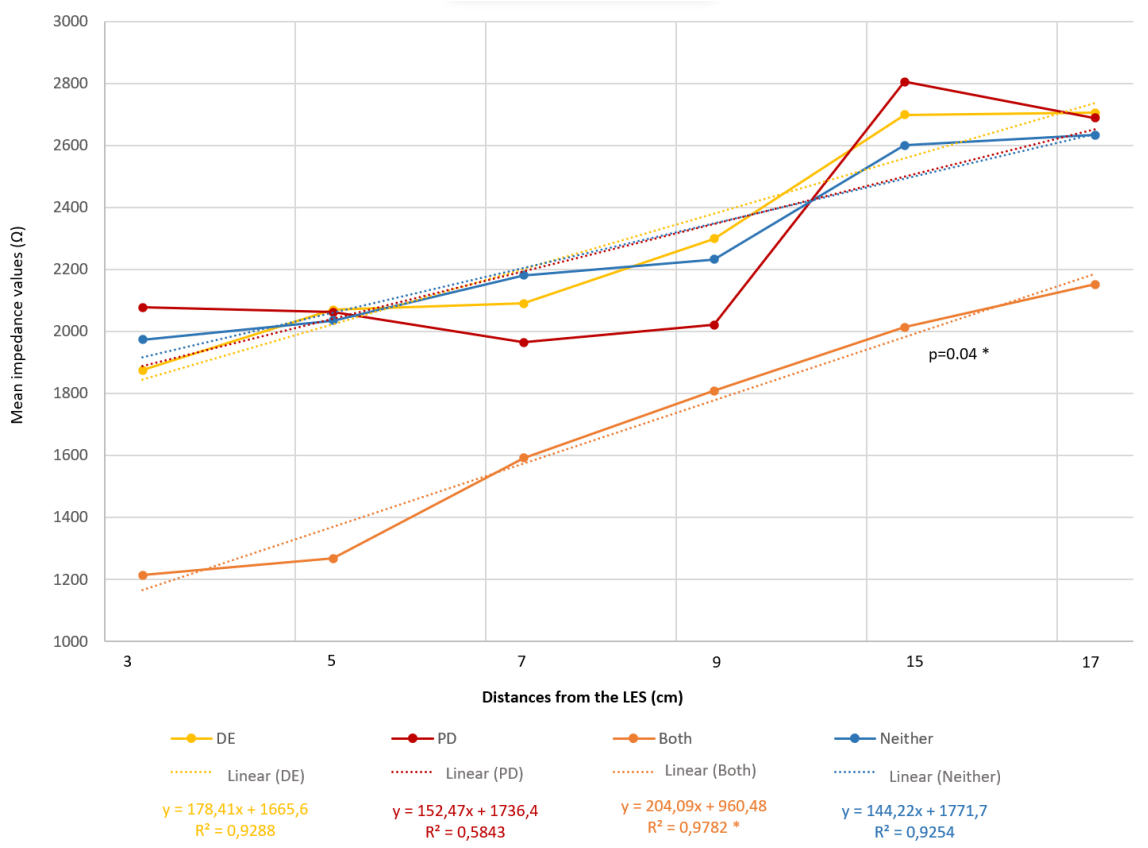

Figure 5. Mean impedance values in patients with or without dental erosion and periodontal disease. The asterisk (*) the curve of "Both" group is significantly different from the others, and similar to the one in patients with gastroesophageal reflux disease. PD: Periodontal disease; DE: Dental erosion; LES: Lower esophageal sphincter

Besides the abovementioned risk factors, no other ones were detected in the study. Furthermore, there was no difference between the four groups in terms of smoking (P = 0.36), alcohol consumption (P = 0.59), and coffee consumption (P = 0.86). There was also no significant difference in different habits resulting in DEs, such as drinking carbonated drinks (P = 0.58), teeth grinding (P = 0.71), and eating sour foods (P = 0.23).

9. DISCUSSION

Our South-East Hungarian population-based study is the first to establish the epidemiologic characteristics of GERD-related symptoms in Eastern Europe. Our results showed a significantly lower prevalence of these symptoms compared with those in Western countries. Although the

studied population was likely healthier than the general population, GERD-related symptoms were detected and associated with different socioeconomic and other risk factors, such as positive family history, obesity, coffee consumption, and smoking.

