

Dear Reviewer

We thank you for giving us the opportunity to revise our manuscript, and we thank for careful review and insightful comments. We would like to inform you that we have modified the manuscript upon the enclosed comments. We hope that the revision is sufficient and will allow the publication of the article (the revised manuscript is attached). Thank you very much for your valuable advices and efforts with our submission.

With best regards,
Piotr Pardak

TITLE :

Impact of gastroesophageal reflux disease on the quality of life of Polish patients.

Running title:

Impact of gastroesophageal reflux disease on the quality of life.

Institutional review board statement:

The study protocol was approved by the Institutional Ethic Committee at Institute of Rural Health in Lublin, Poland.

Informed consent statement:

All patients gave their written informed consent prior to study inclusion.

Conflict-of-interest statement:

There are no conflicts of interest to report for any of the authors.

ABSTRACT

BACKGROUND:

Gastro-esophageal reflux disease (GERD) is a serious health and social problem leading to a considerable decrease in the quality of life of patients. Among the risk factors with a relation with reflux symptoms and which cause decrease in quality of life are, among others, stress, as well as overweight and an increase in body weight. The concept of health-related quality of life (HRQL) covers an expanded effect of the disease on a patient's wellbeing and activities of daily living and is one of the measures of widely understood quality of life. HRQL is commonly measured using a self-administered, disease-specific questionnaires.

AIM

The aim of the study was determination of effect of reflux symptoms, stress and BMI on the quality of life.

METHODS

The study included 118 patients diagnosed with reflux disease who reported to an outpatient department of gastroenterology or a specialist hospital ward for planned diagnostic tests. Assessment of the level of reflux was based on the frequency of 5 typical of GERD symptoms. Health-related quality of life was measured by a 36-item Short Form Health Survey (SF-36) and level of stress using the 10-item Perceived Stress Scale. Multi-variable relationships were analysed using multiple regression.

RESULTS

Eleven models of analysis were performed in which the subsequent scale of the SF-36 was included as an explained variable. In all models, the same set of explanatory variables: gender, age, reflux symptoms, stress and the BMI were included. The frequency of GERD symptoms resulted in a decrease in patients' results according to 6 out of 8 SF-36 scales-except for mental health and vitality scales. Stress resulted in a decrease in the functioning of patients in all domains measured using the SF-36. Age resulted in a decrease in physical functioning and in an overall assessment of self-reported state of health. An increasing BMI exerted a negative effect on physical fitness and limitations in functioning resulting from this decrease.

CONCLUSION

In patients with GERD the HRQL is negatively determined by the frequency of reflux symptoms and by stress, furthermore an increasing BMI and age decreases the level of physical functioning.

Key words: gastroesophageal reflux disease, stress, psychological factors, health-related quality of life, obesity.

CORE TIP: Gastro-esophageal reflux disease is a serious health problem leading to a decrease in the quality of life. This study determines the effect of reflux symptoms, stress and BMI on the quality of life measured by a 36-item Short Form Health Survey. We prove that in patients with gastro-esophageal reflux, stress decrease the quality of life in a higher degree than the frequency of reflux symptoms. Age and increasing BMI result in a decrease in physical functioning. Therefore, the patient's level of stress should be considered in the diagnosis and therapy, as well as an assessment of the progress of treatment.

Introduction

Gastro-esophageal reflux disease (GERD) is a serious health and social problem, considering the frequency, as well as specificity of symptoms, causing an increase in absenteeism rate, and consequently creating a financial burden for health care, and above all, leading to a considerable decrease in the quality of life of patients. According to the 1999 study, in highly developed countries, the symptoms of reflux disease occurred every day in 7%-10%, and once a week in nearly 20% of the population^[1]. In 2003 in Poland, based on the Carlsson's questionnaire, reflux disease was diagnosed in more than 34% of patients aged over 15 who reported to a family physician^[2]. A special problem for patients is the noxiousness of symptoms at the phase of aggravation of the disease and frequent recurrences after successful therapy. A decrease in the perceived quality of life is symptomatic of GERD^[3-5]. The Montreal definition describes GERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The symptoms are considered troublesome when they occur more frequently than once a week, because only then they cause a decrease in the perceived

quality of life^[3,4].

