

Analysis of selected factors, including vitamin D₃ deficiency, affecting the quality of life of patients with rheumatoid arthritis

Analiza wybranych czynników, w tym niedoborów witaminy D₃, wpływających na jakość życia chorych na reumatoidalne zapalenie stawów

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Key words: rheumatoid arthritis, quality of life, vitamin D₃.

Słowa kluczowe: reumatoidalne zapalenie stawów, jakość życia.

Summary

Aim of the study: To evaluate quality of life of patients with rheumatoid arthritis (RA) and to determine the relationship between the quality of life (QoL) and age, disease duration and activity, joint damage and serum vitamin D₃ concentration.

Material and methods: 119 consecutive RA patients (107 women and 12 men, aged 59.7 ±11.7 years) treated in the Department of Internal Diseases and Rheumatology WIM CSK MON, in whom serum vitamin D₃ concentration was measured, were included in the study. The patients completed SF-36, the Beck Depression Inventory, the Health Assessment Questionnaire, and the severity of pain and general fatigue was determined on a visual-analog scale. Laboratory tests included: blood count, erythrocyte sedimentation rate (ESR), serum concentration of creatinine, calcium, phosphates and 25-hydroxycholecalciferol. Disease activity score (DAS28) was used to assess disease activity. In the statistical analysis the program Statistica version 10 was used.

Results: DAS28 was negatively correlated with the SF-36 and Beck depression scales. The patients with recent RA diagnosis had worse results than the other RA subjects in the depression scale and SF-36 domains associated with the impact of emotions and pain. The patients' age, disease duration, degree of joint damage and 25(OH)D₃ serum concentration did not correlate significantly with QoL indices.

Conclusions: Rheumatoid arthritis has an important impact on quality of life because of pain and physical impairment. The patients with recent RA diagnosis are more susceptible to suffer from increased pain and depressed mood than the patients with established disease. Disease activity has a weak negative influence on quality of life of RA patients. The role of vitamin D deficiency in deterioration of quality of life in RA needs further studies.

Streszczenie

Cel pracy: Zbadanie jakości życia chorych na reumatoidalne zapalenie stawów (RZS) oraz określenie jej związku z wiekiem, czasem trwania, aktywnością i stopniem zaawansowania choroby oraz stężeniem witaminy D₃ w surowicy.

Materiał i metody: Do badania zakwalifikowano kolejnych 119 chorych na RZS (107 kobiet i 12 mężczyzn w wieku 59,7 ±11,7 roku) leczonych w Klinice Chorób Wewnętrznych i Reumatologii WIM CSK MON, u których oznaczono stężenie witaminy D₃ w surowicy. Chorzy wypełnili kwestionariusze: SF-36, skalę depresji Becka, HAQ, oraz określili w skali VAS stopień nasilenia bólu i zmęczenia. W badaniach laboratoryjnych oznaczono: morfologię krwi obwodowej, odczyn Biernackiego, stężenie kreatyniny, wapnia, fosforanów i 25-hydroksycholekalcyferolu w surowicy. Aktywność choroby określono według wskaźnika DAS28. W analizie statystycznej zastosowano metodę Statistica wersja 10.

Wyniki: Wskaźnik DAS28 korelował ujemnie z wynikami skali SF-36 i skali Becka. Chorzy z niedawno rozpoznany RZS wykazywali gorsze wyniki w skali depresji i w podskalach SF-36 dotyczących wpływu emocji i bólu. Wiek chorych, czas trwania choroby, stopień uszkodzenia stawów oraz stężenie witaminy D₃ w surowicy nie korelowały istotnie ze wskaźnikami jakości życia.

Wnioski: Reumatoidalne zapalenie stawów wywiera znaczący wpływ na jakość życia poprzez ból i upośledzenie fizyczne. Chorzy z niedawno rozpoznany RZS częściej cierpią z powodu bólu i obniżonego nastroju niż chorzy przewlekle leczeni. Aktywność choroby wykazuje niewielki negatywny wpływ na jakość życia chorych na RZS. Konieczne są dalsze badania, aby określić znaczenie niedoboru witaminy D₃ dla jakości życia tych chorych.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes damage to joints, and sometimes other organs and systems, and, as a consequence, the deterioration of the physical ability of patients. The progressive nature of the disease may lead to deformities of the joints and disability. Symptoms from other organs and systems (anemia, interstitial pneumonia, exudates to serous cavities, vasculitis, Felty's syndrome) worsen the prognosis. Over the past decade evidence has emerged that early diagnosis and aggressive treatment can change a negative prognosis and stop the progression of the disease. Now the goal of treatment is to achieve remission, not to slow down the course of inflammation [1, 2].

