Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 60; Numer/Number 3/2009
ISSN 0423–104X

Quality of life assessment in patients with Graves' disease and progressive infiltrative ophthalmopathy during combined treatment with methylprednisolone and orbital radiotherapy

Ocena jakości życia u pacjentów z chorobą Gravesa-Basedowa i postępującą naciekową oftalmopatią tarczycową w trakcie skojarzonego leczenia metyloprednizolonem i radioterapią przestrzeni pozagałkowych

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Abstract

Introduction: The aim of the study was to assess quality of life (QoL) in patients with infiltrative form of Graves' ophthalmopathy (GO) during the combined pulse treatment with methylprednisolone and orbital radiotherapy, and also to search for the relation between the results of ophthalmopathy treatment and changes in QoL.

Material and methods: The study involved 29 patients aged 25–74 (the mean age: 52 ± 6 years) with infiltrative form of GO. They were classified for ophthalmopathy treatment on the basis of the following factors: the obtained euthyreosis, progressive character of eye changes, the level of eye changes determined on the basis of NO SPECS classification (at least class 3c), ophthalmopathy index (OI) according to Donaldson ≥ 4. GO was diagnosed as active if CAS (clinical activity score) ≥ 4. During the treatment, the patients received 6 cycles of methylprednisolone sodium succinate in doses of 1,0 g/24 h given as one-hour-long intravenous infusions for three successive days in a week. Between the 2nd and 4th cycle of Solu-Medrol, orbital radiotherapy with 10 MeV X-rays was performed. The control group was made up of healthy volunteers selected with regard to sex, age, educational background and nicotine addiction so as they corresponded with the study group. It involved 53 individuals aged 21–75 (the mean age: 52,4 ± 14 years). QoL was assessed by means of the MOS SF-36 questionnaire.

Results: Patients with GO evaluated their QoL lower than healthy individuals, which referred to physical functioning, physical and emotional role functioning, general health, vitality, social functioning, mental health and bodily pain. No correlation was found between quality of life and such factors as age, sex, or duration time of Graves disease and ophthalmopathy. Analogically, no relation was observed between the activity and stage of clinical development of eye changes and QoL. The use of the combined GO therapy contributed to a considerable decrease in the development of eye changes and the disease activity. After treatment, the patients' QoL improved which referred to physical role functioning, bodily pain, and vitality. Other QoL parameters did not statistically significantly differ.

Conclusions: GO causes a considerable worsening of QoL. The stage of clinical development and activity of GO find no reflection in QoL. Effectiveness of treatment for GO cannot be evaluated on the basis of changes in QoL. **(Pol J Endocrinol 2009; 60 (3): 158–165)**

Key words: *Graves' ophthalmopathy, Graves' disease, quality of life, methylprednisolone, orbital radiotherapy*

Streszczenie

Wstęp: Celem pracy była ocena jakości życia u chorych z naciekową postacią oftalmopatii tarczycowej (GO, *Graves' opthalmopathy*) w trakcie pulsacyjnego leczenia metylprednizolonem w połączeniu z radioterapią oczodołów oraz próba odniesienia wyników leczenia oftalamopatii do zmian w jakości życia.

Materiał i metody: Badaniem objęto grupę 29 pacjentów w wieku 25–74 lat (śr. wieku: 52 ± 6 lat) z naciekową GO. Podstawą kwalifikacji chorych do leczenia oftalmopatii było uzyskanie eutyreozy, postępujący charakter zmian ocznych, stopień zaawansowania zmian ocznych oceniany w oparciu o klasyfikację NO SPECS mieszczący się przynajmniej w klasie 3c, indeks oftalmopatii według Donaldson ≥ 4 punktów. Za aktywną postać GO przyjmowano wartości klinicznego wskaźnika aktywności (CAS, *clinical activity score*) ≥ 4. Podczas leczenia, u chorych zastosowano 6 cykli soli sodowej metyloprednizolonu w dawce 1,0 g/dobę podczas jednogodzinnych wlewów dożylnych, przez kolejne trzy dni w tygodniu. Między 2. a 4. cyklem Solu-Medrolu prowadzono radioterapię tkanek pozagałkowych promieniami X o energii 10 MeV. Grupę kontrolną utworzono ze zdrowych ochotników, dobranych w stosunku do grupy badanej pod względem płci,