The concept of health-related quality of life (HRQL) covers an expanded effect of the disease on a patient's wellbeing and activities of daily living. To-date, there is no commonly accepted definition of this concept, and the basic problem is the specification of contents of the domains of activities to which this definition refers. In practice, HRQL should refer to contents included in a given measurement instrument^[5-7]. HRQL is commonly measured using a self-administered questionnaires completed by patients. Disease-specific and general questionnaires are distinguished. The first provide information concerning disorders and limitations typical of a given disease. However, this limits the possibility to compare the quality of life between patients suffering from different diseases. General (generic) questionnaires provide the comparability of results, measure the respondent's functioning within several basic spheres (domains), which are general enough in that they concern many types of diseases, and may also, within a certain scope, be reasonably measured in healthy individuals. The HRQL with its domains is one of the measures of widely understood quality of life (QOL), which covers many spheres of activity beyond nominally the area of health and disease, but often related with it, such as interpersonal relationships in a family, family social and financial problems^[8].

Etiopathogenesis of GERD is of a multi-factor character and, in the case of individual patients, is difficult to determine unequivocally. Among the risk factors with a documented relation with reflux symptoms are, among others, stress^[9-11], as well as overweight and obesity^[11,12]. Here, stress will be understood in a narrower sense as a psychological distress, i.e. the state of strong or long-term psychological tension, connected with low mood, emotions of fear and anxiety or aggression. Many times and in many ways the relationship was confirmed between stress and reflux symptoms, and the quality of life. In a cross-sectional controlled population study conducted among the Norwegian population including nearly 59,000 respondents^[13], the relationship was assessed between psychiatric disorders (anxiety, depression) and reflux symptoms. It was observed that anxiety and depression are related with a 3- 4-fold increase in the risk of occurrence of reflux symptoms. In the study of patients with reflux disease conducted by B. Nojkova et al.^[14], patients who, in addition to reflux symptoms had concomitant symptoms of psychological distress, showed, at the beginning of therapy, a significantly lower quality of life and more severe reflux symptoms, compared to those without the

symptoms of distress. In a repeated study, after the completion of therapy using a proton pump inhibitor (rabeprazole at a dose 20 mg/d) patients with distress, despite an improvement noted in both groups, continued to show a lower quality of life and higher intensity of reflux symptoms than those without distress.

Despite clear evidence for the relationship between stress and reflux symptoms, a randomized experimental study did not confirm the effect of stress on the number of reflux episodes measured using the method of 24-h esophageal pH monitoring, despite the fact that the group subjected to stress, in subjective evaluations, perceived an increased intensity of symptoms^[15]. While undertaking attempts to explain the relationship between experiencing reflux symptoms and stress the researchers refer to the presence of a strong relationship between the degree of emotional tension accompanying stress and a decreased threshold of sensitivity to pain. It was also observed that patients with reflux disease emphasize the lack of the possibility to control pain and randomness with which it occurs. At the same time, they are often strongly convinced about the presence of a relationship between their psychological condition and the intensity of the complaints experienced^[16,17]. An important study, casting light on the relationship between stress and the symptoms of heartburn, is the experimental research by R. Farré et al.^[18] concerning the effect of stress on the esophageal mucosa in rats. The researchers traced changes in the esophageal mucosa using electron microscopy and concluded that strong stress may result in an increase in the permeability of the esophageal mucosa. They also observed that there is an enhancement effect between stress and exposure of the esophageal mucosa to acid, leading to an increase in its permeability and dilatation of the intracellular spaces. Also the other factor, overweight and obesity, is related with GERD. Epidemiological studies coherently indicate the highest percentages of patients with GERD among persons with overweight and obesity^[19-21], and in the population of nurses, Jakobson et al. observed a nearly linear increase in the GERD risk ratio, together with an increase in the BMI^[22]. Among the factors explaining the relationship between GERD symptoms and an increase in BMI it was confirmed that obesity is related, among other things, with a lower esophageal sphincter pressure (LES) and a higher intragastric pressure^[20,23]. Simultaneously, an increase in body weight is negatively correlated with the level of HRQL, both in the case of somatically healthy individuals^[24], and in the case of a number of diseases where, apart from the symptoms of the main disease, it is an additional factor

decreasing HRQL of patients^[25-28].

Aim

The primary goal of the study was determination of the independent effect of reflux symptoms, stress and increasing BMI on the quality of life of patients measured using the SF-36 questionnaire.

