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THE ROLE OF QUALITY OF LIFE IN MELATONIN CONTENT AS A REGULATOR OF DEFENSE AND AGGRESSION FACTORS IN GASTROESOPHAGEAL REFLUX DISEASE PATIENTS WITH SLEEP APNEA SYNDROME

Anatoliy Oparin
Doctor of Medical Sciences, Professor
Department of Therapy, Rheumatology and Clinical Pharmacology[1]

Aleksey Oparin
Doctor of Medical Sciences, Professor
Department of Therapy, Rheumatology and Clinical Pharmacology[1]

Murghuz Murghuzov
Postgraduate student
Department of Therapy, Rheumatology and Clinical Pharmacology[1]
murghuzov.murghuz@gmail.com

[1]*Kharkiv Medical Academy of Postgraduate Education*
58 Amosova str., Kharkiv, Ukraine, 61176

Abstract

The aim of the study: to study the effect of the quality of life on the melatonin content, and at the same time to assess the state of the factors of aggression and protection of the esophageal mucosa in patients with GERD without comorbidities and with concomitant obstructive sleep apnea/hypopnea syndrome (OSAHS).

Methods. 45 patients were taken for the study. 23 of them had GERD concomitant COPD, 22 were with isolated GERD with a non-erosive form.

Melatonin levels were determined using the enzyme immunoassay method (ELIZA). Quality of life was assessed using the SF-36 questionnaire. Antioxidant protection of the mucous membrane (protection factor) – was assessed by the activity of superoxide dismutase (SOD). SOD activity in blood serum was determined by calorimetric method. Determination of the DC level was carried out in the blood by the spectrofluorimetric method.

Results. The study showed that in patients with GERD with concomitant COPD, there is a significant decrease in the indicators of antioxidant activity and melatonin, both with indicators from the control group and with indicators of patients with GERD without comorbidity.

At the same time, in patients with GERD without comorbidities, an increase in the level of DC was observed in comparison with the control group and patients with GERD with concomitant pathology and acidity of gastric juice.

When analyzing the indicators of QOL in patients with GERD with concomitant pathology, there is a significantly more pronounced decrease in mental health, role emotional functioning and vitality.

Conclusions. It has been established that in patients with GERD in the stage of exacerbation of the disease, there is a statistically significant decrease in QOL indicators with a high degree of reliability, manifesting itself in patients without combined pathology in the spectrum of indicators of the physical component of health, and in patients with GERD with concomitant obstructive sleep syndrome – in the spectrum of the psychological component quality of life.

It has been shown that with a decrease in QOL in patients with GERD, the level of melatonin decreases, the decrease in which more clearly increases in patients with concomitant obstructive sleep apnea.

Simultaneously with a drop in the level of melatonin in patients with GERD without associated pathology, the aggression factor increases with a high degree of certainty – that is, a decrease in the pH of gastric juice and an increase in the content of DC, while in patients with GERD with concomitant sleep apnea syndrome, the factor decreases with a high degree of certainty. Protection of the esophageal mucosa – (that is, a decrease in SOD activity), which must be taken into account when treating this category of patients.

Keywords: gastroesophageal reflux disease, melatonin, obstructive sleep apnea/hypopnea syndrome, quality of life.

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1. Introduction

Gastroesophageal reflux disease (GERD) due to its wide prevalence, variety of clinical manifestations, frequent development of relapses is one of the urgent problems of clinical medicine and is rightfully considered as an epidemia of the XXI century [1, 2].

Obstructive sleep apnea/hypopnea syndrome (OSAHS) has been considered as a disease that often accompanies reflux pathology and affects the features of its course [3, 4].

It was found that OSAGS negatively affects the course of GERD, as it increases the frequency and duration of reflux from the stomach into the esophagus, aggravates damage to its mucous membrane and increases the risk of developing Barrett's esophagus [5, 6].

However, the peculiarities of lesions of the esophageal mucosa in patients with GERD with both isolated pathology and concomitant syndrome (OSAGS) remain not fully disclosed and require further research [7, 8].

In solving this problem, many researchers have paid special attention to the pituitary hormone – melatonin [9, 10]. This biogenic amine, according to many researchers, is able to inhibit intestinal motor function by blocking the action of cholecystokinin and other activators of the contractile the ability of the muscles of the gastrointestinal tract [11, 12], increases the protective properties of the epithelium by improving microcirculation [13], as well as regulating cell proliferation and increasing the density of intraepithelial contacts [14, 15].