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wieku, posiadanego wykształcenia i uzależnienia od nikotyny. Składała się ona z 53 osób, w wieku 21–75 lat (śr. wieku: 52,4 ± 14 lat). Badania jakości życia przeprowadzano, opierając się na kwestionariuszu MOS SF-36.
Wyniki: Pacjenci z GO gorzej oceniali jakość życia w stosunku do osób zdrowych w zakresie ogólnej sprawności, ograniczeń fizycznych i emocjonalnych w pełnieniu funkcji, stanu zdrowia, witalności, funkcjonowania społecznego, zdrowia psychicznego oraz występowania i nasilenia bólu. Nie wykazano korelacji pomiędzy jakością życia a wiekiem, płcią, czasem trwania choroby Gravesa-Basedowa i oftalmopatii. Podobnie nie stwierdzono zależności pomiędzy aktywnością i zaawansowaniem klinicznym zmian ocznych a jakością życia. Zastosowanie skojarzonej terapii GO spowodowało znamienne zmniejszenie stopnia zaawansowania zmian ocznych i obniżenie aktywności choroby. Po leczeniu pacjenci wskazali na poprawę jakości życia w zakresie ograniczeń fizycznych w odgrywaniu ról, występowania i nasilenia bólu oraz witalności. Pozostałe parametry jakości życia nie różniły się istotnie statystycznie.
Wnioski: Oftalamopatia tarczycowa powoduje znaczne pogorszenie jakości życia. Stopień zaawansowania klinicznego i aktywność oftalmopatii nie wykazują związku z jakością życia. Skuteczności leczenia oftalmopatii nie można oceniać, kierując się zmianami w jakości życia pacjentów. **(Endokrynol Pol 2009; 60 (3): 158–165)**

Słowa kluczowe: *oftalmopatia tarczycowa, choroba Gravesa-Basedowa, jakość życia, metyloprednizolon, radioterapia oczodołów*

Introduction

Graves' ophthalmopathy (GO) is the most common non-thyroid clinical manifestation of Graves' disease [1]. It develops in 25–50% of patients afflicted with this condition. In most cases, eye symptoms result from hyperthyroidism and increased activation of the sympathetic nervous system. They manifest as small oedemas of the upper and lower eyelids, widening of the palpebral fissure, slight exophthalmos, and excessive lacrimal secretion. The clinical course of the disease is mild. During treatment for hyperthyroidism, the described changes usually naturally regress [2]. In some patients, such changes may become established, but they do not produce any trouble and do not cause visual impairment.

The infiltrative form of GO is observed in 5–8% of patients with Graves' disease [3]. Eye changes appear as a consequence of an inflammatory process which has an autoimmunological character and spreads over orbital soft tissue. This form of ophthalmopathy usually has a progressive character and, if not treated, can even lead to the loss of sight. Pathological lesions manifest as massive circumorbital oedema, considerable exophthalmos, diplopia, reduced visual acuity, and damaged cornea.

Infiltrative ophthalmopathy requires the combined immunosuppressive therapy, initially with methylprednisolone and orbital radiotherapy, and then continuation with prednisone. At present, this is the most effective treatment for this disease.

Analysis of the regression level of particular clinical GO symptoms is not the only essential element of the applied treatment efficacy; it is also important to fully restore the patient's general fitness, which guarantees their proper functioning in the family and society. Quality of life is measured by means of questionnaires.

Both Graves' disease and Graves' ophthalmopathy contribute to a considerable worsening of quality of life. Unfavourable changes are related to the sphere of physical functioning, physical and emotional role functioning, vitality, social functioning, and mental health [4–7]. Patients afflicted with GO have problems with proper functioning in the family and society. Many patients face serious difficulties in continuing their work at existing posts.

