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The contribution of abdominal ultrasound in diagnosis and evaluation of gastroesophageal reflux

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Abstract. Objective: To determine the role of abdominal ultrasonography in evaluation of gastroesophageal reflux (GER), to compare this method with esophageal scintigraphy and to make correlations between these investigations, GERDQ 2009 reflux questionnaire and the histologic aspects in patients with Barrett's esophagus (BE). Material and methods: 30 patients with BE were subjected to upper digestive endoscopy with biopsy, esophageal scintigraphy and abdominal ultrasound. They also filled out the GERDQ 2009 reflux questionnaire. We tried to find correlations between these data using Kolmogorov-Smirnov test in order to find the normality of distributed variables, Mann-Whitney test and Student test for comparing two groups of variables and ANOVA test, Scheffer or Kruskal-Wallis test for comparing three groups of variables. We used X^2 or Fischer test for investigating the dependence between two nominal variables and Pearson and Spearman coefficient for two continuous variables. Results: Ultrasonography determined that female sex is correlated with a more severe GER ($r=-0.4$; $p=0.02$). There was a statistically significant correlation between the severity of GER estimated during scintigraphy and during ultrasonography ($r=0.755$; $p<0.001$). We obtained a statistically significant correlation between GERDQ 2009 and scintigraphy ($r=0.604$; $p<0.01$) and between GERDQ 2009 and ultrasonography ($r=0.57$; $p=0.001$). Previous treatment was correlated with GERDQ 2009 ($p<0.001$) but the duration of treatment was not ($p=0.1$). Conclusion: Female patients had a more severe GER. Ultrasonography and scintigraphy have similar results in diagnosis and grading GERD and the results are correlated with GERDQ 2009 questionnaire. There is no correlation between histological aspects and the severity of GER. Patients with demonstrated severe reflux during the study used more often antisecretory treatment.
Key Words: GERD, Barrett`s esophagus, ultrasonography, scintigraphy, GERDQ 2009.

Rezumat. Obiectiv: Evaluarea rolului ultrasonografiei abdominale în diagnosticul refluxului gastroesofagian (RGE) şi compararea metodei cu scintigrafia esofagiană de reflux precum şi corelarea acestor metode cu chestionarul de reflux GERDQ 2009 şi cu aspectele histopatologice la pacienţii cu EB. Material şi metode: La 30 de pacienţi cu EB s-au efectuat endoscopie digestivă superioară cu biopsie, scintigrafie esofagiană şi ultrasonografie abdominală. De asemenea aceştia au completat chestionarul de reflux GERDQ 2009. Am făcut corelaţii între datele obţinute utilizând testul Kolmogorov-Smirnov pentru variabilele cu distribuţie normală, testul Mann-Whitney şi Student pentru compararea a două grupe de variabile şi testul ANOVA, Scheffer sau Kruskal-Wallis pentru compararea a trei grupe de variabile. Am folosit testul X^2 sau Fischer pentru analiza dependenţei dintre două variabile nominale şi coeficientul Pearson şi Spearman pentru două variabile continue. Rezultate: Ultrasonografia a demonstrat o prevalenţă mai mare a RGE sever la femei ($r=-0,41$; $p=0,02$). Există o corelaţie semnificativă statistic între severitatea RGE estimat scintigrafic şi ultrasonografic ($r=0,755$; $p<0,001$). Am obţinut o corelaţie semnificativă statistic între scorul GERDQ 2009 şi datele scintigrafice ($r=0,604$; $p<0,01$) precum şi între GERDQ 2009 şi datele ultrasonografice ($r=0,57$; $p=0,01$). Administrarea prealabilă a tratamentului antisecretor a fost corelată cu scorul GERDQ ($p=0,001$), în schimb durata tratamentului anterior nu a fost corelată ($p=0,1$). Concluzii: În studiul nostru femeile au prezentat RGE mai sever decât bărbaţii. Scintigrafia şi ultrasonografia furnizează rezultate similare în diagnosticul şi cuantificarea RGE şi rezultatele acestor metode sunt corelate cu chestionarul GERDQ 2009. Nu există corelaţii între severitatea RGE şi aspectul histopatologic. Pacienţii cu RGE mai sever au folosit mai frecvent tratament antisecretor anterior.
Cuvinte cheie: BRGE, esofag Barrett, ultrasonografie, scintigrafie, GERDQ 2009.