Materials and Methods

The study protocol was approved by the Institutional Ethic Committee at Institute of Rural Health in Lublin, Poland. Assessment of the level of reflux symptoms was based on 5 symptoms considered as typical of GERD. The frequency of each symptom was rated by respondent on the 5-point Likert-type scale. These were: 1. heartburn after meals (scores from 0- never to 4- after every meal/almost after every meal), 2. heartburn in a lying position (scores from 0- never to 4- always/almost always), 3. waking from sleep due to heartburn (scores from 0- never to 4- every night/almost every night), 4. regurgitation, and 5. acid reflux (scores from 0- never to 4- always/almost always). The sum of ratings was transformed into 0-100 range. Transformed score represents the percentage of the possible maximum score achieved. It was taken as a measure of the overall level of reflux symptoms (ORS).

Reliability measured using Cronbach's alpha homogeneity coefficient for ORS was 0.83, which evidences a good level of homogeneity of the scale.

Health-related quality of life was measured by a generic questionnaire, 36-item Short Form Health Survey (SF-36) which measures the quality of life across 8 domains: (1) physical functioning (PF), (2) role limitations due to physical problems (RP), (3) bodily pain (BP), (4) general health perceptions (GH), (5) vitality (Vt), (6) social functioning (SF), (7) role limitations due to emotional problems (RE), (8) mental health perceptions (MH). In addition, Single item scale Health Transition (HT) identifies perceived change in health in the last year. Based on 8 basic scales, 2 standardised summary scales are calculated: Physical Component Summary (PCS) and Mental Component Summary (MCS), which represent physical and mental dimension of HRQL. Calculating the results within these 2 dimensions, the authors of the test provided the values of factor score coefficients for individual 8 scales of the test in each dimension, calculated based on a validation study in

the USA. Level of stress was measured using the S. Kohen 10-item Perceived Stress Scale (PSS-10) as adapted by Z. Juczyński and N. Ogińska-Bulik^[29].

Study population

The study included 127 patients aged 19-64, diagnosed with reflux disease at various phases of treatment, who reported to a specialist outpatient department of gastroenterology or a specialist hospital ward for planned diagnostic tests. Each patient who fulfilled preliminary criteria of age and health status and expressed consent to participate in the study, participated in a research session carried out by a psychologist. The study was conducted individually with each patient, or in small groups of up to 4 patients. Ultimately, the results of 118 patients- 43 (36.4%) males and 75 (63.6%) females were considered in the analyses.

Statistical analyses

Statistical analyses were performed using the statistical package SPSS v.22.

The results of eight SF-36 scales were expressed in the form of transformed scores, i.e. the percentage of the raw score to the maximum possible score in the given scale. For each of 8 scales the value 0 is assigned to the worst, and value 100 to the best quality of functioning. Standardised results according to the PCS and MCS scales were converted, according to the instruction, into T-scores, with the mean 50 and standard deviation 10. Evaluations of changes in the state of health remained in a raw form, i.e. according to the 5-point scale within the range of values from 1-5. Multi-variable relationships were analyzed using multiple regression. Eleven models of analysis were performed in which the subsequent scale of the SF-36 was included as an explained variable. In all models, the same set of explanatory variables: gender, age, GERD symptoms (ORS), stress (PSS-10), and the BMI was included. Analyses were performed using the backward elimination technique, the final effect of which is leaving in the model only the set of variables which have a significant effect on the explained variable.

Results

In the examined population, females were older than males ($p = 0.004$): mean age 48.4 ± 12.09 and 41.8 ± 13.21 , respectively. Also, females had a lower BMI compared to males:

24.7±4.51 and 26.0±3.37), respectively ($p = 0.034$). However, the 2 groups did not significantly differ according to the frequency of GERD symptoms (mean value for the examined population was 45.0±25.26), nor by the mean value of any of the SF-36 scales and the level of stress. The age group < 50 had a lower BMI value (24.0±3.78, within the normal range) than the age group ≥ 50 years (26.4±4.25, overweight, $p = 0.003$). These groups differed neither by the level of GERD symptoms, nor the level of stress. In the HRQL examination, the older group showed a generally lower level of physical functioning than the younger group (PCS: 41.7±7.92 and 47.6±6.33, respectively, $p < 0.0001$). In the case of detailed scales, significant differences were noted not only to the disadvantage of the older group in the scales: PF, RP, BP, GH, but also in the RE scale (Table 1)

Table 1. Mean values of variables analyzed in the study population in general and according to gender and age.