The aim of this study was to assess the quality of life in patients with the infiltrative form of Graves' ophthalmopathy treated with cycles of methylprednisolone and orbital radiotherapy, and to search for the relation between the results of ophthalmopathy treatment and changes in quality of life.

Material and methods

The study involved 29 patients aged 25–74 (mean age: 52 ± 6 years) with progressive infiltrative ophthalmopathy developed in the course of Graves-Basedow disease. In 4 patients hyperthyroidism was previously treated with ^{131}I, and 4 others underwent strumectomy. The rest of the patients received conservative treatment with thyreostatics. All the patients were in a state of clinical euthyreosis at the beginning of GO therapy. The duration of Graves-Basedow disease was 8–64 months, 37.4 ± 7 months on average. GO-related eye changes lasted 1–16 months, 8 ± 3 months on average.

The patients were classified for ophthalmopathy treatment on the basis of the following factors: the obtained euthyreosis, progressive character of eye changes, the level of eye changes determined on the basis of NO SPECS classification (at least class 3c), and ophthalmopathy index according to Donaldson ≥ 4, (Table I) [8]. GO was diagnosed as active if CAS (clinical activity score) ≥ 4 [9]. Maximum opthalmopathy index (OI) and CAS values were 15 and 7, respectively. Opthalmopathy index and CAS were calculated for each eye separately.

Exclusion criteria for deciding that a patient was not allowed to participate in the therapy included: coexistence of an autoimmunological disease, relapsing form of Graves' ophthalmopathy, administration of oral steroids before hospital admission, treatment by means of orbital irradiation only or cyclical administration of methylprednisolone only, cessation of treatment because of complications, cessation of oral treatment with

Table I. *Categories of eye changes in Graves-Basedow disease according to Donaldson*

Tabela I. *Kategorie zmian ocznych w chorobie Gravesa-Basedowa według Donaldson*

Orbital soft tissue	Exophthalmos in mm above the upper normal limit	Eye muscles	Cornea	Visual acuity	Result
Slight conjunctival congestion, eyelid oedema, mild symptoms	3–4	Occasional diplopia at extreme position of eyeballs	Minimal stippling	0.8–0.5	1
Moderate conjunctival congestion, eyelid oedema, medium symptoms	5–7	Frequent diplopia, moderate limitation of eyeball mobility	Considerable stippling	0.45–0.2	2
Severe conjunctival congestion and oedema, massive eyelid oedema, severe symptoms	> 8	Persistent diplopia, substantially impaired eyeball mobility	Ulceration	< 0.2	3

prednisone, or a patient's refusal to be examined after completing the full therapy.

Ophthalmological examinations included: visual acuity determination checking for near- and farsightedness, eyeball protrusion measured with a Hertel exophthalmometer at the same eyeball distance each time, measurement of palpebral fissure width, slit lamp examination of the front part of the eye considering corneal damages, eyeball mobility and diplopia examination, ophthalmoscopy, and measurement of intraocular pressure.

Ophthalmological examinations were performed twice, *i.e.* before and after the pulse treatment with methylprednisolone.

The treatment scheme was based on therapy with glucocorticoids combined with orbital irradiation. The patients received 6 cycles of methylprednisolone sodium succinate (Solu-Medrol TM Pharmacia & Upjohn). Each cycle was composed of three one-hour-long intravenous infusions of methylprednisolone in doses of 1.0 g/24 h, administered for three successive days in a week.

The control group consisted of healthy volunteers selected with regard to sex, age, educational background, and nicotine addiction, so that they corresponded with the study group. This involved 53 individuals aged 21–75 (mean age: 52.4 ± 14 years).

On the day of ophthalmological examination, each patient's quality of life was assessed by means of the MOS SF-36 (Medical Outcomes Study Short-Form-36), which included analysis of physical functioning, physical and emotional role functioning, bodily pain, general health, vitality, social functioning, and mental health [10]. In the control group, quality of life was assessed once.