Introduction. Barrett's esophagus (BE) is an acquired condition in which normal squamous esophageal epithelium is replaced with columnar epithelium, more resistant to injuries (Shaheen et al 2009). The main cause of this histologic transition is the cell injury caused by GER. As BE is the most important risk factor for esophageal adenocarcinoma, early diagnosis and management of GER is crucial (Shaheen et al 2009). The actual tendency is to detect GER with less invasive or irradiant methods, but with high sensitivity (the ability of the investigation to describe GER when present) and specificity (the ability of the investigation to give a negative result when GER is not present) (Sifrim et al 2006). Nowadays the golden standard in diagnosis and monitoring GER is represented by Holter esophageal pH-metry, but a lot of other more or less complicated explorations come to complete our image of GER (Perez et al 2010). In principle, along with a high sensitivity and specificity a method dedicated to the study of GER should meet some characteristics: less possible invasive, easily accepted and tolerated by the patient, non-irradiating, less operator dependent, easily repeatable, reproducible, cost-efficient, accessible and last but not least with a short period of training. Considering these facts, we may conclude that ultrasound could offer a reliable alternative for the moment. In current literature there are many studies to compare various techniques for the diagnosis of GER (scintigram vs. pH-metry for example) (Dobrek et al 2009) but none of them compares abdominal ultrasound with scintigram or corroborates explorational data with a reflux questionnaire.

Aim. The main objective of our study was to define the role played by abdominal ultrasound in diagnosis and characterization of GER in patients with BE and to compare this method with esophageal reflux scintigraphy, a technique usually used and accepted for this purpose. We also made correlations between data obtained during ultrasonography and scintigraphy and the symptoms as they were evaluated using the latest generally accepted reflux questionnaire GERDQ 2009.

Material and Methods. We included in our study 30 patients (18 male and 12 female) recent diagnosed with intestinal metaplasia, who received occasional treatment or treatment during six or more weeks. The diagnosis of BE has been done during upper digestive endoscopy and biopsy so we could estimate also the presence of dysplasia and its degrees. In order to demonstrate the presence of GER the patients underwent esophageal scintigraphy and esophageal abdominal ultrasound. They also answered the questions included in GERDQ 2009 questionnaire.

Endoscopies were performed using an Olympus GIF type 1000 EVIS endoscope (Olympus Europe, Hamburg) with field of view of 120^0, depth of field 3-100 mm, outer diameter 9.8 mm, maximum deflection 240^0, total length 1330 mm and inner diameter of the instrumental channel of 2.2mm.

Biopsies were performed using a FB36K biopsy forceps. The histologic diagnosis was made using the classic technique of paraphin block inclusion and microtome section. In all cases we used haemathoxilin-eosin staining and in selected cases we used alcian blue staining for detecting sulphomucines. For describing metaplasia we used Vienna classification of BE.

For the scintigrams, it was used a Siemens Symbia E Gamma camera apparatus with both parallel and circular collimator with a 20% window of 135 KeV. Prior to the investigation the patient was administrated 40 mg of yogurt with ^{99m}Tc-DTPA in an irradiant dose of 101 Bq. Then, in order to increase the material that can produce GER, the patient drank 500 ml of still water in approximately 10 minutes. The reflux was graded according to the next scale: 0=no reflux-stomach scintigram; 1=mild reflux-mild esophageal scintigram; 2=moderate reflux scintigram on a distance less than 2 cm from esogastric junction, 3=severe reflux – scintigram on a distance more than 2 cm from esogastric junction.

The ultrasound has been performed using a GE Logiq 6 apparatus (Fairfield Conneticut USA) with variable frequency 2,5-5 MHz convex transducer and an Esaote

Mylab 25-7300 apparatus (Esaote SPA, Firenze, Italy) with 5 MHz fixed frequency convex transducer. The optimal position for detecting abdominal esophagus was 45 degrees right side up oblique position with the transducer on the left subcostal region at a 45 degrees angle medially from the body axis. The patient was offered 250ml of still water and after 5 minutes ultrasound was performed, noticing the reflux episodes in 20 minutes and the severity of the reflux according to the following scale: grade 0=no reflux; grade 1=mild reflux in distal esophagus; 2=moderate reflux up to the last 2 cm of esophagus; 3=severe reflux - on more than the last 2 cm of the esophagus.

