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THE ROLE OF GASTROESOPHAGEAL REFLUX DISEASE QUESTIONNAIRE IN THE REPUBLIC OF MACEDONIA

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A b s t r a c t: *The aim of the study:* Gastroesophageal reflux disease is a common disease with a multifactorial pathogenesis. Our aim was to analyse the role of the Gastroesophageal Disease Questionnaire in diagnosing reflux disease in the population of the Republic of Macedonia.

Methods: The questionnaire on the severity of the symptoms related to GERD was used. An evaluation of the distal portion of the oesophagus was carried out in all patients with positive questionnaire results. All mucosal injury was classified by the Los Angeles criteria (LA).

Results: 642 patients were included. 58.73% females, with an average age of 37.5 ± 8.2. Females had a higher BMI than males 26.8 ± 4.1 vs. 24.9 ± 3.8 $p < 0.001$. Of the total number of examinees (642 patients), in those with erosive reflux disease and also in those with nonerosive reflux disease, as shown respectively in endoscopy, the sensitivity of the RDQ was 100%, and the specifity was 0%. The100 sensitivity means that the questionnaire verified/diagnosed patients with erosive reflux disease with 100% certainty.

Conclusions: Results were found in some studies comparing the positive Reflux Disease Questionnaire and the level of erosive esophagitis (LA classification). This study provides evidence that the RDQ represents a viable instrument for assessing symptom severity and response to treatment in clinical trials of patients with GERD, but in patients with a high score, endoscopic evaluation should not be excluded

Key words: Gastroesophageal reflux disease (GERD), Reflux Disease Questionnaire, Upper Endoscopy.

Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition in which reflux of stomach contents causes troublesome symptoms and/or complications [1]. The disease can present in the form of a range of oesophageal and extra-osofageal syndromes, but its cardinal symptoms are heartburn and regurgitation. In 2006 a world-wide consensus was published, in which a pathophysiological-oriented basis for the definition of GERD was employed, and its possible clinical presentations described as oesophageal or extra-oesophageal syndromes which may manifest alone or in combination [2].

GERD is presumably the most common disease of the digestive tract that brings large numbers of patients to physicians every day. It lowers the quality of life of affected individuals and exposes them to potentially dangerous complications. An increasing awareness exists among patients, doctors and authorities of the relevance of this pathological condition. Despite an improved understanding of many aspects of gastroesophageal reflux disease, clinical management of several cases is still unsatisfactory. Atypical cases with extra-oesophageal manifestations often defy diagnosis. Even typical symptoms are often misunderstood and considered to be part of the poorly defined area of dyspepsia by both patients and doctors. Roughly one half of the adult population in industrialized countries have personal experience of reflux symptoms, and 20–30% suffer from the disease [3]. Symptoms associated with GERD include heartburn, acid regurgitation and chest pain as well as "extra-oesophageal" manifestations such as nausea, chronic coughing, asthma and hoarseness. All the symptoms may compromise the health-related quality of life [4–6]. Symptom-focused questionnaires have an important role in clinical trials of gastroesofageal reflux disease management.

The aim of the study

Gastroesophageal reflux disease (GERD) is diagnosed based on symptoms. Various countries have published several guidelines, recommendations and questionnaires for the diagnosis and management of GERD [7, 8]. There was no data on patients in the Republic of Macedonia. The purpose of this study was to register and analyse the distribution of GERD symptoms in patients in the Republic of Macedonia in correlation with sex, age, BMI and life style. It was also to analyze the correlation between endoscopic findings and a positive reflux questionnaire.

Patients and Methods

This three-year prospective study clinical trial was conducted at the University Gastroenterohepatology Clinic and gathered data from 642 patients with GERD symptoms. Patients between 18 and 55 years old were included (we restricted older people to decrease the risk of malignancy) with a clinical history of heartburn, acid regurgitation, or both during the previous 3 months. All the participants were asked to respond to the questionnaire, along with another detailed questionnaire consisting of 16 original questions. An additional 12 questions included enquiries about symptoms related to the upper gastrointestinal tract, medical history, lifestyle factors, etc. Upper endoscopy was performed on all patients.

All subjects were interviewed by the physician, and their weight (with minimal clothing) and standing height were recorded at the clinic. BMI was calculated with a formula.

Those who had a negative endoscopy finding and positive symptom questionnaire and who signed an agreement underwent a 24-hour pH monitoring. A PPI two-week test was done on those who did not agree to have a 24 pH-monitoring test.

Subjects with major symptoms of malignancy, oesophageal stenosis, previous gastrointestinal surgery (except cholecystectomy), cardiovascular disease, intake of alcohol, drugs, severe psychiatric disorder, pregnancy, or breastfeeding were excluded. Those patients who were using proton pump inhibitors, H2 antagonist, glucocorticoid or ketoconazole 2 weeks before the endoscopy were also excluded.