Statistical analysis

Normality of distribution of the continuous variables was analysed using Shapiro-Wilk test. Before comparison of the mean values, variance homogeneity was analysed (F-Snedecor test). Statistical significance of parameters in the particular groups was assessed using the non-parametric Mann-Whitney U test. In order to assess the correlation between two measurable continuous characteristics, Pearson's correlation coefficient was calculated when the distribution of both characteristics corresponded with normal distribution, and Spearman's rank correlation coefficient was used when the distribution of at least one of the characteristics was statistically significantly different than normal. Statistical significance was defined as $p < 0.05$.

Results

After the 6-week combined therapy with methylprednisolone and orbital radiotherapy, a statistically significant decrease in the development of eye changes was obtained, which was expressed as considerably lower OI values in both eyes. In addition, the applied treatment contributed to a considerable decrease in the disease activity (Table II).

Positive correlations between OI and CAS values were proven both before treatment and after 6 cycles of methylprednisolone combined with orbital radiotherapy (Fig. 1, Fig. 2).

In the group of GO patients, no correlation was observed between quality of life and such factors as age, sex, or duration time of Graves' disease and Graves'

Table II. *Comparison of the stage and the activity of Graves' ophthalmopathy before and after treatment*

Tabela II. *Porównanie stopnia zaawansowania klinicznego i aktywności oftalmopatii tarczycowej przed i po leczeniu*

		Before treatment	After treatment	*p < 0.05
Stage of Graves' ophthalmopathy (OI)	Right eye	5.1 ± 2.1	1.3 ± 1.4	*
	Left eye	4.9 ± 2.2	1.3 ± 1.5	*
	Average score of two eyes	4.9 ± 1.9	1.3 ± 1.4	*
Activity of Graves' ophthalmopathy (CAS)	Right eye	5.2 ± 2.6	1 ± 1	*
	Left eye	5.1 ± 3.0	1.1 ± 1.2	*
	Average score of two eyes	5.1 ± 2.5	1 ± 1	*

*Test for Spearman rank correlation coefficient

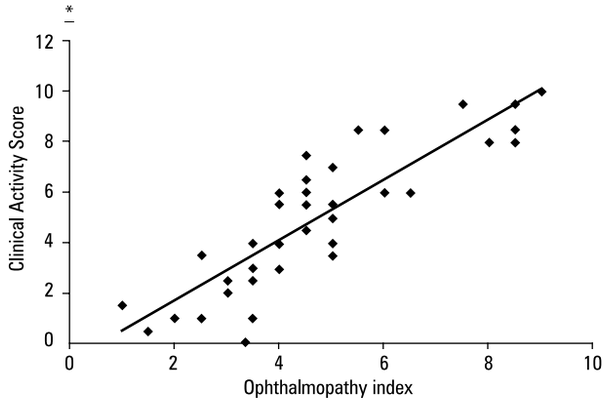

Figure 1. *Correlation between the activity (CAS) and stage of clinical development of Graves' ophthalmopathy (OI) before treatment*

Rycina 1. *Korelacja pomiędzy aktywnością (CAS) i stopniem zaawansowania klinicznego oftalmopatii (IO) przed rozpoczęciem leczenia*

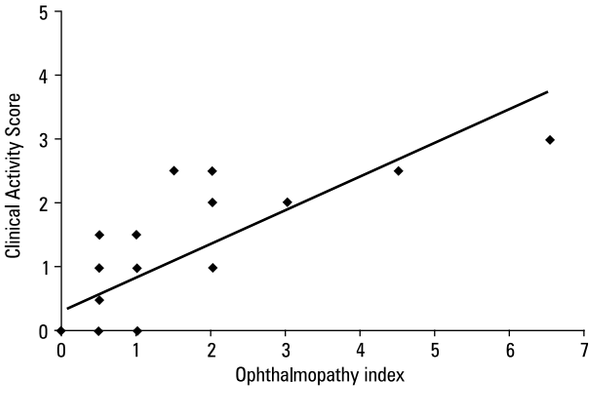

Figure 2. *Correlation between the activity (CAS) and stage of clinical development of Graves' ophthalmopathy (OI) after treatment*