GERDQ 2009 questionnaire developed by Astrazeneca (Sweden) contains a number of questions addressed to the GER symptoms and another set of questions addressed to the life impact symptoms (impact factor) (Table 1) (Jones et al 2009).

Table 1

GERDQ 2009 questionnaire (Mark et al 2010)

Category	*Reflux questions*	*Days a week*			
A	How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2-3	4-7
	How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2-3	4-7
B	How often did you have a pain in the center of the upper stomach?	0	1	2-3	4-7
	How often did you have nausea?	0	1	2-3	4-7
C (IF)	How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2-3	4-7
	How often did you take additional medication for your heartburn and/or regurgitation other than what the physician told you to take?	0	1	2-3	4-7
Points		0	1	2	3

GERDQ 2009 estimates the probability of GERD: 0-2 points= low probability of GERD, 3-7=probably present GERD, 8-10 points= surely present GERD, 11-18 points surely present GERD with annoying symptoms. All the investigations have been performed after correct information of the patient and after we obtained a written consent in this direction. Data were statistically analyzed by comparing the means of two or more independent groups for the normal distributed variables and by comparing range mean for nonparametric distributed variables or ordinal variables. For normal distributed data we used Kolmogorov-Smirnov test. For comparing two groups we used Student test and Mann-Whitney test. For comparing three groups we used ANOVA test, Scheffe or Kruskal-Wallis test. For determining the relationship between two nominal variables we used X^2 or Fisher test. The dependence between two continuous variables we used correlation method by calculating Pearson and Spearman coefficient. Significance limit was considered alfa=0,05. The statistical analysis was performed with SPSS 13.0 and Microsoft Excel Analysis Tool Pack and Statistica 6.0.

Results. We included in our study 12 (40%) women and 18 (60%) men of which, 16 subjects (53.3%), 7 women (43.8%) and 9 men (56.3%) had BE without dysplasia. About 8 subjects (26.7%) – 3 women (37.5%) and 5 men (62.5%) - had BE with low grade dysplasia (LGD) and 6 subjects (20%) – 2 women (33.3%) and 4 men (66.7%) - had high degree dysplasia (HGD). During scintigraphy 13 patients presented mild GER, from which 6 patients (46.2%) had BE-NFD (negative for dysplasia), 3 (23.1%) had LGD and 4 (30.8%) had HGD. About 13 patients presented moderate reflux at scintigraphy and from this group 8 (61.5%) had BE-NFD, 4 (30.8%) had LGD and 1 (7.71%) had HGD. Severe scintigraphic reflux was noticed in 4 patients and from these, 2 (50%) had BE-NFD and one (25%) had LGD and another one (25%) had HGD. During esophageal ultrasonography 16 patients had mild reflux (8 with BE-NFD, 4 with LGD and 4 with

HGD), 10 patients had moderate reflux (6 with BE-NFD, 2 with LGD and 2 with HGD) and 4 patients had severe reflux (2 with BE-NFD, 2 with LGD and no patient with HGD). After the calculation of GERDQ 2009 score, 14 patients had possible GERD (9 NFD, 2 LGD, 3 HGD), 12 patients had definite GERD (6 NFD, 4 LGD, 2 HGD) and 4 patients had definite GERD with annoying symptoms (2 NFD, 1 LGD, 1 HGD). 10 patients (6 NFD, 1 LGD, 3 HGD) used no reflux medication prior to current study and the other 20 patients (10 NFD, 7 LGD, 3 HGD) used medication occasionally or for al least 6 weeks.

From 13 patients with mild reflux at scintigraphy, 12 had mild and 1 moderate reflux at ultrasonography. From 13 patients with moderate reflux at scintigraphy 8 has moderate, 4 mild and 1 moderate reflux at ultrasonography and from 4 patients with severe scintigraphic reflux, one had moderate and 3 had severe reflux estimated by abdominal ultrasound.

