

GERD Symptom Relief under PPI Treatment Smoking, Alcohol and Physical Activity Impact in Gastroesophageal Reflux Disease: Some Evidence in Albania

Ilir Bibolli^{ab}, Jonida Uku^a, Bledar Kraja^a, Indrit Këlliçi^c, Marsela Sina^a, Redi Çapi^a

^aDepartment of Gastroenterology, University Hospital Center “Mother Theresa”, Tirana, Albania

^aDepartment of Gastroenterology-Hepatology, Faculty of Medicine, University of Medicine, Tirana, Albania

^aDepartment of Biomedical Sciences, Faculty of Medicine, University Of Medicine, Tirana, Albania

Abstract

The aim of this article was to review how the behavioral factors such as smoking, alcohol and physical activity are involved in gastroesophageal reflux diseases pathogenesis and how the PPI treatment does effect GERD and erosive oesophagitis. Different pathogenic mechanisms for the association between these behavioral factors and GERD development have been suggested. However, there is sufficient evidence to show that modulation of these agents is either effective or ineffective in GERD symptoms. Further prospective studies are warranted to investigate the impact of these modifiable behavioral factors which, with prevention mechanisms, can help to reduce the burden of GERD in general population. As to the PPI treatment, this drugs have demonstrated a strong effect on reducing acidity, treating erosive oesophagitis and totally remedying the gastroesophageal reflux disease symptoms at the very first days of treatment. Because of this, and some other reasons proton-pump inhibitors are highly recommended in clinical, even clinical-endoscopic GERD manifestation.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in the Western world (1). It was compared to an “iceberg”: only a small part is visible, which has been growing steadily in the developed countries (2).

GERD is a chronic disease, with a large clinical spectrum of signs and symptoms, usually interesting many other regions of the body, such as mouth, lungs, ear, nose, throat, and it is associated with frequent relapses (3).

GERD is a multi-factorial process and its physiopathology is complex. Many different aggressive and defensive factors effect on mechanisms which promote or retard the reflux of gastric content into the oesophagus (4). These mechanisms can interplay with epidemiological risk factors, such as smoking, alcohol, physical education (5). However, the exact role of these factors in the pathophysiology of GERD is still under debate and the efficacy of recommended changes in lifestyle habits is also controversial (6).

The classic symptoms of GERD are heartburn and acid regurgitation. The presence of these symptoms leads to diagnosis and is sufficient to start empiric therapy, which consists on the use of proton-pump inhibitor drugs. PPIs, by inhibiting proton pump, localized in the membrane of the parietal cells of the stomach, affecting acid

secretation, lead to strong and lasting reduction of stomach acidity (10). Clinical trials found that PPIs are superior to H₂-receptor antagonists or other drugs, in treating diseases related to the stomach acidity, such as duodenal ulcerous disease, erosive oesophagitis, Zollinger-Ellison syndrome or GERD (7).

About 20% of patients suffering gastroesophageal reflux disease, may develop deep oesophageal ulcers, strictures or Barret oesophagitis. PPI treatment has especially manifested high efficacy in patients with erosive oesophagitis (11). Patients taking PPIs reveal prompt symptom relief and imminent recovery, compared to placebo. PPIs have resulted to be effective in preventing disease relapse.

There are no significant pharmacodynamic differences among PPIs. However, rabeprazole and esomeprazole are more effective, because they cause a prompt long lasting reduce of the acid secretion (8,9).

It is often difficult to evaluate a drug efficacy. On the other hand, when a drug enters the market, it is also used in an extended group of patients, such as those suffering from other systemic diseases and using other drugs at one time, which would be systematically excluded from previous trials.

The first goal of this review is to find out how do the behavioral factors affect gastroesophageal reflux disease pathogenesis. The second goal is to evaluate the degree of the symptom relief after an eight-week-PPI treatment in a group of patients diagnosed with erosive oesophagitis by endoscopy and the healing of oesophagitis as well, and to provide data for the safety and efficacy of PPI use.

Lifestyle characteristics and gastro-esophageal reflux disease

It is a common believe that *smoking* and its intensity is a risk factor for GERD. Different studies have analyzed the relationship between smoking and GERD but conflicting results have been obtained. Multiple studies have shown that smoking increase the risk for developing GERD (12-21), whereas some studies did not show any significant association or reported a negative association (12-29). Recently, a prospective study of the population of Nord-Trondelag County, Norway did not find any association between cessation of tobacco use and improvement of GERD symptoms in individuals not using regular anti-reflux medication (31).