GERD diagnosis

Endoscopic findings

Endoscopy was carried out at pretreatment of the patients who gave agreement and evaluated according to the 2nd modified Los Angeles (LA) classification [9, 10] (Grade N, no endoscopic mucosal changes; Grade M, minimal changes; Grade A, one or more mucosal breaks = 5 mm long that do not extend between the tops of two mucosal folds; Grade B, one or more mucosal breaks > 5 mm long that do not extend between the tops of two mucosal folds; Grade C, one or more mucosal breaks that are continuous between the tops of two or more mucosal folds, but do not involve the entire oesophageal circumference; and Grade D, a mucosal break that involves the entire esophageal circumference).

Reflux Disease Questionnaire (RDQ)

Symptom-focused questionnaires have an important role in clinical trials of gastroesophageal reflux disease (GERD) management. This is especially the case given that symptom relief is a major goal of treatment for patients with GERD [11], and that a patient's self-report on symptom status is now believed to be more reliable than a physician's assessment [12]. To assess the GERD symptoms, several questionnaires have been proposed, such as QUEST [13], Manterola's Scale [14], FSSG (Frequency Scale for the Symptoms of GERD) [15], Zimmerman's Scale [16], and so forth. Whereas typical symptoms of GERD are heartburn and regurgitation [17], it is well known that GERD patients present very diverse symptoms [1]. In the present study, we chose FSSG scoring, as it can evaluate not only the acid-reflux related symptoms but also the dyspeptic symptoms [15–16].

The questionnaire for the Macedonian population was made as a modification of GERDAS (gastroesophageal reflux disease symptom assessment scale), the Majo Clinic questionnaire and the frequency scale for the symptoms of GERD (FSSG) [19]. It was designed to measure patient perception of the severity of symptoms of GERD. The questionnaire was in the and the Albanian language. In the first part age, sex and Body Mass Index are notified. In the second part patients should answer 16 questions, for every question two answers should be given. These answers are used for qualification of the symptoms (Table 1).

Table 1

GERD Questionnaire

Symptoms	Symptom strength	Frequency
Chest pain		
Pyrosis		
Regurgitation		
Throat burning		
Hoarseness		
Throat pain		
Need to clear throat		
Chonic cough		
Dysphagia		
Nose to throat secretion		
Feeling of a lump in the throat		
Tongue burning		
Laringeal spasm		
Otitis media inflammation		
Sleeping disturbency		

Two answers should be indicated:

1. *Symptom strength:* 0 – absent; 1 – mild/can be ignored; 2 – moderate/cannot be ignored, but do not disturb the way of life; 3 – severe/symptoms affect the way of life; 4 – very severe/seriously disturb the way of life

2. *Frequency of symptoms:* 0 – none; 1 – once a year; 2 – less than once a month; 3 – once a month; 4 – once a week; 5 – several times during the week; 6 – daily.

The additional 12 questions include enquiries about symptoms related to the upper gastrointestinal tract, medical history, lifestyle factors and so on:

1) Do you take any proton pump inhibitors (PPIs)?

2) Do you take any histamine H2 – receptor antagonists (H2 RAs)?

3) Do you take any digestive drugs other than antacids (PPIs or H2 RAs)?

4) Do you have a history of cardiovascular disease?

5) Has your body weight markedly increased in adulthood (more than 10kg from age 20)?

6) Have you lost weight in the last 3 months which could be caused by problems of the disease?

7) Do you have a feeling of inadequate sleep?

8) Do you have a habit of having dinner within two hours before going to bed?

9) Do you have a habit of quick eating?

10) Do you have a habit of smoking?

11) Do you have a habit of drinking alcohol (almost every day)?

12) Do you have a habit of eating spicy food?

Answer: "yes" or "no"

Statistics

Univariate statistics were used to examine means, standard deviations and shapes of distribution for continuous variables and frequencies for categorical variables. Missing or extreme values were identified and corrected as necessary; no data were imputed. Study participant test scores were eliminated if all questions on a test were answered with the same answer choice. For bivariate analysis, outcome measures were examined using t-tests for variables with two categories, the Mann-Whitney U Test and one-way ANOVA for variables with more than two categories.

Multiple linear regression was used to determine the relationship between GERD manifestation and quality of life outcomes while controlling for potential confounding factors (age, gender, race, BMI, current alcohol use, current

smoking, current use of spicy food, current use of an antireflux medication and comorbidity) and patient perception of GERD severity. Subjects with missing data on relevant variables were excluded from the multivariable analyses.