Rycina 2. *Korelacja pomiędzy aktywnością (CAS) i stopniem zaawansowania klinicznego oftalamopatii tarczycowej (IO) po leczeniu*

Table III. *Quality of life assessment depending on educational background in the group of Graves' ophthalmopathy patients*

Tabela III. *Ocena jakości życia w zależności od wykształcenia w grupie pacjentów z oftalmopatią tarczycową*

	Education			
Parameter	**Elementary school level**	**High school level**	**University level**	***p**
Physical functioning	65 ± 47.6	57.2 ± 30.2	82.5 ± 9.5	0.75
Role functioning — physical	8.3 ± 14.4	13.8 ± 33.3	12.5 ± 25	0.96
Bodily pain	38.3 ± 37.0	55.3 ± 25.2	46.7 ± 18.7	0.89
General heath	58.2 ± 10.5	47.1 ± 20.5	54.7 ± 21.2	0.66
Vitality	45 ± 31.2	43.8 ± 12.9	38.7 ± 10.3	0.43
Social functioning	37.5 ± 21.6	44.4 ± 31.3	46.8 ± 11.9	0.69
Role functioning — emotional	0 ± 0	44.4 ± 52.7	75 ± 50	< 0.05
Mental health	56 ± 4	58.2 ± 25.3	61 ± 7,5	0.59

*Test for Spearman rank correlation coefficient

Table IV. *Quality of life assessment depending on sex in the control group*

Tabela IV. *Ocena jakości życia w zależności od płci w grupie kontrolnej*

Parameter	Gender		p Mann-Whitney test
	Females	Males	
Physical functioning	88.3 ± 16.6	87.3 ± 14.5	0.57
Role functioning — physical	86.9 ± 27.1	52.3 ± 48.0	0.02
Bodily pain	72.6 ± 23.2	64.9 ± 28.3	0.38
General heath	70.6 ± 16.7	67.0 ± 20.0	0.64
Vitality	61.3 ± 12.8	51.4 ± 16.1	0.03
Social functioning	83.0 ± 15.5	53.4 ± 24.4	0.01
Role functioning — emotional	87.2 ± 24.3	42.4 ± 33.6	< 0.01
Mental heath	72.0 ± 14.3	63.6 ± 17.3	0.16

Table V. *Quality of life assessment depending on educational background in the control group*

Tabela V. *Ocena jakości życia w zależności od wykształcenia w grupie kontrolnej*

Parameter	Education			*p
	Elementary school	High school	University	
Physical functioning	79.1 ± 21.0	85.1 ± 17.6	94.7 ± 9.24	0.0007
Role functioning — physical	70.8 ± 40.0	79.6 ± 33.2	82.5 ± 37.2	0.24
Bodily pain	52.0 ± 13.4	68.3 ± 25.6	80.3 ± 21.3	0.01
General heath	59.3 ± 12.5	69.5 ± 19.0	73.4 ± 15.4	0.12
Vitality	55.0 ± 17.8	61.4 ± 15.5	57.5 ± 10.4	0.33
Social functioning	77.0 ± 27.8	77.7 ± 19.4	75.6 ± 22.7	0.64
Role functioning — emotional	77.7 ± 40.3	80.2 ± 29.6	74.9 ± 33.9	0.69
Mental heath	58.6 ± 23.0	70.9 ± 15.2	72.8 ± 11.3	0.24

*Test for Spearman rank correlation coefficient

ophthalmopathy. The higher level of education of ophthalmopathy patients was reflected in better emotional role functioning compared to individuals with only primary or high school level education (Table III).

However, no correlation was found between the stage of Graves' ophthalmopathy or activity and quality of life in these patients.