In recent years apart from the physical aspects of the disease and the direct effects of therapy, less evident psychological, social and economic impact of the disease has been taken into account in research on treatment of chronic diseases. This perspective displays a more realistic picture of the problems associated with the disease, and allows us to assess treatment effects better. From the very beginning, the disease has a significant impact on all spheres of life: physical, emotional and social. It is accompanied by pain-related stress, fatigue and deterioration of physical function. Physical impairment in early RA is primarily associated with inflammation. In the advanced stages of the disease it also depends on joint destruction and organ complications. The activity of the disease and the degree of joint damage are therefore the main factors determining the patients' physical abilities. Functional impairment can be worsened by concomitant disorders. It is estimated that more than half of RA patients suffer from other chronic disease (cardiovascular diseases, diabetes, diseases of the respiratory system and gastrointestinal tract) [3].

Quality of life (QoL) of patients is affected by additional factors, such as age, gender, education, personality, environmental, social and economic conditions. Many standardized questionnaires are applied in the evaluation of QoL. They can be divided into two large groups: disease-specific and general. Among the disease-specific questionnaires the most widely used is the Health Assessment Questionnaire (HAQ). It is limited to assessment of the difficulty of daily physical activities. The HAQ consists of 8 groups of questions rated on a scale from 0 to 3. The highest score in questions from each group is taken into account, and then the average of the sum of the obtained points is calculated.

The world's most widely used generic scale is the Medical Outcome Study Short Form 36 (SF-36). The questions in this questionnaire have been chosen to not exhibit specificity for a particular disease, age of patients or treatment, and thus to enable comparison of results between differ-

ent groups of patients and different studies. The scale includes 36 questions grouped into 8 domains, representing the most frequently measured and most susceptible to changes in areas of QoL. These domains include general health perception (GH), physical functioning (PF), reduction in performing roles resulting from physical problems (RP), reduction in performing roles resulting from emotional problems (RE), social functioning (SF), physical pain (BP), vitality and mental health. The results are calculated according to a specific key for each scale separately, and then converted to percentages (expressed as a percentage of the maximum wellbeing in a given area) [4, 5]. The results can also be presented in the form of a summary of the two main domains: physical component (PCS) and mental summary (MCS).

One of the modifiable factors which may have an impact on the QoL of RA patients is vitamin D₃. The discovery of receptors for vitamin D in a number of immune system cells (lymphocytes, neutrophils, macrophages, and dendritic cells), and confirmation of the capacity of immune cells for local synthesis of the active metabolite of this vitamin, have led to the numerous studies on its role in regulating the immune response. It is suspected that vitamin D deficiency may increase the risk of various autoimmune diseases, including RA, and negatively affect the activity of RA [6–8]. In addition, many researchers have shown the association between vitamin D deficiency and chronic pain, skeletal muscle weakness, mood disorders and deterioration of cognitive function in the elderly [9–14]. It is possible that vitamin D deficiency can be associated with worsening of physical and emotional wellbeing of patients with RA.

The aim of the present study was to investigate the self-evaluation of the quality of life of patients with RA and to determine the relationship between the QoL and factors such as age, disease duration, disease activity, joint damage, as well as the serum vitamin D₃ concentration.

Material and methods

One hundred nineteen consecutive RA patients (107 women and 12 men) treated in the Department of Internal Diseases and Rheumatology WIM CSK MON from April 2011 to April 2013, in whom serum vitamin D concentration was measured during routine diagnostic procedures, were included in the study. The patients signed their written consent to answer the questionnaires and the study was approved by the local ethical committee. The mean age of patients with RA was 59.7 ± 11.7 years, and the mean disease duration was 10.2 ± 9.5 years (0.1–45 years). In 24 patients with RA the survey was performed before treatment or during the first weeks of treatment. The average age of these patients was 55.1 ± 10 years, and the average duration of symptoms of arthritis was 6 months (± 4 months). Four patients from this group fulfilled the

new ACR/EULAR criteria from the year 2010 [15]; the others met both the old (ACR 1987) and the new criteria [16]. During interviews with the patients data regarding disease duration, previous treatment, comorbidities, calcium and vitamin D supplementation, the frequency of being outdoors and physical activity were collected.