Alcohol consumption is a huge international problem, associated with many adverse health problems, including GERD (1). Most of the studies have concluded that drinking alcohol worsens esophageal acid exposure and is frequently associated with GERD symptoms (24, 30, 32-34). Some other surveys have demonstrated that alcohol consumption has been inversely associated with GERD symptoms or did not affect the risk of reflux (12, 13, 21, 23, 26-29). Furthermore, a recent systematic review reported that there is insufficient evidence to support the stopping alcohol use benefit on esophageal pH levels or GERD symptoms (6).

Previous investigations have demonstrated that frequent leisure *physical activity* is inversely associated with GERD symptoms (12, 13, 21), whereas strenuous exercise and physical activity at work exacerbated symptoms of GERD (21, 35, 36). On the other hand, other studies have been unable to show any association between physical activity and reflux episodes or LES parameters (37-39). In a population-based study Djärv et al. reported that intermediate physical activity in obese individuals was associated with decreased risk of GERD, in comparison to normal or overweight individuals, where no effect was found (39).

Some evidence in Albania

Population-based data on prevalence and the contribution of lifestyle factors to GERD in transitional countries of Southeast Europe, including Albania, are scarce. Traditionally, Albanian population consume Mediterranean diet, rich in olive oil, fruits and vegetable and relatively low in meat and dairy products. Since the 1990s, the Albanian diet has become more diversified, including some “western” eating behaviours, consisting in high saturated fats, trans-fatty acids, free sugars and salted foods. Therefore, two studies were conducted, to assess the prevalence of GERD and lifestyle correlations in adult population of Albania (40, 41). A case-control study was conducted in Tirana, from 2005 to 2007. The 378 inpatient participants underwent a structured questionnaire and upper endoscopy. Assessment of GERD was based on the Los Angeles criteria (40). A cross-sectional study was conducted in Tirana during the year of 2012. A total of 845 individuals, over 18 years old, a representative sample of Albanian population, were interviewed. Assessment of GERD was based on Montreal definition (41). Important evidence was obtained. 101 individuals (11.9%) had GERD symptoms. There were no significant sex-differences, while those who had GERD symptoms were older. Smoking and physical inactivity resulted to be a risk factor for GERD, whereas alcohol consumption did not affect the risk of GERD (Table 1). However, findings from these studies should be replicated in future longitudinal studies in Albania.

Table 1. Association of smoking, alcohol consumption, physical activity with GERD in the Albanian population

Author	Study design	Population size	Method of data collection	Exposure	OR (95%CI)	P value	Adjustment
Kraja et al., 2008 (49)	Case-control	126 cases 252 controls	Questionnaire Upper endoscopy	Smoking (no/yes)	1.64 (1.04-2.59)	0.03	Age
				Alcohol (drinks/day)	1.01 (0.84-1.22)	Ns	
				Physical activity (little vs. moderate)	0.54 (0.32-0.91)	0.02	
Çela et al., 2013 (50)	Cross-sectional	845	Questionnaire	Smoking (never vs. current)	29.3 (13.9-61.2)	<0.001	Age, sex, socio-economic variable and behavioral factors
				Alcohol (moderate/heavy vs. no/occasional)	1.83 (1.10-3.06)	Ns	
				Physical activity (low vs. high)	5.47 (2.32-12.9)	<0.001	

Efficacy of PPI treatment

Method

A randomized trial, included 62 patients suffering GERD symptoms, diagnosed with erosive oesophagitis by endoscopy, treated with proton-pump inhibitor, daily doses of 20 mg, for 8 weeks. Patients suffering erosive esophagitis were identified by the clinic presentation, followed by endoscopy(LosAngeles criteria). Patients chosen were over 18 years old, so they could understand and accept the study protocol. Patients not included in this trial were those known to be hypersensitive to PPIs, pregnant women and the ones used PPIs ten days before the trial. After taken their consent, these participants underwent some examinations, including blood analyses.