Most population-based epidemiological studies have reported a high prevalence of GERD-related typical symptoms appearing at least monthly. In general, prevalence ranges from 20% to 30% in Western countries. A study in the UK, which enrolled 3,179 patients, reported GERD in 28.7% of the sample population and found it was more common among socially disadvantaged individuals ($P < 0.005$). Although we also examined these potential associations, we were unable to show a correlation between the presence of GERD-related symptoms and the different measurements of socioeconomic status of our participants. Another study conducted in the USA reported that the prevalence of heartburn and/or acid regurgitation experienced at least weekly was 19.8%. In that study, heartburn and acid regurgitation were associated with noncardiac chest pain, dysphagia, dyspepsia, and globus sensation but not with asthma, hoarseness, bronchitis, or history of pneumonia. A recent Italian study reported that the prevalence of gastroesophageal reflux was 26.2% (792/3012). The authors found significant differences in the frequency of the disorder according to sex, smoking habits, and BMI. GERD-related symptoms were more common among females, smokers, and those with higher BMI values [31-33].

In contrast, a study conducted in India reported a lower prevalence of GERD-related symptoms, with 7.6% of the 3,224 participants experiencing heartburn and/or acid regurgitation at least once a week. Older age and consumption of non-vegetarian, fried foods, aerated drinks, and tea/coffee were associated with GERD. The frequency of smoking and BMI were similar among participants with or without GERD [34].

A study conducted in Iran including 803 patients (age: 11–84 years) reported that GERD was more common in females than males. Furthermore, the disease became more prevalent with age. In the present study, there was an interesting association between sex and the presence of GERD-related symptoms. As the frequency of GERD-related symptoms increased, the blood donors were more likely to be female. In our participants, there was no difference according to age [35].

We identified only one study in the literature that was conducted in Japan that reported a positive relationship between the upper gastrointestinal symptoms and shorter height (in elderly, mostly female Japanese participants). In our blood donor volunteers, this correlation was also detected, and the height became shorter as the frequency of GERD-related symptoms increased [36].

Obesity plays a role in the development of GERD symptoms as well as its complications (erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma) [37]. Obesity was a detected risk factor in this population but the presence of overweight or obesity alone was not associated with a higher prevalence of symptoms. Most recent epidemiological studies detected an association between BMI and GERD, for both the symptomatic form and various complications (e.g., erosive esophagitis, Barrett's esophagus). It should be also highlighted that obesity is one of the major risk factors of obstructive sleep apnea (OSA). The international literature demonstrates a high incidence of LPR (45.2%) in OSA patients. Moreover, a recent meta-analysis showed a significant correlation between OSA-hypopnea syndrome and GERD [38, 39]. Therefore, obesity has become a risk factor for these diseases. The present study examined this feature using two approaches. First, participants with mild, chronic, non-exclusionary diseases showed a greater frequency and prevalence of GERD-related (typical/atypical) symptoms than overweight/obese, otherwise healthy participants. Second, a positive linear correlation was found between the prevalence of GERD-related symptoms and the presence of obesity. In another study, the prevalence, frequency, and severity of symptoms of GERD increased with increasing BMI [40].

Smoking significantly exacerbates GERD via direct provocation of acidic reflux and a long-lasting reduction of lower esophageal sphincter pressure [41]. In our study, smoking was also a significant risk factor (Table 3).

It remains unclear whether coffee consumption is a factor in the development of GERD. A recent study reported no association between coffee consumption and the symptoms or erosive esophagitis [42]. In another study, coffee (in contrast to tea) increased the prevalence of GERD. Therefore, factors other than caffeine may be responsible for the induction of GERD [43]. Coffee consumption was a significant risk factor in our study population (Table 3).

A meta-analysis of 26 cross-sectional studies and three case–control studies showed a potential association between drinking alcohol and risk of GERD. Increased alcohol consumption and frequency showed a stronger correlation with GERD [44]. This association was not observed in the present study.

Taken together, these findings indicate that the prevalence of GERD-related symptoms in South-East Hungary was closer to the Eastern values. Interestingly, some of the detected risk factors

supported previous results from Eastern studies while others supported the findings from Western studies.

Some chronic diseases may be associated with upper gastrointestinal motility disorders. However, epidemiological studies of symptomatic GERD have not evaluated their influence on the prevalence of GERD-related symptoms. In the present study, an association was found between GERD-related symptoms and chronic diseases. Furthermore, their prevalence was three times higher in individuals with mild, chronic non-exclusionary diseases compared with apparently healthy individuals. Therefore, primary GERD is likely less common based on the findings from epidemiological studies. This difference may be explained by upper gastrointestinal hypomotility associated with these disorders or their pharmaceutical treatment.

Many risk factors are common in cardiovascular diseases and GERD and GERD can be a risk factor for cardiovascular diseases (such as hypertension). A significant correlation was previously found between GERD and hypertension, as well in our study population [45]. Our findings support some well-known symptom–disease associations, such as coughing and respiratory disorders, chest pain and heart diseases, and globus sensation and thyroid problems. All typical and atypical symptoms were significantly more common ($P < 0.05$) in individuals with known minor respiratory diseases (44/2,002, 2.2%).