The patients completed the SF-36, Beck Depression Inventory and HAQ questionnaires, and the severity of pain and general fatigue was determined on a visual-analog scale (VAS). To calculate the grades of the SF-36 scale the rules developed for the Polish version of the scale by Tylka [17] were used. Then the results were recalculated as percentages assuming that 100% means maximum welfare in a given subscale. During the physical examination of patients with RA the number of tender and swollen joints was assessed. On this basis, and the values of the erythrocyte sedimentation rate (ESR), disease activity score (DAS28) was calculated. Laboratory tests included blood count, serum concentration of creatinine, calcium, phosphates and 25-hydroxycholecalciferol – 25(OH)D₃. For the measurement of 25(OH)D₃ we used an automated immunoassay (DiaSorin Liason). The degree of the radiological progression of RA according to Steinbrocker's scale was determined in 116 patients (radiographs of 3 patients were not available).

In the statistical analysis Statistica version 10 was used. The normality of the variables was checked using histograms and Kolmogorov-Smirnov or Shapiro-Wilk tests. Student's *t* test and one-way analysis of variance (ANOVA) were used for the comparison of independent variables. Pearson correlation was used for determining correlation. *P* values < 0.05 were considered statistically significant.

Table I. Comorbidities and organ complications in RA patients

Parameters	RA patients N = 119 (90% women)
hypertension	64 (53.8%)
coronary disease	13 (10.9%)
diabetes	15 (12.6%)
chronic kidney disease	5 (4.2%)
interstitial lung disease	8 (6.8%)
osteoporosis	39 (32.8%)
inflammatory bowel disease	2 (1.7%)
C1/C2 instability	4 (3.4%)

Results

Rheumatoid arthritis patients suffered from comorbidities such as hypertension (53.3%), osteoporosis (32.8%) interstitial lung disease, chronic kidney disease, nonspecific enteritis and instability in the atlanto-axial junction (Table I). Oral vitamin D₃ and calcium supplementation was reported by 51 (42.8%) RA patients. The mean serum concentration of vitamin D₃ was 15.2 ± 8 ng/dl (4–52.5). In this group 11 (9.2%) patients reported being outdoors for a few days a week, 6 (5%) patients stated they were outdoors a few times a month, and only two (1.7%) almost never went outside the house. The other RA patients reported being outdoors for a minimum of one hour a day. Despite this vitamin D deficiency occurred in 86 (72.3%) patients. Physical activity was quantified on a 5-grade scale from 0 (no exercises) to 5 (exercises at least 3 times a week for a minimum of one hour). Among RA patients 33 (27.7%) did not exercise at all, 25 (21%) exercised extensively, 48 (40.3%) occasionally or less intensely, and 13 patients (10.9%) did not respond to the question. The results of the Beck scale among patients with RA (33.6%) met the screening criteria for suspicion of depressive disorders. One of the RA patients was treated due to depression. The mean outcomes of SF-36 subscales and Beck's depression inventory are summarized in Table II.

Analysis of factors which may affect the quality of life of rheumatoid arthritis patients

Disease activity score (DAS28) was calculated for 113 RA patients (6 patients were excluded due to lack of data).

Table II. Mean values of SF-36 and Beck's depression scale and VAS fatigue in RA patients

Parameters	RA patients N = 119
general health (GH)	30.2 ± 15.8
physical performance (PF)	35 ± 23
role physical (RP)	22 ± 36
role emotional (RE)	51 ± 43.7
social functioning (SF)	55.8 ± 27
body pain (BP)	23.9 ± 24.6
vitality (VT)	50.8 ± 18.6
Becks' inventory	77.2 ± 15.2
VAS fatigue (mm)	58.5 ± 21

Values are converted to percentages of maximum possible wellbeing.

The mean DAS28 in the examined group was 4.09 ± 1.4 (1.85–7.45). A correlation of DAS28 with the physical ($r = -0.3, p = 0.002$) and mental component ($r = -0.25, p = 0.01$) of the SF-36 scale, as well as with the Beck's depression scale ($r = 0.3, p = 0.02$) was found. The physical component of the SF-36 scale scores strongly correlated with HAQ ($r = 0.7, p < 0.05$). There were no significant correlations of indicators of the QoL of patients with age and duration of disease (Figs. 1 and 2). Also the degree of joint damage according to Steinbrocker's scale did not differentiate patients in terms of QoL indicators (3 cases were excluded due to lack of up-to-date radiograms) (Table III).