The patients went through four medical appointments. The first one aimed to define the study protocol and the esophagitis grade. The patients underwent a detailed anamnesis focused on the clinical symptoms and the use of drugs recently, especially PPIs and a careful examination. Blood samples were taken from each of them. In this appointment we also defined the involvement and exclusion criterias.

The criterias set at the first medical appointment, were carefully estimated at the second appointment. We noted for GERD related symptoms: day heartburn, night heartburn, belching and epigastric pain. The symptoms were estimated with a four-point score: 0- no symptoms, 1- mild, 2- moderate and 3- severe. After assessing the symptoms severity and esophagitis grade by endoscopy, the patients began the treatment with PPIs, daily dose 20mg, for 28 days. They recorded their symptoms after the four-point score day after day and filled the protocol paper.

At the third medical appointment, we reappraised the patients symptoms and analyzed the protocol filled by the patients, which contained two daily symptoms' evaluations for the first week, and one symptoms' evaluation for the three other weeks. A second endoscopic reassessment was realized to evaluate the efficacy of the PPI treatment. If the esophagitis was healed the medication was interrupted, if not it continued for 4 other weeks. PPIs side effects were recorded.

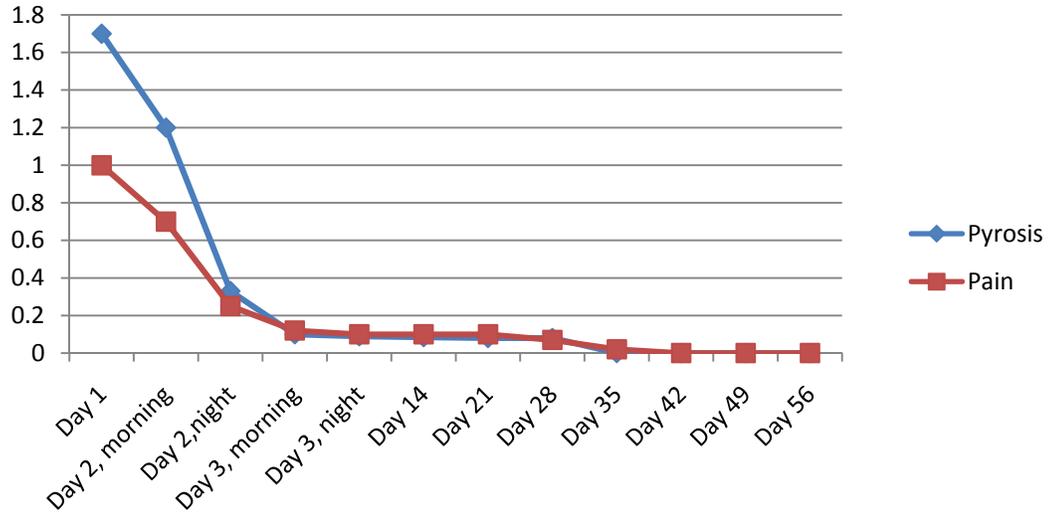
After 8 weeks of treatment, the symptoms were evaluated once again at the fourth appointment. The patients underwent a third endoscopic reevaluation. They were divided in two groups: those with total improvement, that means the symptoms present at the beginning (score \geq 1) had disappeared (score=0) during the treatment, and those with a satisfactory improvement that means mild symptoms were present. Chi-squared test was used to analyze the data obtained from the patients.

Results

In a group of 62 patients suffering GERD symptoms, were assessed the severity of pyrosis, belching and pain with a score 0-3, and the grade of esophagitis by endoscopy, after the Savary-Miller classification. 44 patients (71%) are males, and 18 of them (29%) are females. Patients age varies from 24 to 68 years old, with an average of 43.5 years old. About 60% of patients had moderate or severe pyrosis during the day or the night before treatment, with an average score of 1.67 and 1.70 respectively during the day and night. We found out a drastic improvement of pyrosis after the first day of treatment, about 45%, and 90% at the 28th day. The number of patients without pyrosis is about 60% at midday of the second day of treatment, and it goes at 80% late in the evening. At the