It has been experimentally proven that melatonin inhibits the production of hydrochloric acid, increases the secretion of bicarbonates [16, 17], exhibits powerful antioxidant properties, which allows preventing damage to the mucous membrane of the digestive tract, which occurs under the influence of various aggressive factors [18].

In addition, melatonin is able to stimulate the activity of antioxidant enzymes – glutathione peroxidase and glutathione reductase, as well as inhibit inducible NO synthase [19, 20].

However, many pathogenetic mechanisms of fluctuations in the level of melatonin, on which the state of the factors of aggression and protection of the mucous membrane of the esophagus depends, in patients with GERD both without concomitant pathology, and with concomitant obstructive apnea/hypopnea syndrome (OSAGS), remain not fully understood and require further research, which is the purpose of our work.

The aim of the study was to study the effect of the quality of life on the melatonin content, and at the same time to assess the state of the factors of aggression and protection of the esophageal mucosa in patients with GERD without comorbidities and with concomitant obstructive sleep apnea/hypopnea syndrome (OSAHS).

2. Materials and methods

Studies were conducted on the base of Kharkiv state medical hospitals No. 20 in 2019–2020 years. The study included two groups of patients, homogeneous by gender and age.

The first group included 23 patients (15 men and 8 women) in age of 18 to 25 years (average age 21.7 ± 1.8) suffering from GERD (20 patients had a non-erosive form, 3 had an erosive form) with concomitant obstructive sleep apnea syndrome (OSAHS) of mild severity, who, along with characteristic complaints of GERD (heartburn, nausea, belching, regurgitation, dyspepsia) there was a periodic appearance of snoring at night, sleep disturbances, partial cessation of breathing no more than 2 times per night.

The second group included 22 patients (14 men and 8 women) in age of 19 to 28 years (average age 24.3 ± 2.8) suffering from GERD (in 19 patients – the non-erosive form, in 3 patients – the erosive form) with typical complaints. That is, the patients of both the first and the second groups were homogeneous in terms of sex, age and duration of the disease – from 1 to 2 years (the average duration of the disease was 1.57 ± 0.81 years).

20 healthy individuals of the same age (18 to 25 years) and sex (12 men and 8 women), who also voluntarily agreed to participate in this study, were included in the control group, and their study averages were taken as the norm.

GERD was verified according to the criteria of the Montreal Consensus (2006) and the order of the Ministry of Health of Ukraine No. 28 dated 03.19.2007, as well as the European (Gstaad

Treatment Guidelines) and American (American Gastroenterological Association Medical Position statement on the Management of GERD) guidelines on the strategy for the treatment of GERD. We also used a GERD screening questionnaire developed at the National Institute of Therapy named after L. T. Malaya NAMI of Ukraine to assess the severity of clinical symptoms of the disease (Algorithm for early detection of gastroesophageal reflux disease. Certificate No. 2618, registered 2008). The study design was approved by the Ethics Commission at the Kharkiv Medical Academy of Postgraduate Education, Protocol No. 9, 11/21/2018.

The presence and severity of OSAGS was determined using the method of OSAGS screening diagnostics by the Somnocheck-micro method (Weinmann, Germany).

Quantitative determination of the level of melatonin in patients of all three groups was carried out by studying the concentration of the metabolite of this hormone 6-sulfatoxymelatonin (6-SOM) in morning urine by the method of enzyme immunoassay (ELIZA). We took the peculiarities of collecting morning urine into account (excluding the use of lighting devices at the time of urine collection to prevent the destruction of this substance under the influence of light), used a standard laboratory set 6-Sylfatoxymelatonin ELIZA (BUHLMANN LABORATORIES A G Switzerland).

The quality of life (QOL) was assessed using the SF-36 unified questionnaire, which included an assessment of the scales of physical and psychological health. The scores on each scale ranged from 0 to 100, where one hundred points is the level of overall health.

The questionnaire was completed by the patient independently, therefore, the results of health assessment by the subjects themselves are objective criteria for the quality of life.