Results

We recruited 642 patients. Of these, (58.73% females) subjects had complete data and were included in the analysis. The average age was 37.5 ± -8.2 years (no gender difference).

BMI for females was higher than males (26.8 ± 4.1 vs. 24.9 ± 3.8, $p < 0.001$)

Table 2

General data and BMI associated with grade of oesophageal damage (mean +/-SE)

	None	A	B	C-D	*p*-value
n(F/M)	72/46	112/84	178/120	22/8	< 0.001
Age(years)	37.5(0.5)	38.2(0.4)	39.1(0.4)	41.2 (1.2)	< 0.001
BMI < 25	35	60	82	3	0.159
BMI 25–30	65	88	163	20	0.026
BMI > 30	18	48	53	7	< 0.001

Oesophageal damage differed by sex: men had severe LA(C-D damage) [OR 5 3.7, 95% CI 1.7–8.2] and mild damage (B damage) [OR51.56, 95% CI 1.1–2.3] compared to women and this was associated with BMI: lesions grade C-D in BMI between 25 and 30 was OR52.8 (95% CI 1.16–6.7) and for those with BMI > 30, OR52.1 (95% CI 0.65–6.8), compared to BMI < 25.

The mean value of the questionnaire score for all pts.was 7.61 ± 3.10 (min = 3 and max = 15).

Endoscopic finding were negative in 120 (18.3%) and positive in 504 (81.7%) pts.

There is a statistically significant difference between patients with negative and positive endoscopic findings according to mean values of questionnaire score Mann-Whitney U Test: Z = - 9.54 p = 0.000001) (Table 3 and Fig. 1)

Table 3

Mean values of questionnaire score according to endoscopic findings

Endoscopic findings	Mean	SD
negative	3.42	0.50
positive	8.57	2.60

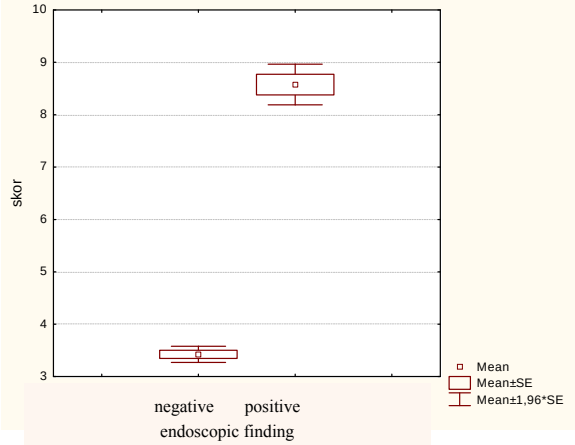

Figure 1 – Mean values of questionnaire score according endoscopic findings

Table 4

Mean values of questionnaire score according to endoscopic findings

Endoscopic finding	Mean	SD	Number of pts.
negative	3.42	0.50	120
A	5.89	1.25	180
B	9.84	1.37	300
C - D	13.89	0.78	42

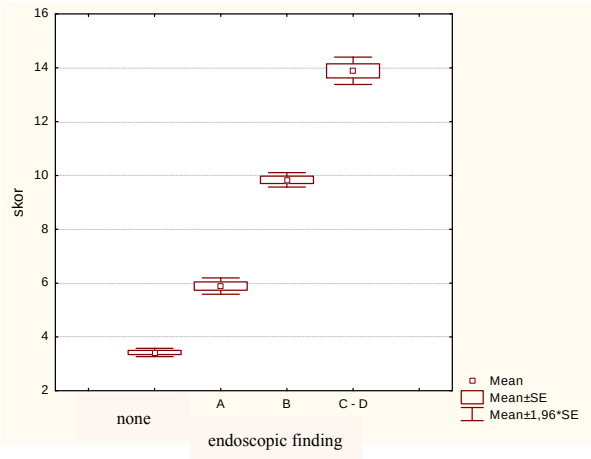

Figure 2 – Mean values of questionnaire score according to endoscopic findings

Analysis of variables (ANOVA) showed that in patients with different endoscopic findings there were big differences according to the disease questionnaire score (F = 403.87 p = 0.00000). According to the Tukey HSD test, between all groups of evaluated patients (none, A, B and C-D) there are statistically significant differences according to the disease questionnaire score (p = 0.00001) (Table 4 and Fig. 2)

Table 5

Sensitivity and specificity of reflux disease questionnaire in patients with erosive and non-erosive reflux disease

Questionnaire	Endoscopic finding		total
	positive	negative	
positive	522	120	642
negative	0	0	0
total	522	120	642

Se = 100% Sp = 0

In the total number of examinees (642 patients), those with erosive reflux disease, also those nonerosive reflux disease, shown in endocopy respectively, the sensitivity of the RDQ is 100%, and specificity is 0%. The 100% sensitivity means that the quesionnaire verified/diagnosed patients with erosive reflux disease with 100% certainty.