Comparing the probability of GERD estimated by GERDQ with the severity of reflux analyzed scintigrafically we noticed that from 13 patients with mild reflux at scintigraphy 10 had possible GERD, 2 definite GERD and 1, definite GERD with annoying symptoms. From 13 patients with moderate reflux at scintigraphy, 4 had possible GERD and 9 definite GERD. From 4 patients with severe reflux at scintigraphy, 1 had definite GERD and 3 definite GERD with annoying symptoms. Comparing the results of GERDQ with the results of ultrasonography we noticed that from 16 patients with mild ultrasound reflux, 11 had possible GERD, 4 had definite GERD and 1 had GERD with annoying symptoms. From 10 patients with moderate reflux, 3 had possible GERD, 6 had definite GERD and 1 had definite GERD with severe impact on life quality. From 4 patients with severe ultrasound reflux 2 had definite GERD and the other 2 had definite GERD with annoying symptoms.

The distribution of patients in our study had no significant distribution by sex ($p=0.64$) and there was no statistically significant link between BE and the severity of reflux estimated by scintigraphy ($p=0.65$), ultrasonography ($p=0.11$) or between BE and the probability of GER estimated by the GERDQ score ($p=0.28$). Neither the use of reflux medication prior to enrollment in the study ($p=0.96$) or the duration of treatment ($p=0.11$) had no statistically significant impact on the histological issues.

There was no statistically significant correlation between patients' sex and scintigraphic reflux severity, but there was a statistically significant correlation between patients` sex and the severity of the reflux estimated during ultrasonography. In order to evaluate the direction of this association we applied a Spearman correlation and we determined that female sex is correlated with a more severe reflux ($r=-0.41$; $p=0.02$). There was no statistically significant correlation between patients` sex and GERD probability estimated by GERDQ ($p=0.64$) or previous medication administration ($p=0.24$) and its duration ($p=1$) there was a statistically significant correlation between the severity of GER estimated during correlation and with the use of ultrasonography ($p<0.001$). We applied a Spearman correlation which demonstrated the existence of a high power positive correlation between the severity of GER observed using these two investigations ($r=0.755$; $p<0.001$).

There was a statistically significant correlation between GER` s probability assessed by GERDQ 2009 and the scintigraphic estimation ($p=0.003$). Using a Spearman correlation we demonstrated a high power positive correlation between GERDQ score and the scintigraphic quantification of GER ($r=0.604$; $p<0.001$). There was no statistically significant link between the scintigraphic characterization of GER and the duration of previous treatment ($p=0.74$). There was a statistically significant relationship between GERDQ score and ultrasound evaluation of GER ($p=0.01$) and the result of Spearman correlation was a high power correlation between GERDQ and the severity of GER assessed by ultrasonography ($r=0.57$; $p=0.001$).

We found no statistically significant correlation between the degree of GER during ultrasonography and the duration of the treatment ($p=0.1$) but there was a significant link between GERDQ-TS and the presence of previous treatment ($p=0.001$) so we may conclude that the patients with a higher probability of GER at GERDQ took more often antisecretory medication.

Patients` age (p=0.3), NRE (p=0.76), GERDQ total score (p=0.68), GERD-IF (p=0.86) and symptoms duration (p=0.19) were not significantly different between male and female patients. Age (p=0.60), NRE (p=0.51) and symptoms duration were not significantly different between the group of patients with treatment and the group without treatment. Age (p=0.57), NRE (p=0.60), GERDQ-TS were not significantly different between people with occasional treatment and people receiving treatment 6 weeks or more. GERD impact factor was significantly different in people with six or more weeks treatment comparing with people taking occasionally treatment (p=0.05). Age, (p=0.61), NRE (p=0.6) GERDQ-TS (p=0.3), GERDQ-IF (p=0.26) and symptoms duration (p=0.79) were not significantly different among people with different histopatologic aspects (NFD, LGD, HGD). Age (p=0.23) NRE (p=0.62) and symptoms duration were not significantly different among people with different classes of reflux severity estimated by scintigraphy. Neither the results obtained during ultrasound examination of the reflux were not different according to age (p=0.24), NRE (p=0.18) and symptoms duration (p=0.91).