The state of the aggression factor of the esophageal mucosa was assessed by the pH-metre level of gastric juice and the level of diene conjugates (DC). Antioxidant protection of the mucous membrane (protection factor) – was assessed by the activity of superoxide dismutase (SOD).

Determination of the DC level was carried out in the blood by the spectrofluorimetric method [9].

SOD activity in blood serum was determined by calorimetric method [9].

Statistical processing was carried out by the method of variation statistics using standard correlation analysis programs with the calculation of average values: M, m. The reliability of the indicators was assessed by the Student's *t*-test. The difference was considered notable at $p < 0.05$. To establish the relationship between the indicators, correlation analysis was used with the calculation of the correlation coefficient (r) and the assessment of its reliability.

3. Results

In our study, we found that in patients with GERD both without comorbidities and with concomitant obstructive sleep apnea, quality of life (QOL) indicators were reduced and, compared with the control group of healthy individuals, the difference was statistically significant on all scales of the SF-36 questionnaire (**Table 1**).

Moreover, in patients with GERD without concomitant pathology (second group of patients), indicators of physical health – that is, scales of role physical functioning (34.5 ± 2.8 points) and especially the scale of pain intensity (37.2 ± 3.3 points) were determined on a lower level not only in comparison with the norm, but statistically significantly lower than in patients with GERD with concomitant OSAHS (43.8 ± 3.1 and 48.3 ± 3.9 points, respectively).

While the indicators of mental health levels – especially of role emotional functioning (36.8 ± 4.0 points), vitality (32.9 ± 4.1 points) and mental health (35.5 ± 2.8 points), on the contrary, in patients with GERD with concomitant OSAHS syndrome were the lowest, not only in comparison with the norm ($p < 0.001$), but also lower than in patients without associated pathology (55.2 ± 3.9; 51.4 ± 3.1 and 52.4 ± 3.1 points, respectively), making up a statistically significant difference with them on average ($p < 0.05$).

Scale scores – general health (GH), physical (PF) and social functioning (SF) – were also lower in patients with GERD with concomitant OSAHS (39.1 ± 4.2 points, 47.2 ± 3.4 points and 50.1 ± 4.9 points, respectively) than in patients with GERD without associated pathology (45.6 ± 4.0 points, 50.6 ± 3.9 points and 52.2 ± 4.1 points, respectively), but the difference between them was statistically unreliable (**Table 1**).

Table 1

Average QOL values in GERD patients without comorbidities and with concomitant obstructive sleep apnea syndrome

Indicators of QOL scales	GERD patients		Healthy persons of the control group
	No associated pathology	With concomitant apnea syndrome	
Physical functioning (PF)	50.6±3.9	47.2±3.4	84.5±4.0
Role-based physical functioning (RP)	34.5±2.8	43.8±3.1	71.4±3.0
Pain intensity (BR)	37.2±3.3	48.3±3.9	76.3±4.0
General health (GH)	45.6±4.0	39.1±4.2	75.1±4.1
Viability (VT)	52.4±4.1	32.9±4.1	80.5±3.2
Social functioning (SF)	52.2±4.1	50.1±4.3	81.4±4.2
Role-based emotional functioning (RF)	55.2±3.9	36.8±4.0	78.6±3.1
Mental health (MH)	51.4±3.1	35.5±2.8	75.5±3.7

However, we found that in all patients with GERD, both without comorbidity and with concomitant obstructive OSAHS syndrome, in parallel with a decrease in quality of life (QOL) indicators, a decrease in the level of melatonin was observed. Moreover, if in the group with isolated GERD the level of melatonin (6-SOM) in the morning urine on average was reduced to 20.66±1.62 mg/L with a norm of 29.6±2.91 mg/L, making up a statistically significant difference ($p < 0.001$), then in the group of GERD patients with concomitant apnea syndrome, its level dropped even lower – to 14.62±1.54 mg/L and when compared was statistically significantly lower than the norm ($p < 0.001$), but also average indicators of the group of patients with GERD without associated pathology (**Table 2**).

Also, in these observed patients, in parallel with a decrease in the level of melatonin, which is closely associated with a decrease in QOL, there are disturbances in the system of factors of aggression and protection of the esophageal mucosa.