In the control group, the women assessed their quality of life higher than men when referring to vitality; they also complained less about physical and emotional limitations in role functioning, and evaluated their social functioning higher (Table IV).

The younger the surveyed were, the higher they assessed their physical functioning, physical role functioning, and general health ($p < 0.08$). There were no significant correlations between other parameters of quality of life and age in the control group. In the healthy individuals, a high level of education was associated with better assessment of physical functioning and considerably lower levels of bodily pain (Table V).

Quality of life patients with infiltrative ophthalmopathy before the therapy was significantly different than in the healthy individuals, which referred to all assessed parameters, namely physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health (Fig. 3).

The use of the combined therapy for Graves' ophthalmopathy significantly reduced the intensity of eye changes and the activity of the disease, and at the same time considerably improved the quality of life related to physical role functioning, bodily pain, and vitality (Fig. 4). In accordance with patients' opinions, other parameters did not change to any statistical significance.

The older the examined patients were, the more their mental health improved after the applied treatment ($Rs = 0.47$, $p < 0.02$). Analogically, the longer the Gra-

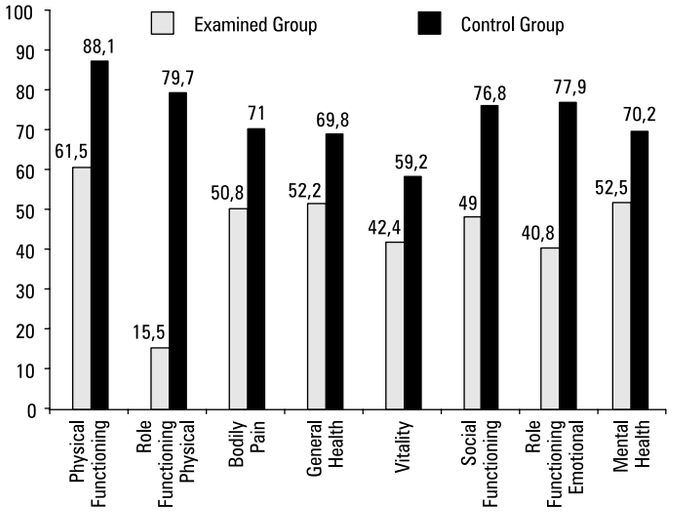

Figure 3. *Comparison between quality of life in patients with Graves' ophthalmopathy and healthy individuals*
Rycina 3. *Porównanie jakości życia u pacjentów z oftalmopatią tarczycową i osób zdrowych*

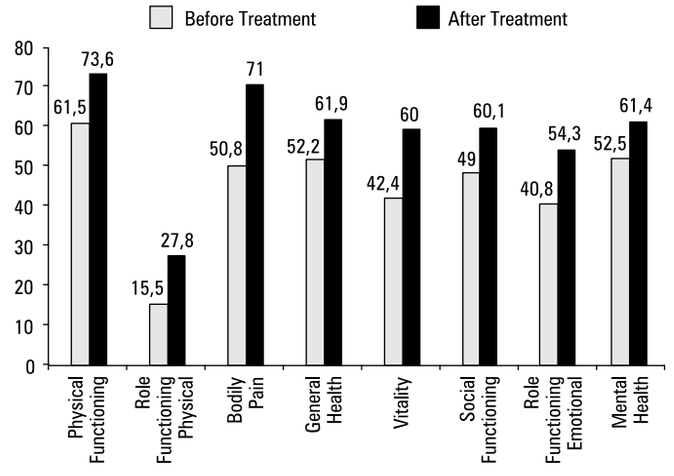

Figure 4. *Quality of life in patients with Graves' ophthalmopathy before and after the therapy*
Rycina 4. *Jakość życia pacjentów z oftalmopatią tarczycową przed i po zastosowanym leczeniu*

ves' disease lasted, the better the patients assessed their mental health after the completed treatment (Rs = 0.41, $p < 0.05$).