Quality of life questionnaires were completed by 24 newly diagnosed RA patients with the scores of the patients treated for more than a year. Being newly RA diagnosed negatively affected Beck's depression scores and SF-36 domains associated with the impact of emotions and

pain on performance; however, the patients treated for more than a year expressed a higher degree of overall fatigue on a VAS scale (Table IV).

No relationship between serum vitamin D₃ concentration and the individual components of the QoL scales, severity of pain, fatigue and depression symptoms was found. There was a positive correlation between the vitamin D₃ concentration and regular physical activity ($p = 0.003$) (Fig. 3). An analysis of QoL of RA patients divided into four groups in accordance with the degree of vitamin D₃ deficiency was performed: a group with severe deficiency (0–10 ng/dl), medium deficiency (levels 11–19 ng/dl), with relative vitamin D₃ insufficiency (20–25 ng/dl), and with sufficient serum vitamin D₃ concentration (> 25 ng/dl). The patients with severe deficiency showed noticeably worse results on the SF-36 scale (especially in physical domains) and in the Beck Inventory compared with the patients whose concentration of 25(OH)D₃ was considered

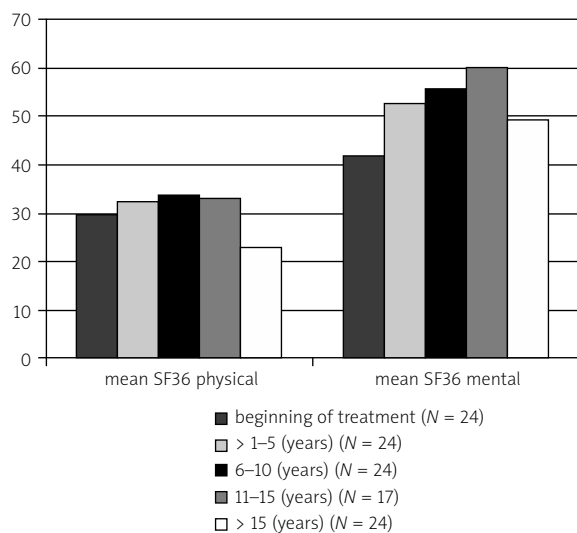


Fig. 1. PCS and MCS SF-36 domains in relation to disease duration.

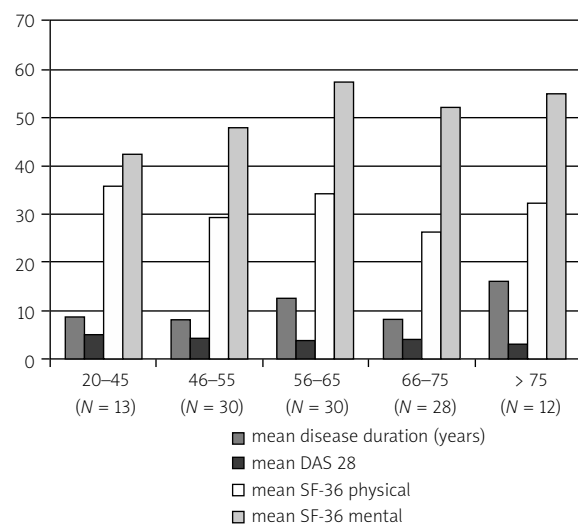


Fig. 2. The mean values of disease duration and activity, and SF-36 domains in different age ranges in RA patients.

Table III. The stage of joint destruction according to Steinbrocker's grading in relation to results of SF-36 scale

Steinbrocker's grade	RA patients N = 116*	Mean SF-36 values	SD	Mean SF-36 PCS values	SD
without radiographic changes	23 (19.8%)	38.8%	12.9	31.1%	6
1	19 (16.4%)	41%	11.5	29.1%	8.1
2	29 (25%)	36.8%	28	22.8%	24
3	19 (16.4%)	27%	17.5	26.6%	19.5
4	26 (22.4%)	30.4%	18	17.2%	14

*There were no available radiographs for 3 patients.