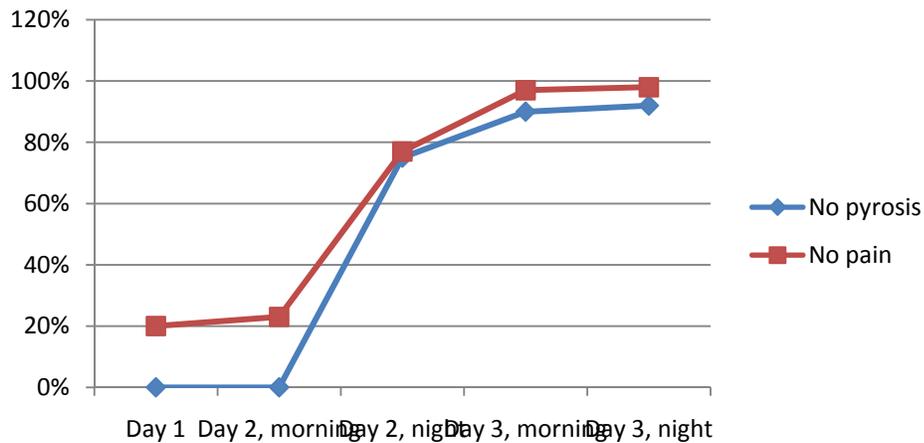
third day almost no patient suffers pyrosis (98.5%). This data is similar to that obtained from Robinson bp. study in 2001 (9).

Average score for pyrosis and pain during PPI treatment

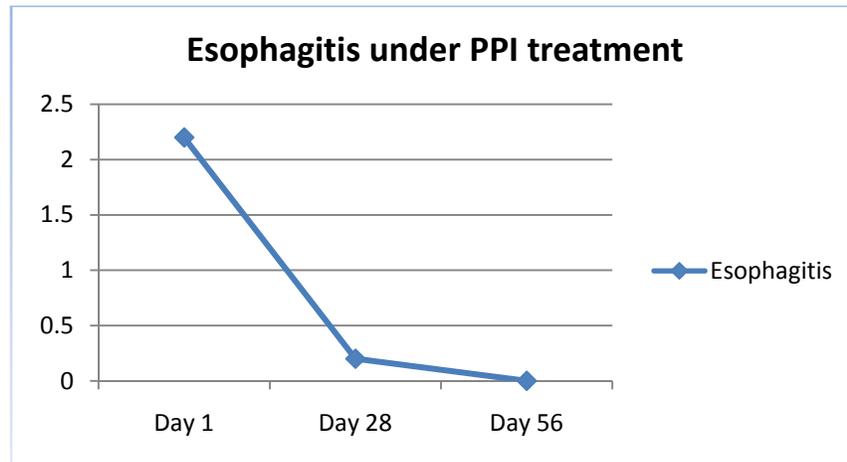


Pain has not been a problematic symptom in our group of patients, evaluated as mild (score=1). On one hand, its intensity reduces progressively after the first day of PPI treatment, till the 28th day, respectively from 75% to 99%. On the other hand, the number of patients who have no pain increases progressively; at the second day of treatment 80% of patients feel no pain, at the third day over there are 98% of them having no pain at all. As to regurgitation, it improves slowly, with a reduction of 30% after 2 weeks of treatment.

Patients' symptoms disappear during PPI treatment



Esophagitis is one of the worst consequences of GERD disease. It was evaluated continuously by endoscopy to assess the efficacy of PPI treatment. 10 patients (16%) had grade I esophagitis, 36 patients (58%) had grade II esophagitis, 14 patients (22%) had grade III esophagitis and 2 patients (4%) had grade IV esophagitis. Under PPI treatment there was an evident improvement, leading to full recovery after 4-week-treatment for 84% of patients. While the remaining 16% recovered after 8 weeks of PPI treatment, as they were diagnosed grade III (8 patients) or IV (2 patients) esophagitis.



We found no correlation between symptom improvement and esophagitis recover. Where as symptom improvement is the same, despite of the esophagitis grade.

Conclusions

This review has emphasized our understanding on the role of lifestyle factors such as smoking, alcohol consumption and physical activity on GERD symptoms. There is sufficient evidence to show that modulation of these agents is either ineffective or effective in GERD symptoms. Even though in Albanian population we found out that smoking and physical inactivity were risk factor for GERD, further prospective studies are warranted to investigate the impact of these modifiable behavioral factors which with prevention mechanism can help to reduce the burden of GERD in the population.