Positive family history of GERD has been examined in several studies, but these mostly occurred for the genetic markers. Epidemiological studies have not examined the positive family history of the disease in larger populations along with GERD-related symptoms. Our findings indicate that individuals with a higher frequency of typical GERD symptoms were more likely to have a positive family history of GERD. While the prevalence was twice as high for those experiencing less than weekly symptoms, the likelihood of a positive family history was three times higher in individuals with at least weekly symptoms [46, 47].

The present study has some limitations. The study was limited to a questionnaire survey of symptoms and medical history. No instrumental examinations (e.g., endoscopy and esophageal function testing, such as the gold standard pHmetry) were performed on the participants. Therefore, only the prevalence value of the examined symptoms could be given and there was no data to state whether symptoms were caused by GERD (acidic/weakly acidic/non-acidic reflux) or functional disease (e.g., functional heartburn). In this study, the lack of RSI score is a limitation, which is

mainly used for LPR but can be also performed for GERD patients for an evaluation of the symptoms [48, 49]. Patients with OSA and/or obesity were not observed in our study because there were no questions for sleeping disorders in the questionnaire.

The complete symptom similarity of GERD and FHB makes the differential diagnosis of heartburn complicated and resource-intensive. According to the Rome IV classification, it is not possible to differentiate the role of acid and hypersensitivity in the development of heartburn based on the frequency and subjective severity of heartburn symptoms. To confirm the diagnosis, detailed esophageal examinations are mandatory. That is why the necessity of comparative studies was also raised in the latest Rome IV criteria [50]; however, such studies had not been carried out. To the best of our knowledge, this study attempted the first differentiation between FHB and GERD based on oral manifestations. The rationale behind the use of oral evaluation is based on its low cost, wide availability, and the fact that the suggested parameters are not temporary symptoms but long-term consequences of GERD.

In the literature, there are many studies on the association between GERD and DE or PD. However, to the best of our knowledge, studies assessing the hard and soft tissue injuries, namely DE and PD, together have not been conducted yet. Furthermore, none of the previous studies examined their relations from both dental and gastroenterological perspectives.

Several studies discussed and concluded a clear but variable relationship between DE and GERD [51, 52]. The proposed pathogenesis of DEs is attributed the direct contact of acid and the enamel, resulting in the dissolution of the enamel crystals and the destruction of the interprismatic matrix and subsequently, the dentin [53-56].

As a result of our research, 41.2% of those with DE had reflux, which did not prove to be a significant result. However, this result differed from the findings recorded in the literature. Pace *et al* [21] published a recent systematic review involving 17 eligible studies, mainly observational and case-control studies on GERD and DE, in which they reported a strong association between the two conditions. The median prevalence of DE among all patients with GERD was 24%, and the median prevalence of GERD among adults with DEs was 32.5% (21.0%-83.0%) However, in this population, there were wide percentage ranges and degrees of tooth tissue loss, and not all studies and evaluations of patients included esophageal endoscopy and/or 24-hour esophageal pHmetry [21].

Another systematic review was carried out and used different references since 2007. From a total of 273 articles, the mean prevalence values of DE were 48.8% in GERD patients and 20.5% in non-GERD controls. The prevalence of DE among adults with GERD was 38.9%, compared to 98.1% among children with GERD [57].

The total prevalence of DE (23.3%) in all subjects was less than the known global prevalence of DE. It can be stated that in the patient group we examined, the prevalence of DEs was found to be significantly higher among patients with GERD (33.1%) than among patients with FHB (12.0%) ($P < 0.01$). Our findings differ from those of studies conducted in different parts of the world.

A recent study conducted in China in 2016, reported a 60.8% presence of DE among patients diagnosed with GERD [58]. Another study carried out in Italy could not establish a significant co-appearance in the association between GERD and DE [59].

Previous studies have confirmed the association between DE and GERD. However, other manifestations (xerostomia, halitosis, oral burning, altered taste, bruxism, and soft tissue injuries, such as mucositis/stomatitis, aphthous-like ulcerations, gingivitis, and periodontal disease) are less likely to be investigated. The relationship between these diseases and GERD could either be direct or indirect [60].

In the literature, the presence of extrinsic factors resulting in DE was uncertain. According to a cross-sectional study, there was a clear relationship between DE and extrinsic dietary factors in patients with GERD [61]. This result was supported by a systematic review that highlighted the etiological complexity of DE (dietary habits, lifestyle, abrasion, bruxism, *etc.*), and the importance of taking a detailed medical history [62]. In contrast, based on an Indian cross-sectional study, extrinsic factors were not related to DE in GERD. In our study, there was no significant difference between the different habits resulting in DE ($P = 0.23$) [63].