Table IV. Comparison of the QoL scales in RA patients before treatment and during prolonged therapy

Parameters	Patients before treatment, N = 24 (mean value and SD)	Prolonged therapy, N = 89* (mean value and SD)	Statistical significance
general health (GH)	30.5 ±18.7%	30.5 ±16.3%	
physical functioning (PF)	37.2 ±27.2%	34.7 ±22%	
role physical (RP)	22 ±32%	23 ±37%	
role emotional (RE)	33 ±39%	53.5 ±43%	p = 0.01
social functioning (SF)	45.5 ±32%	58.5 ±24%	
body pain (BP)	10.7 ±17.8%	27.8 ±25%	p = 0.049
vitality (VP)	43 ±17.8%	52.4 ±18.2%	
Beck depression score	19 ±13	13.3 ±8.7	P = 0.004
VAS fatigue	39 ±35 mm	59 ±21 mm	
HAQ	1.5 ±0.9	1.3 ±0.5	
DAS28	4.8 ±1.5	3.9 ±1.3	p = 0.005

*Six patients excluded because of lack of actual DAS28.

sufficient, but the differences did not achieve statistical significance (Figs. 4 and 5).

Discussion

In the present study we found that patients with RA rate lowly the QoL aspects associated with pain perception and physical activity, as well as (to a lesser extent) their overall health. The average value of mental scales (MCS) in RA patients was 51.8%, and was similar to values from general population studies [18, 19]. The mean value of the physical scale (PCS) was 30.8% – less than in a comparative study of Polish RA patients treated with traditional and biological therapy (39%) and more than in a study from Italy performed in RA patients treated with etanercept [18, 20]. The average disease activity (DAS28 4.9 vs. 4.1) was higher in patients in the latter study than in our work. The dif-

ference between the patients in the current study and the above-mentioned study done by Wysocka-Skurska *et al.* was associated with the impact of pain (BP).

In our study average BP was scored 22% (of maximum possible wellbeing), and in the cited study 56% (as in the general population); however, the average intensity of pain on a VAS scale was similar in both studies (52% vs. 58.6%). The researchers did not evaluate the disease activity, but the HAQ scale only (here the results were similar), so it is difficult to determine whether the activity of the disease could be the cause of the difference. Comparing the results of the SF-36 scale in the examined RA group to the average for the Polish population we did not find significant differences in the mental subscales; moreover,

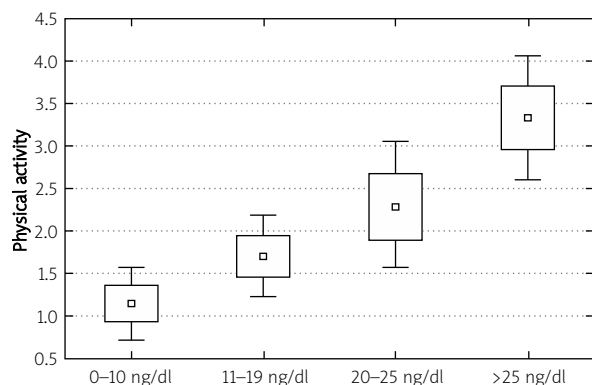


Fig. 3. Vitamin D₃ concentration ranges.

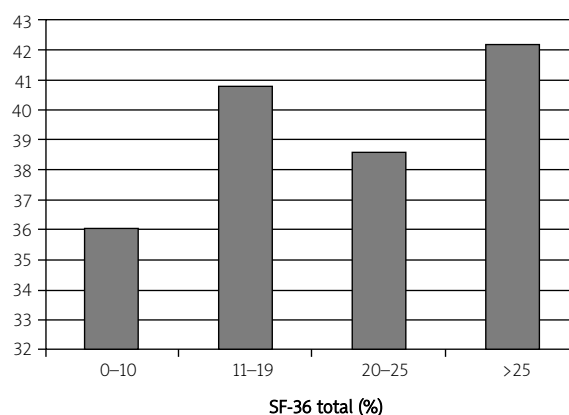


Fig. 4. Mean SF-36 values for patients with different 25(OH)D₃ serum concentration ranges.

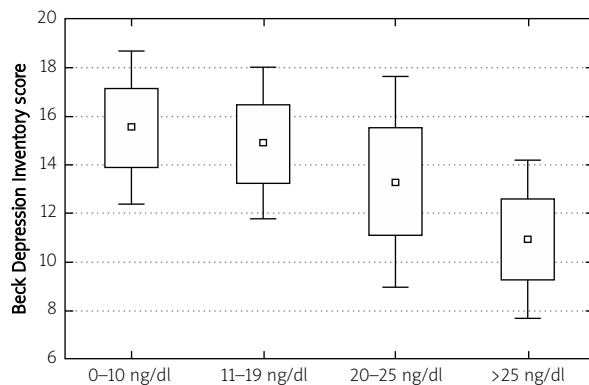


Fig. 3. Vitamin D₃ concentration ranges.