Besides, if in patients with GERD without concomitant pathology, the aggression factor more clearly increases, as evidenced by a statistically significant ($p < 0.001$) decrease in the pH-metric indicators of gastric juice (in the body up to 0.72±0.06 and in the antrum up to 5.10±0.12 with a norm of 1.63±0.12 and 7.21±0.11) and an increase in DC values (up to 104.4±6.1) not only in comparison with the norm (62.4±4.4, $p < 0.001$), but also in comparison with the parameters of patients with concomitant OSAHS (up to 0.96±0.07; 5.92±0.11; 80.2±4.9; and $p < 0.01$, respectively), while the level of activity of superoxide dismutase (SOD) – that is, the factor of protection of the esophageal mucosa, on the contrary, in patients with GERD with concomitant OSAGS syndrome dropped to 0.49±0.05 and was statistically significantly lower (**Table 2**), not only the norm (1.28±0.07), but with a lesser degree of reliability was lower ($p < 0.05$), than the average indicators of patients with GERD without associated pathology (0.74±0.05).

Table 2

Average indicators 6-SOM in daily urine, pH-metry level of gastric juice, DC and SOD in blood in patients with GERD without comorbidity, with concomitant sleep apnea syndrome and healthy controls

Indicators	GERD patients		Control group
	No associated pathology	With concomitant apnea syndrome	
pH (body)	0.72±0.06	0.96±0.07	1.63±0.12
pH (antrum)	5.10±0.12	5.92±0.11	7.21±0.11
DC μmol/l	104.4±6.1	80.2±4.9	62.4±4.4
SOD μg/ml	0.74±0.05	0.49±0.05	1.28±0.07
6-SOM mg/l	20.66±1.62	14.62±1.54	29.60±2.91

The changes we identified in the spectrum of the studied parameters and the presence of a close correlation between them clearly indicate that a decrease in the QOL level of patients, having a direct effect on a decrease in the level of melatonin, leads to an increase in the aggression factor in patients with GERD without comorbidity (**Table 2**), that is, an increase in the acidity of gastric juice and the level of DC, and in patients with GERD with concomitant apnea syndrome – to a more pronounced decrease in the protective factor of the esophageal mucosa, that is, a decrease in SOD, which must be taken into account when developing a plan of therapeutic and preventive measures.

4. Discussion

From our results, we can see the mechanism of formation of concomitant obstructive sleep apnea/hypopnea syndrome in patients with gastroesophageal reflux disease at an earlier stage of the disease comparing with the results of other researchers [3, 4].

Thus, the course of both GERD and OSAS were influenced by other concomitant pathologies, which hindered the identification of the mechanisms of OSAS formation in patients with GERD.

Our data are consistent with the results of other researchers who also stated in patients with GERD with both esophageal and extraesophageal manifestations, a decrease in the level of QOL [21, 22], a decrease in the level of melatonin and the presence of an imbalance in the system of factors of aggression and protection of the esophageal mucosa [23, 24].

Study limitations. We did not include patients with other concomitant diseases in the study group.

Further research is that the study of the mechanisms of the formation of OSAS in patients with GERD will allow, by studying the state of melatonin and oxidative stress for a month, the way for the development of complex therapy for GERD with concomitant OSAS using the drug melatonin, which will significantly increase the QoL of patients in these groups.

5. Conclusions

Thus, the following conclusions can be drawn from the results of the study and analysis of literature data.

1. It was found that in patients with GERD in the stage of exacerbation of the disease, there is a statistically significant decrease in QOL indicators, with a high degree of reliability manifested in patients without combined pathology in the spectrum of indicators of the physical component of health, and in patients with GERD with concomitant obstructive sleep syndrome – in the spectrum of the psychological component of the quality of life.

2. It has been proven that, in parallel with a decrease in QOL in patients with GERD, the level of melatonin decreases, the degree of decrease in which more clearly increases in patients with concomitant obstructive sleep apnea syndrome.

3. It was revealed that simultaneously with a drop in the melatonin level in GERD patients without comorbidities, the aggression factor increases with a high degree of certainty – that is, a decrease in the pH of gastric juice and an increase in the content of DCs, while in patients with GERD with concomitant sleep apnea syndrome, it decreases with a high degree of certainty, a factor of protection of the esophageal mucosa – (that is, a decrease in SOD activity), which must be taken into account when treating this category of patients.

Conflict of interests

The authors declare that they have no conflicts of interest.

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