Variable	Sex			Age			Total (n = 118)
	M (n = 43)	F (n = 75)	Sig.	< 50 yrs (n = 62)	≥ 50 yrs (n = 56)	Sig.	
Age	41.8 (13.21)	48.4 (12.09)	0.0044	n/a	n/a	n/a	46.0 (12.86)
BMI	26.0 (3.37)	24.7 (4.51)	0.034	24.0 (3.78)	26.4 (4.25)	0.003	25.2 (4.17)
GERD							
Symptoms	47.6 (26.4)	43.6 (24.65)	0.43	44.4 (23.24)	45.7 (27.53)	0.75	45.0 (25.26)
Stress	19.9 (6.87)	18.8 (3.79)	0.65	18.5 (4.98)	20.0 (5.2)	0.13	19.2 (5.13)
PF	79.8 (19.88)	78.7 (17.69)	0.54	87.1 (12.66)	70.3 (19.85)	0.000001	79.1 (18.44)
RP	60.3 (29.06)	61.7 (22.12)	0.88	67.1 (24.59)	54.6 (23.43)	0.011	61.2 (24.76)
BP	51.3 (29.45)	42.8 (21.18)	0.12	50.4 (25.41)	40.9 (23.19)	0.027	45.9 (24.74)
GH	53.0 (20.46)	52.4 (16.44)	0.96	58.9 (18.51)	45.7 (14.5)	0.00003	52.6 (17.92)
Vt	47.7 (17.31)	51.1 (17.19)	0.42	51.7 (16.29)	47.7 (18.14)	0.21	49.8 (17.23)
SF	62.5 (23.31)	64.0 (24.05)	0.74	65.3 (24)	61.4 (23.39)	0.35	63.5 (23.69)
RE	65.5 (29.07)	68.8 (24.05)	0.70	74.5 (24.97)	60.0 (25)	0.0022	67.6 (25.92)
MH	56.5 (18.47)	55.5 (17.18)	0.49	57.4 (17.15)	54.2 (18.06)	0.39	55.9 (17.59)
HT	3.5 (1.03)	3.4 (0.84)	0.62	3.3 (0.84)	3.6 (0.97)	0.12	3.4 (0.91)
PCS	45.7 (8.69)	44.3 (7.07)	0.42	47.6 (6.33)	41.7 (7.92)	0.000068	44.8 (7.69)
MCS	39.1 (11.47)	40.4 (10.38)	0.73	40.9 (10.78)	38.9 (10.74)	0.39	39.9 (10.76)

n/a - not applicable.

The frequency of GERD symptoms resulted in a decrease in patients' results according to 6 out of 8 F-36 scales. Only in 2 scales, MH and Vt, the effect of the symptoms of GERD was insignificant. Consequently, a significant decrease in the results under the effect of symptoms was observed according to both summary scales: PSC and MSC. Stress resulted in a decrease in the functioning of patients in all domains and dimensions measured using the SF-36. Age resulted in a decrease in physical functioning, according to the results of both PF scale and PCS. Age was also the factor resulting in a decrease in an

overall assessment of self-reported state of health (GH). An increasing BMI exerted a negative effect on physical fitness (PF) and limitations in functioning resulting from this decrease (RP). In addition, which is noteworthy, it also caused limitations in social relations which resulted from emotional disorders (RE) (Table 2)

Table 2. Effect of selected variables on HRQL measured using SF-36.

Variable Explained (Percent of variability explained ^A)	Explanatory Variables ^B	Beta	Sig.
PF (41%)	Stress	-0.37	0.000002
	Age	-0.31	0.000097
	BMI	-0.24	0.0022
	GERD		
	Symptoms	-0.15	0.045
RP (36%)	Stress	-0.47	<0.000001
	BMI	-0.26	0.0006
	GERD		
	Symptoms	-0.18	0.022
BP (29%)	Stress	-0.41	0.000002
	GERD		
	Symptoms	-0.25	0.002
	Sex (1=M, 2=F)	-0.17	0.028
GH (37%)	Stress	-0.43	<0.000001
	Age	-0.31	0.00005
	GERD		
	Symptoms	-0.17	0.028
Vt (45%)	Stress	-0.67	<0.000001
SF (32%)	Stress	-0.49	<0.000001
	GERD		
	Symptoms	-0.21	0.010
RE (44%)	Stress	-0.56	<0.000001
	GERD		
	Symptoms	-0.21	0.004
	BMI	-0.20	0.005
MH (59%)	Stress	-0.77	<0.000001
PCS (30%)	Stress	-0.29	0.00041
	Age	-0.35	0.000017
	GERD		
	Symptoms	-0.22	0.0061
MCS (53%)	Stress	-0.68	<0.000001
	GERD		
	Symptoms	-0.13	0.047

^AAdjusted R Square x 100. ^BVariables: Stress, Age, PF and BP were transformed to minimise their skewness.