RA patients from our study showed better results in the scale of social contacts (mean SF 55.8% vs. 46%). Differences were found only in physical subscales (GH 30.2% vs. 48.67%, PF 35% vs. 56%, RP 22% vs. 45.6%, BP 22% vs. 55.75%) [19].

Similar results to those presented, but measured by the scale WHOQOL BREF, were published by Sierakowska *et al.* In their study also RA patients achieved the highest scores in the domains of social contacts and the lowest scores in the domains of physical functioning [21]. In the present study we have found no relationship among disease duration, articular lesions, age of patients and indices of QoL. It can be presumed (Fig. 1) that initially lowered QoL indicators gradually improve during treatment (this concerns especially the mental sphere), to deteriorate only after many years of illness. This conclusion has already been presented by other authors. It is in concordance with the observation that the rapid progression of the disease occurs in the early years of its duration, then the course of the disease is slower. In addition, patients gradually adapt to the situation of living with a chronic disease [22, 23].

In this study, patients with an early form of RA had significantly higher indicators of disease activity, the degree of pain and at the same time, worse results in most scales that measure mental and social welfare. It may be an expression of an adaptive response to the deterioration of the health status and information of chronic character of the disease. These patients would require more attention from the doctor to reduce anxiety, uncertainty and fear about the future. In a study carried out in Sweden, the patients diagnosed with early RA showed significantly worse outcomes in all domains of the SF-36 scale in comparison to persons suffering from RA for more than twenty years. Not until two years of illness did those indices improve and achieve the same level as in long-lasting disease [24]. Some authors claim that the degree of physical and emotional problems faced by patients within the first 18 months of

RA is comparable to patients with heart failure or newly detected diabetes [25].

The disease activity in our study correlated with QoL indices, but at a fairly low level, reflecting no more than 10% of the variability of indicators. Similar results were obtained in other studies. A negative correlation (-0.37) between physical domains of WHOQOL and DAS28 was demonstrated in the study published by Haroon *et al.* [26]; however, after adjustment to HAQ scores the relation turned out to be insignificant. Researchers from Australia reached similar conclusions. They performed a multicenter trial to find out which of the existing questionnaires best reflects the physical domain of the QoL in patients with RA [27]. The highest level of correlation with SF-36 physical scales (PCS) was observed for the HAQ questionnaire (it explained about 62% of the variation of the functional scale). The second in order, but with a much lesser importance, was DAS28 ($< 10\%$ of the variation). The number of tender and swollen joints and inflammation indicators counted separately had a minimal influence on PCS.

We failed to demonstrate a statistically significant correlation between vitamin D deficiency and QoL; however, we showed that the patients with severe vitamin D deficiency are characterized by lower values of the PCS and higher values on depression scales than patients with an appropriate serum concentration of vitamin D. Currently, it is considered that the optimal concentration of 25(OH)D₃ is approximately 30 mg/dl, while the previously accepted value of 20 mg/dl is already a limit below which a growing risk of osteomalacia occurs [28].

In our study only a few patients achieved the "optimal" vitamin D level. If the relationship is non-linear in nature, it cannot be demonstrated without a sufficient sample of subjects which vitamin D₃ concentration is within normal limits. The other weakness of our study is that the serum vitamin D₃ was measured only once and we did not adjust the results to the seasons of the year. An additional factor that could interfere with our results was the fact that the patients in advanced stages of RA, with concomitant osteoporosis and potential physical disability, were less likely to be vitamin D deficient due to systematic vitamin D supplementation. In addition, some patients did not remember what type of oral vitamin D they received (some of them could have taken 1(OH)D₃, concentrations of which were not measured). The correlation between serum vitamin D₃ concentration and physical activity can indirectly indicate the importance of this vitamin for overall strength and vital energy, but it can also be the simple result of exercising outdoors (the patients were not asked about the type of exercise performed). An observational study is planned, which will help to clarify whether the optimal concentrations of vitamin D₃ will improve the quality of life of patients with RA.

Conclusions

Rheumatoid arthritis has an important impact on quality of life of patients, especially because of pain and difficulty in performing physical tasks. Patients with recent RA diagnosis are more likely to suffer from increased pain and depressive mood than patients with established disease. There were no significant correlations of indicators of QoL with age, disease duration, joint damage and 25(OH)D₃ serum concentration. We found a weak negative correlation between disease activity (measured with DAS28) and both physical and mental domains of the SF-36 scale, as well as with Beck's depression scale.

The authors declare no conflict of interest.

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