In contrast to Song *et al* [64], our results could not confirm a close association between GERD and such manifestations except PD. The mechanism by which PD develops in GERD is mainly attributed to the direct action of acid on the mucosa, although hyposalivation is also suggested to play a role [65, 66]. Watanabe *et al* reported a significant presence of soft tissue symptoms (stinging, bad breath, and burning sensation), oral cavity symptoms (sour/sour taste sensation), and the presence of GERD [67].

Di Fede *et al* assessed the occurrence of oral pathological changes and symptoms in patients with GERD. Two hundred patients with GERD and 100 matched healthy controls were enrolled and studied. Univariate analyses revealed that xerostomia, oral burning sensation, subjective halitosis, and soft, hard palate mucosa, and uvula erythema were more common among patients with GERD than among matched controls ($P < 0.05$). The main outcome of this study was that no significant association between GERD and DEs was found, whereas some other symptoms or objective oral mucosal changes were found to be significantly associated with GERD [59]. In contrast, based on the responses of the patients we interviewed and examined, we did not find any data indicating a significant occurrence of oral complaints (such as mouth and tongue burning, unpleasant breath, taste perception problems, inflammation of the mucous membrane, hypersensitivity, and sensations of sour taste).

A Chinese study found that periodontal factors were significantly associated with the risk of GERD in the studied 50183 patients. Severe periodontitis (OR = 1.40, $P < 0.001$) and lower frequency of tooth brushing (OR = 2.01, $P < 0.001$) were significantly associated with GERD [68].

In our study, neither DE nor PD alone was predictive of the presence of pathological reflux. There is not significantly more reflux in these cases. However, if both are present, the simultaneous presence of pathological reflux is more likely, as evidenced by the characteristic impedance deviations following the reflux pattern.

Increased BMI is commonly mentioned as a predictor of GERD. In their population-based study, Locke *et al* found a significant relationship between higher BMI and the presence of GERD compared to subjects without reflux disease [68]. Conversely, Watanabe *et al* failed to establish a significant correlation between an increase in BMI and the presence of GERD [67]. Our results seem to support the suggested association because our patients with GERD had significantly higher BMIs than those with FHB. However, the observed difference is not significant enough to allow the prediction of GERD based on this parameter alone.

In our study, higher esophagitis scores were detected in patients with DE and PD together than in those without any dental diseases. This result suggests that there is more severe esophagitis in case of DE and PD than in the other groups. The correlation between the degree of DE and the severity of esophagitis was barely studied. A study conducted among the Mexican population found that 3/4 of the patients with mild grade DE had normal esophageal mucosa or LA-A esophagitis,

whereas patients with severe DE were associated with a higher frequency of esophagitis LA-C and -D ($P = 0.021$) [69].

There are limitations to our study: First, the study was carried out in a single tertiary referral center; therefore, the prevalence of GERD phenotypes is different from the values of the general population. Second, during the process of pH-MII, inpatients were examined under standard conditions that do not correspond to their everyday conditions at home. DEs could be considered as cumulative lesions, representing the long-term consequences of reflux. Therefore, the dental status does not necessarily correlate with the current reflux state, since the bolus exposure time is not always the same, and it may significantly vary day by day, especially in the proximal part of the esophagus.

10. CONCLUSIONS

In conclusion, the prevalence of GERD-related symptoms among South-East Hungarian blood donor volunteers was significantly lower than in the Western countries and closer to the Eastern values. In otherwise healthy, non-obese individuals, the prevalence of at least weekly occurring GERD-related symptoms was <5%. The presence of mild, non-exclusionary chronic diseases significantly increased the prevalence of GERD-related symptoms, as well as positive family history, coffee consumption, smoking, shorter height, and increased BMI.

Dental examination of patients with heartburn seems to be useful in the differential diagnosis of GERD and FHB. The co-occurrence of dental erosions and periodontal diseases was associated with reflux disease, while their absence was associated with functional heartburn. Neither DE nor PD (especially its mild forms) alone were predictive of the examined pathologies.

11. NEW RESULTS ESTABLISHED IN THE THESIS

1. Our study was the first population-based research that examined the prevalence of GERD in Hungary.
2. In South-East Hungarian blood donor volunteers, the prevalence of GERD was significantly lower than in the Western countries.
3. The presence of mild, non-exclusionary chronic diseases significantly increased the prevalence of GERD-related symptoms.
4. The co-appearance of dental erosions and periodontal diseases in patients with heartburn was highly associated with GERD.
5. The absence of dental disorders in patients with heartburn was predictive of FHB.
6. The dental evaluation of patients with heartburn seems to be useful in the differential diagnosis of GERD and FHB.
7. Patients with functional heartburn have different mean, 24-hour esophageal impedance profiles than patients with GERD. The mean, 24-hour esophageal impedance profile could be a new, useful parameter in the diagnosis of GERD.

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14. FIGURES

15. TABLES