Discussion

In the presented study of the quality of life of patients with GERD, the control group was not considered. To compensate for this deficiency, the results of own studies using SF-36 (Lublin) were compared with the results obtained in a random sample of 8,801 inhabitants of Great Britain drawn from General Practitioner Records held by the

Health Authorities for Berkshire, Buckinghamshire, Northamptonshire, and Oxfordshire (GBS), and the subpopulation of chronically ill patients in this sample (GBS- longstanding illness)^[30]. The sample covered 8,801 patients aged from 18- 64, including 43.4% of males and 55.6% of females. Both groups (GBS and Lublin) did not significantly differ according to age and gender (Figure 1).

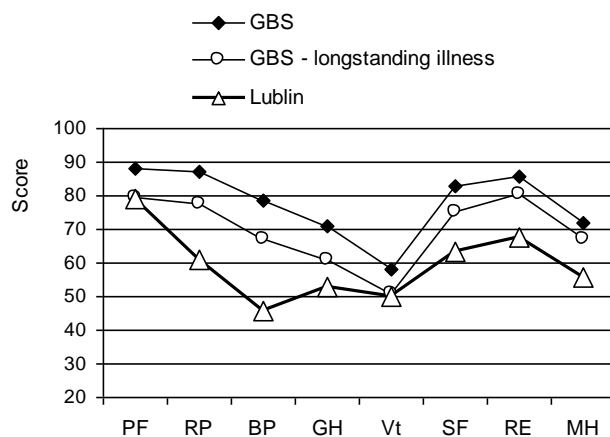


Figure 1. Mean scores for the 8 scales of SF-36 for GB samples and Lublin sample.

Patients from Lublin showed a lower quality of life in all 8 domains, compared to GBS (significance of differences was analyzed using t-Student test). In turn, compared to the GBS- long-standing illness, they did not significantly differ according to the PF and Vt scales. The highest difference between the quality of the assessed domains was observed for BP. In the Lublin population, it occupied the lowest position, while in the GB sample it obtained the evaluation by 30 scores higher. Similarly, in American studies^[31], 533 adults with a history of heartburn symptom showed a lower quality of functioning in all 8 domains, compared to the general USA population.

The result of analysis of regression showed stress and reflux complaints as 2 separate sources of the effect on HRQL, in the general measures of physical and psychological functioning, as well as individual domains considered in SF-36. The strength of the effect of stress is especially noteworthy, stress being the factor decreasing HRQL of patients in all the domains and spheres (PCS, MCS) analyzed. In the domains Vt and MH, stress remained the only variable resulting in the deterioration of the results. It is difficult to unequivocally refer to the dominant position of stress in the examined group, especially

considering the fact that the selection of the sample for the study was not of a random character, and it cannot be excluded that it favoured its more frequent occurrence among respondents distressed more than in the general population of patients with GERD^[32]. The effect of stress on the domains of physical functioning might have been partly an artefact of the instrument for measurement of functioning in this sphere. SF-36 does not measure the actual level of physical functioning, but the subjective self-evaluations of patients. These self-evaluations, under the effect of long-term stress accompanied by low mood and overall self-esteem, might have been subject to a decrease non-proportional to the actual fitness. The use of objective measures of the quality of physical functioning would be a desired supplementation of the study. It is noteworthy that HRQL measurement using SF-36 questionnaire does not consider a number of domains of functioning which are potentially important for the quality of life. Here, on the one hand, the sphere of intimate relations and sexual activity may be mentioned. Among patients with GERD-impaired sexual activity and avoidance of intimacy due to the disease is often observed^[33]. On the other hand, SF-36 omits a widely-handled spiritual sphere- beliefs and religious activity, participation in culture- reading, interests and artistic activity.