Discussion

The RDQ was developed to facilitate the identification of GERD in primary care and this was the setting in which its psychometric properties were established [20]. This study demonstrated the utility of the RDQ in evaluating treatment response in a clinical trial of a new medication. The questionnaire effectively differentiated various levels of patient-assessed symptom severity compared to physician-assessed severity. Consistency of performance in the two languages was also observed. The study population, being highly enriched for GERD, precluded determination of the predictive validity of the RDQ for a GERD diagnosis.

The European observational study made in 2009 by Javier P Gisbert et al. shows that the heterogeneous population of primary care patients who seek medical attention for GERD continue to experience substantial impairment of their daily lives, as shown by RDQ and GIS scores. Indeed, the combined use of the questionnaires provided a comprehensive overview of the frequency, intensity and impact of GERD symptoms on patients' daily lives, aspects that would not necessarily have been captured by the use of one questionnaire alone [21].

Thus, RDQ allowed for an evaluation of the frequency and intensity of GERD symptoms, the GIS providing complementary information in terms of the use of additional medication for GERD symptoms and the impact of such symptoms on work and daily productivity, eating/drinking and sleep. An association between GERD and sleep disturbance was apparent, and has more impact on the daily lives of GERD patients than atypical GERD-related symptoms such as coughing, hoarseness, and difficulty swallowing food [22–23].

Our study concluded that in patients with erosive reflux disease the sensitivity of the disease questionnaire is 100%, but a larger number of patients is needed to prove the results of the study. Also a group with negative endoscopic findings which have positive RDQ, and positive PPI test or positive 24-pH-metry should be part of the investigation.

Conclusion

Gastroesophageal reflux disease is a common problem that is expensive to diagnose and treat in primary and specialised settings. GERD is increasing in prevalence in the Western world, as well as in the Republic of Macedonia, with important risk factors being obesity and life style.

The sensitivity to classic reflux symptoms in our study was 65% for diagnosing the GERD. The response to PPI has good sensitivity (76%). Outpatient oesophageal pH testing is the most sensitive for the GERD, but there is the problem of agreement for it to be performed. Endoscopy is most specific for diagnosing GERD with oesophageal damages.

This study provides evidence that the RDQ represents a viable instrument for assessing symptom severity and response to treatment in clinical trials of patients with GERD, but in patients with a high score, endoscopic evaluation should not be excluded.

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Резиме

УЛОГАТА НА ПРАШАЛНИКОТ ЗА ГАСТРОЕЗОФАГЕАЛНА РЕФЛУКСНА БОЛЕСТ ВО Р. МАКЕДОНИЈА

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Апстракт: *Цел на студијата*: Гастроезофагеалната болест е често заболување со мултифакоријална патогенеза. Нашата цел беше да ја одредиме улогата на прашалникот за гастроезофагеален рефлукс во дијагностиката на рефлуксната болест на популацијата во Република Македонија.

Методи: Прашалникот за тежина на симптомите на гастроезофагеална рефлуксна болест беше применуван кај сите проследувани пациенти. Ендоскопска евалуација на храноводот, желудникот и дванаестопалечното црево беше направена кај сите пациенти со позитивен прашалник. Сите мукозни оштетувања беа класифицирани според Лос Анџелеската класификација.

Резултати: 642 пациенти беа вклучени во студијата, 58,73% жени со просечна старост од 37,5 ± 8,2. Боди мас индексот кај жените беше поголем отколку кај мажите 26,8 ± 4,1 наспроти 24,9 ± 3,8 $p < 0,001$. Кај вкупниот број на испитаници (Н = 642), односно и кај оние кои имаат ерозии и кај оние кои

немаат ерозии при ендоскопија, сензитивноста на прашалникот е 100%, а специфичноста е 0%. Сензитивност 100% значи дека прашалникот со 100% сигурност ги верификува/дијагностицира сите кои имаат рефлуксна болест и присуство на ерозии.

Заклучоци: Резултатите од одделни студии ги споредуваат позитивниот паршалник за рефлуксната болест со нивото на ерозивниот езофагитис според Лос Анџелес класификацијата. Оваа студија укажа дека прашалникот за рефлуксната болест е инструмент во дијагностиката на пациентите со ГЕРД со ерозивни оштетувања на хранопроводникот, коишто не можат да бидат занемарени. Сепак кај пациентите со висок скор на прашалникот ендоскопското иследување не треба да биде исклучено.

Клучни зборови: гастроезофагеална рефлуксна болест (ГЕРД), прашалник за рефлуксна болест, ендоскопија.

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