As to the disease treatment, we concluded that clinical improvement under PPI treatment is huge, over 97% after the third dose of 20mg of PPI. The dose of 20mg PPI per day is the day dose to treat esophagitis. We found out a great efficacy of this drug on relieving the symptoms in the very first days of treatment and on healing oesophagitis at the end of the treatment. The PPI treatment goes on for 4 weeks in esophagitis grade I or II, where as esophagitis grade III or IV need 4 more weeks of treatment to recover, that means 8 weeks altogether.

Because of its great efficacy, tolerance, cost effectivity, the impact on life quality, and rare side effects we recommend proton-pump inhibitor drugs use in clinical, especially clinical-endoscopic manifestations of gastro-oesophageal reflux disease.

References

1.El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014;63:871-80.

2. Rubenstein JH, Chen JW. Epidemiology of gastroesophageal reflux disease. *GastroenterolClin North Am* 2014;43:1-14.
3. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006;101:1900-20.
4. Boeckxstaens GE, Rohof WO. Pathophysiology of gastroesophageal reflux disease. *GastroenterolClin North Am* 2014;43:15-25.
5. Sonneberg A. Effects of environment and lifestyle on gastroesophageal reflux disease. *Dig Dis* 2011;29:229-34.
6. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965-71.
7. Farley A, Wruble LD, Humfries TJ. Rabeprazole versus ranitidine for the treatment of the erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial. Rabeprazole Study Group. *Am J Gastroenterol* 2000;95:1894-9.
8. Dekkers CPM, Beker JA, Thjodleifsson B et al. Double-blind, placebo-controlled comparison of rabeprazole 20mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. *Aliment PharmacolTher* 1999;13:49-57.
9. Robinson M, Maton PN, Rodriguez S, et al. Effects of oral rabeprazole on oesophageal and gastric pH in patients with gastro-oesophageal reflux disease. *Aliment PharmacolTher* 1997;11:937-80.
10. Horn J. The proton-pump inhibitors: similarities and differences. *ClinTher* 2000;22:266-80.
11. Earnest DL, Sacks FD, Decktor DL, Levy SJ. Heartburn/stomach symptoms during chronic proton pump inhibitor therapy; evidence for occasional symptom breakthrough. *Gastroenterology* 2000;118:A62.
12. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastroesophageal reflux. *Gut* 2004;53:1730-5.
13. Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastro-oesophageal reflux – a population-based study. *Aliment PharmacolTher* 2006;23:169-74.
14. Yamamichi N, Mochizuki S, Asada-Hirayama I, Mikami-Matsuda R, himizu M, et al. Lifestyle factors affecting gastroesophageal reflux disease symptoms: a cross-sectional study of healthy 19864 adults using FSSG scores. *BMC Med* 2012;10:45.
15. Minatsuki C, Yamamichi N, Shimamoto T, Kakimoto H, Takahashi Y, Fujishiro M, et al. Background Factors of Reflux Esophagitis and Non-Erosive Reflux Disease: A cross-sectional study of 10,837 subjects in Japan. *PLoS One* 2013;8:e69891.
16. FriedenberG FK, Makipour K, Palit A, Shah S, Vanar V, Richter JE. Population-based assessment of heartburn in urban Black Americans. *Dis Esophagus* 2013;26:561-9.
17. Park Ch, Kim Ko, Baek IH, Choi MH, Jang HJ, Kae SH, et al. Differences in the risk factors of reflux esophagitis according to age in Korea. *Dis Esophagus* 2014;27:116-21.
18. Sharma PK, Ahuja V, Madan K, Gupta S, Raizida A, Sharma MP. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in Northern India. *Indian J Gastroenterol* 2011;30:128-34.
19. Eslick GD, Talley NI. Gastroesophageal reflux disease (GERD): Risk factors and impact on quality of life – A population-based study. *J ClinGastroenterol* 2009;43:111-7.