Apart from stress and reflux complaints, an increasing BMI had a limited effect on HRQL. This resulted in a decrease in the quality of life in the domains of physical functioning: PF and RP. However, it also increased the probability of occurrence of situations when emotional disorders lead to problems in relations with others, and limitations in the frequency of social contacts (RE). Carr and Friedman^[34], in a survey of more than 3,000 adults, did not observe any deterioration in the quality of relations with others, together with an increase in BMI, except for severely obese persons who experienced a higher level of tension and less support in family relations. Nevertheless, in a randomized British study, a negative effect of BMI was confirmed on the level of social functioning of females^[35].

Correlation analyses do not allow drawing conclusions concerning the cause-effect relationships between variables. Correlation and regression coefficients provide quantitative estimations of common variability of the analyzed variables, while determination of the directions of relationships between variables is of a non-statistic character, and is based mainly on essential knowledge concerning relations in a given domain. Hence, conclusions drawn from correlation analyses possess rather the status of

hypotheses, the accuracy of which strengthens the scientific plausibility of the correlations revealed. Properly planned longitudinal studies may provide the ultimate solution.

Conclusions

The level of HRQL in patients with GERD is negatively determined by both the frequency of reflux symptoms and, to an even higher degree, by stress. An increasing BMI, irrespective of reflux symptoms, stress, and age, decreases the level of physical functioning of patients with GERD. It also leads to an increase in limitations in functioning ascribed to emotional disorders. The patient's level of stress should be considered in the diagnosis and therapy, as well as an assessment of the progress of treatment.

Article Highlights

Research background

Gastro-esophageal reflux disease is a common and serious health problem leading to a decrease in the quality of life of patients. The concept of health-related quality of life covers an expanded effect of the disease on a patient's wellbeing and activities of daily living. This study evaluates the effect of gastro-esophageal reflux symptoms and factors which cause decrease in quality of life such as a level of stress, age and body weight on the health-related quality of life.

Research motivation

Since GERD leads to a considerable decrease in the quality of life, therefore we conducted an observational study to assess the importance of its impact on the 8 domains of life (physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health perceptions) measured in a generic questionnaire. Moreover, we evaluated the importance of stress, excessive weight and age on the above-mentioned domains life.

Research objectives

The research objective was to determinate the independent effect of reflux symptoms, age, stress and increasing BMI on the quality of life of patients measured using the SF-36

questionnaire.

Research methods

A total of 118 patients diagnosed with reflux disease who reported to an outpatient department of gastroenterology or a specialist hospital ward for planned diagnostic tests were recruited. Assessment of the level of reflux was based on 5 typical of GERD symptoms, health-related quality of life was measured by a 36-item Short Form Health Survey and level of stress using the 10-item Perceived Stress Scale. Multi-variable relationships were analysed using multiple regression. The results of our study were compared with the results obtained in a random sample of 8,801 inhabitants of Great Britain drawn from General Practitioner Records held by the Health Authorities for Berkshire, Buckinghamshire, Northamptonshire, and Oxfordshire and the subpopulation of chronically ill patients in this sample.

Research results

In the examined population the frequency of reflux symptoms resulted in a decrease in patients' results according to 6 out of 8 SF-36 scales- except for mental health and vitality scales. Stress resulted in a decrease in the functioning of patients in all domains measured using the SF-36. Age resulted in a decrease in physical functioning and in an overall assessment of self-reported state of health. An increasing BMI exerted a negative effect on physical fitness and limitations in functioning resulting from this decrease. When compared to GBS group, patients from our study showed a lower quality of life in all 8 life domains. In turn, compared to the GBS-longstanding illness group, they did not significantly differ according to the physical functioning and vitality scales. The highest difference between the quality of the assessed domains was observed for bodily pain, which in the Lublin population occupied the lowest position, lower by 30 scores than in GB sample.

Research conclusions

The level of HRQL in patients with GERD is negatively determined by both the frequency of reflux symptoms and, to an even higher degree, by stress. An increasing BMI, irrespective of reflux symptoms, stress, and age, decreases the level of physical functioning of patients with GERD. It also leads to an increase in limitations in functioning ascribed to emotional disorders. The patient's level of stress should be considered in the diagnosis and therapy, as well as an assessment of the progress of treatment.

Research perspectives

In our study, the level of stress reported by the patient turned out to be more important for health-related quality of life than the severity of gastroesophageal reflux disease. Future studies assessing the impact of diseases on HRQL should take into account factors that are not symptoms of the disease. Moreover, in assessing the effectiveness of treatment, we should take into account the improvement of the HRQL as well as the reduction of disease-related symptoms.