Discussion

Research conducted on GO patients indicate that their quality of life worsens considerably. Even though ophthalmopathy is not recognized as a chronic disease, the quality of life of people afflicted with this condition is as bad as in the case of patients with chronic circulatory and respiratory failure [11, 12].

What is more, the feeling of a decline in quality of life may last for a relatively long time in GO patients. Terwee et al. proved the unfavourable influence of ophthalmopathy on quality of life even after a period of more than 11 years from the end of therapy [13]. It was also noticed that hyperthyroidism itself, without coexisting eye changes, negatively affects quality of life [7, 14].

In order to eliminate the adverse effects of hyperthyroidism on quality of life, patients in a state of euthyreosis and suffering from Graves' disease for 37.4 months on average were included in this study.

In the examined group of GO patients, quality of life was significantly lower than in the control group, which referred to all analysed spheres of life included in the MOS SF-36 form. The differences were related to patients' opinions about their physical functioning, physical and emotional role functioning, general health,

vitality, social functioning, mental health, and bodily pain. According to a Dutch study, the only quality of life parameter which did not substantially differ in patients with ophthalmopathy compared to healthy individuals was bodily pain [5].

The relationship between sex and age of GO patients and their quality of life assessment was not confirmed. Other authors have reported that older patients perceive their quality of life as lower, whereas young people with GO are mainly upset by changes in their external appearance [6, 13, 15].

In the case of healthy individuals, sex- and age-dependent differences in quality of life assessment mostly concerned vitality, physical and emotional role functioning, social functioning, and general health.

Graves' ophthalmopathy causes worsening of quality of life because it disturbs the widely understood psychic and social sphere, and affects economic aspects of patients' and their families' lives.

In the analysed group of GO patients, no correlation was found between quality of life assessment and duration time of Graves' disease and ophthalmopathy. By contrast, in the research by Kaahaly G et al., the duration of the disease was longer, which was reflected in a more negative assessment of quality of life [16]. Ophthalmopathy symptoms reduce the differences in quality of life assessment resulting from age, sex, and duration of Graves' disease and eye changes.

A higher level of education of ophthalmopathy patients combines with higher assessment of quality of life. A similar correlation was observed by Terwee et al. [15].

Surprisingly, there is no correlation between quality of life assessed before the therapy, the disease activity (CAS), and the level of OI. One would expect that patients with very advanced and/or active disease would assess their quality of their life to be lower than those in whom pathological symptoms are less intensive. Our results, however, coincide with the results obtained by other authors who, using special questionnaires designed exclusively for GO patients, also did not note any correlation between ophthalmopathy activity or stage of development and quality of patients' lives [4, 5, 15].

The lack of such correlations probably proves that quality of life deteriorates considerably in the initial phase of the disease, before typical clinical symptoms of the infiltrative form of ophthalmopathy appear.

In GO patients, positive changes in quality of life were observed after oral treatment with steroids, orbital radiotherapy, and orbital decompression surgeries [17, 18].

In our research, the mean OI and CAS values considerably decreased after the six-week therapy. Additionally, a positive correlation was proven between CAS and OI. On the other hand, the patients perceived the quality of their lives as significantly better only when referring to physical role functioning, bodily pain, and vitality. A direct correlation between OI, CAS, and quality of life was not observed either.

To our amazement, the good results of ophthalmopathy treatment in the described group of patients was not reflected in a substantially improved quality of life. Perhaps the means of classification of the disease development and activity do not reveal the full range of the problem associated with the evaluation of patients' living comfort. On the other hand, one should remember the 6-week hospital stay of such patients, and the high doses of glucocorticoids administered in cycles and their influence on the central nervous system. Probably these factors also had an impact on the patients' perception and caused them to find very little improvement in their quality of life.

Conclusions

1. Graves' ophthalmopathy causes a considerable worsening of quality of life.
2. The stage of clinical development and activity of ophthalmopathy are not reflected in quality of life.
3. Effectiveness of treatment for ophthalmopathy cannot be evaluated based on changes in quality of patients' lives.

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