20. Gunasekaran TS, Dahlberg M, Ramesh P, Namachivayam G. Prevalence and associated features of gastroesophageal reflux symptoms in a Caucasian-predominant adolescent school population. *Dig Dis Sci* 2008;53:2373-9.
21. Zheng Z, Nordestend H, Pedersen NL, Lagergren J, Ye W. Lifestyle factors and risk for symptomatic gastroesophageal reflux in monozygotic twins. *Gastroenterology* 2007;132:87-95.
22. Bretagne JF, Richard-Molard B, Honnorat C, Caekaert A, Barthelemy P. Gastroesophageal reflux in the French general population: National survey of 8000 adults. *Presse Med* 2006;35:23-31.
23. Sevindir I, Keskin FE, Erturk K, Yasar N, Kaptanogullari OH, Soyly A. Does the increase of body mass index aggravate gastroesophageal reflux disease? *J Clin Anal Med* 2014;5:35-8.
24. Natalini J, Palit A, Sankineni A, FriedenberG FK. Diabetes mellitus is an independent risk for gastroesophageal reflux disease among urban African Americans. *Dis Esophagus* 2014.
25. Nandurkar S, Fett S, Zinsmeister AR, Cameron AJ, Talley NJ, Locke GR 3rd. Relationship between body mass index, diet, exercise and gastro-oesophageal reflux symptoms in a community. *Aliment Pharmacol Ther* 2004;20:497-505.
26. Bhatia SJ, Reddy DN, Ghoshal UC, Jayanthi V, Abraham P, Choudhuri G, et al. Epidemiology and symptom profile of gastroesophageal reflux in the Indian population: report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol* 2011;30:118-27.
27. Zagari RM, Fuccio L, Wallander MA, Johanson S, Fiocca R, Casanova S, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. *Gut* 2008;57:1354-9.
28. Dore MP, maragkoudakis E, Fraley K, Pedroni A, Tadeu V, Realdi G, et al. Diet, lifestyle and gender in gastroesophageal reflux disease. *Dig Dis Sci* 2008;53:2027-32.
29. Pandeya N, Green AC, Whiteman DC, Australian Cancer S. Prevalence and determinants of frequent gastroesophageal reflux symptoms in the Australian community. *Dis Esophagus* 2012;25:573-83.
30. Singer MV, Feick P, Gerloff A. Alcohol and smoking. *Dig Dis* 2011;29:177-83.
31. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Tobacco smoking cessation and improved gastroesophageal reflux: a prospective population-based cohort study: the HUNT study. *Am J Gastroenterol* 2014;109:171-7.
32. He J, Ma X, Zhao Y, Wang R, Yan X, Yan H, et al. Gastroesophageal reflux disease prevalence and associated factors: The systematic investigation of gastrointestinal diseases in China (SILC) epidemiological study. *Gastroenterology* 2009;136:A5.
33. Franke A, Teyssen S, Singer MV. Alcohol-related diseases of the esophagus and stomach. *Dig Dis* 2005;23:201-13.
34. Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract. *Am J Gastroenterol* 2000;95:3374-82.
35. Collings KL, Pierce Pratt F, Rodriguez-Stanley S, Bembem M, Miner PB. Esophageal reflux in conditioned runners, cyclists and weightlifters. *Med Sci Sports Exerc* 2003;35:730-5.
36. PregunI, Bakucz T, Banai J, Molnar L, Pavlik G, Altorjay I, et al. Gastraoesophageal reflux disease: Work-related disease? *Dig Dis* 2009;27:38-44.

37. Jozkow P, Wasko-Czopnik D, Dunajska K, Medras M, Paradowski L. The relationship between gastroesophageal reflux disease and the level of physical activity. *Swiss Med Wkly* 2007;137:465-70.
38. Wasko-Czopnik D, Jozkow P, Dunajska K, Medras M, Paradowski L. Association between the lower esophageal sphincter function and the level of physical activity. *AdvClinExp Med* 2013;22:185-91.
39. Djav T, Wikman A, Nordenstedt H, Johar A, Lagergren J, Lagergren P. Physical activity, obesity and gastroesophageal reflux disease in the general population. *World J Gastroenterol* 2012;18:3710-4.
40. Kraja B, Burazeri G, Prifti S. Anthropometric indices and gastro-esophageal reflux disease in adult population in Tirana, Albania. *Med Arh* 2008;62:139-41.
41. Cela L, Kraja B, Hoti K, Toci E, Muja H, Roshi E, et al. Lifestyle characteristics and gastroesophageal reflux disease: a population-based study in Albania. *Gastroenterol Res Pract* 2013;936792.