Age (p=0.81), NRE (p=0.81), symptoms duration (p=0.07) were not significantly different among people with different GERDQ scores. Using a Spearman correlation we found no statistically significant correlation between age and NRE (r=- 0.17; p=0.37), GERDQ-TS (r=0.19; p=0.32) GERDQ-IF (r=0.2; p=0.3), symptoms duration (r=0.16; p=0.39), or between NRE and GERD-TS (r=0.09); p=0.63) GERD-IF (r=0.07; p=0.71), symptoms duration (r=0.12; p=0.52). Duration of symptoms does not influence GERD-TS (r=0.13; p=0.48) and GERD-FI (r=0.11; p=0.56), situation partially explained by the fact that the questions included in GERDQ 2009 questionnaire are addressed to the symptoms from the last 7 days.

Discussion. Although golden standard in the diagnosis of GERD is 24h Holter esophageal pH-metry, this method is an invasive one and it is not available in every medical unit dealing with patients having GER complains, so we tried to demonstrate the good and pertinent result of ultrasound for the study of GER.

Ultrasound is a very useful technique in real time examine of different abdominal structures. The distal end of the esophagus is situated behind cardia and it is continued with the stomach, forming a sharp angle with it. Being immediately near the left liver lobe the distal esophagus could be examined with this method. The first ultrasound studies of the esophagus were performed in children in the attempt of discovering anatomic anomalies, but with some practice hiatal hernia and reflux could also be revealed.

In our study we discovered a more severe reflux in female patients, thus we found a moderate power statistically significant correlation, fact that has been also revealed in other studies (Lin et al 2004). It is known for a fact that due to the hormonal mechanisms that decrease esophageal peristalsis and increase intraabdominal pressure, pregnancy leads to GERD (Richter et al 2003, Lin et al 2006). It is not known for sure if the GER occurred during pregnancy is a risk factor for GERD after delivery.

We demonstrated that scintigraphy and ultrasonography have almost similar results in the study of GERD, so the correlation coefficient r of 0.751 determines a percent of overlap between these two methods as high as 60%. In the literature there are no comparative data of the applying of these two methods in adult patients. In pediatric population, ultrasound is superior to classic radiography (80% vs 65%) for the study of GERD (Mantrunola et al 2003). For the evaluation of stomach empting in children the concordant results between ultrasound and scintigraphy reached about 90% (Gomes et al 1991).

After evaluating the overlap of the results of these two methods we compared each of the method with the GERD probability score GERDQ 2009. The questionnaire was developed as an accurate instrument in the diagnosis of GERD on symptomatic basis and in selecting the people with occasional GER from those with frequent symptoms that must be subjects to a systematic treatment. There are recent studies that compared GERDQ 2009 with pH-metry and showed similar results in the diagnosis of GERD (Wang

et al 2011). In our study GERDQ score has been strongly correlated with the severity of GERD as it was described by abdominal ultrasound and reflux scintigraphy (r=0.57, respectively r=0.604). These data comes to support our primary purpose to demonstrate the efficiency of an accessible noninvasive with no side effects method that ultrasound is in the diagnosis and classification of GER.

Among the limits of our study is the small number of patients that did not permit a more complex statistical analysis and the fact that we did not perform esophageal pH-metry in this group of patients.

Conclusions. Female patients had a more severe GER than male patients. Reflux scintigram and reflux ultrasonography results for GERD are concordant with GERDQ score and both imagistic methods show similar sensitivity for diagnosis and grading of GERD. The patients with more abundant and severe GER at the scintigram, used more often antisecretory treatment prior to the diagnosis of GERD and BE. Reflux severity as it is quantified by scintigraphy, ultrasound and GERDQ 2009 score has not been correlated with the presence of BE or the degree of the metaplasia.

Abbreviations. ^{99m}Tc-DTPA=^{99m}Tc-Diethylene Triamine Pentaacetic Acid, NRE=number of reflux episodes demonstrated during ultrasonography, GERDQ-TS=GERDQ 2009 total score, GERDQ-IF=GERDQ 2009 impact factor score.

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