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Vitamin D status and disease activity in patients with rheumatoid arthritis

Witamina D i aktywność choroby u pacjentów z reumatoidalnym zapaleniem stawów

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rheumatoid arthritis, disease activity, vitamin D deficiency

Słowa kluczowe

reumatoidalne zapalenie stawów, aktywność choroby, niedobór witaminy D

Summary

Introduction. Vitamin D is a strong immunomodulator and the role of vitamin D deficiency in the pathogenesis of rheumatoid arthritis (RA) and the course of RA are still not well recognized.

Aim. The aim of the study was to describe the associations between serum level of 25-hydroxyvitamin D and disease activity in patients with rheumatoid arthritis (RA).

Material and methods. The study group comprised 93 patients aged 27-80 years suffering from RA (74.2% women) and 93 controls.

Results. In general, 54.8% of RA patients revealed vitamin D deficiency, and 37.6% – vitamin D insufficiency. No significant difference was found when mean serum 25(OH)D levels in RA patients and healthy controls where compared. 25(OH)D levels appeared markedly lower in patients with the highest activity of RA compared to values noted in patients with the minimal RA activity (16.55 ± 9.26 vs. 22.59 ± 9.74 ng/ml, $p < 0.05$). In RA patients 25(OH)D levels were significantly and negatively associated with markers of disease activity: DAS28-ESR ($\beta = -0.33$; 95% CI = 0.05; -0.01), CRP ($\beta = -0.23$; 95% CI = -0.72; 0.00), and ESR ($\beta = -0.26$; 95% CI = -0.78; -0.10). All these associations remained statistically significant after adjustment for gender, age and BMI. Vitamin D deficiency should be considered as an important predictor of the high RA activity (AUROC = 0.67; 95% CI = 0.513-0.83; $p = 0.05$).

Conclusions. Optimal vitamin D status should be obtained and maintained during RA course.

Streszczenie

Wstęp. Witamina D stanowi istotny czynnik immunomodulacyjny, a rola deficytu witaminy D w patogenezie i przebiegu reumatoidalnego zapalenia stawów (RZS) nie jest ostatecznie zbadana.

Cel pracy. Głównym celem badania było określenie relacji pomiędzy stężeniem 25(OH)D w surowicy oraz aktywnością choroby u pacjentów z reumatoidalnym zapaleniem stawów (RZS).

Materiał i metody. Do badania włączono 93 pacjentów w wieku 27-80 lat, wśród badanych 74,2% stanowiły kobiety. Grupę kontrolną stanowiło 93 praktycznie zdrowych osób.

Wyniki. W ujęciu ogólnym 54,8% chorych na RZS ujawniło niedobór witaminy D, a 37,6% jej deficyt. Stężenia 25(OH)D były wyraźnie niższe u pacjentów z najwyższą aktywnością RZS w porównaniu z wartościami pacjentów z minimalną aktywnością RZS (16,55 ± 9,26 ng/ml vs. 22,59 ± 9,74 ng/ml; $p < 0,05$). Nie zaobserwowano istotnej różnicy między średnim stężeniem 25(OH)D pacjentów z RZS a grupą kontrolną. Odnotowano istotną ujemną zależność między stężeniem 25(OH)D a wskaźnikami aktywności choroby, która zwiększyła się po uwzględnieniu wieku, płci i BMI pacjentów RZS: DAS28-ESR ($\beta = -0,33$; 95% CI = -0,05; -0,01), CRP ($\beta = -0,23$; 95% CI = -0,72; 0,00) oraz ESR ($\beta = -0,26$; 95% CI = -0,78; -0,10). Niedobór witaminy D powinien być traktowany jako ważny czynnik prognostyczny dla wysokiej aktywności RZS (AUROC = 0,67; 95% CI = 0,513-0,83; $p = 0,05$).

Wnioski. W przebiegu RZS istotne jest uzyskanie i utrzymanie optymalnego zaopatrzenia w witaminę D.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Taking into consideration that vitamin D deficiency is associated with an exacerbation of Th1-mediated immune response, the role of vitamin D deficiency in the pathogenesis of rheumatoid arthritis (RA), and the effect of vitamin D on the progress and treatment of RA are extensively examined (1-4).

RA is an autoimmune disease with a complex cascade of pathophysiological components. RA mainly affects the synovial membrane of the joints, which is infiltrated with neutrophils, macrophages, T and B lymphocytes, dendritic cells, all together leading to its gradual damage (5, 6). Despite numerous studies the causes of "abnormal" immune activation have not been established to date. However, the role of some risk factors playing an important role has been proven (7). In particular, the number of publications supporting the hypothesis that vitamin D deficiency affects the development of RA increases (8, 9). At present it is believed that calcitriol inhibits the processes of cartilage destruction by IL-1β-mediated production of matrix metalloproteinase and, therefore vitamin D deficiency can be regarded as one of the potential triggers of the cartilage destruction in RA (10).

AIM

Therefore the aim of the study was to describe the associations between serum level of 25-hydroxyvitamin D [25(OH)D] and disease activity in patients with rheumatoid arthritis.

MATERIAL AND METHODS

93 patients with RA aged 27 to 80 yrs who were admitted to the rheumatology department of Lviv regional clinical hospital with exacerbation of RA were examined. The diagnosis of RA was made under classification criteria as defined by American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) (2010) (11), and Ukrainian adapted clinical guidelines "Rheumatoid arthritis" (2014) (12).

The research was conducted in October and November, 2015. The majority of RA patients in this study were females (74.2%). The mean age of male was (53.3 ± 12.1 yrs) was not different from that in female group (53.4 ± 11.2 yrs; $p > 0.05$). Patients with other inflammatory diseases, thyroid or parathyroid gland diseases, other endocrine disorders or serious liver or kidney diseases were excluded.

All the patients were diagnosed with the joint type of RA. 72 patients (77.4%) were diagnosed with seropositive type of RA. The average duration of disease was 8.6 ± 6.0 years.

Control group consisted of 93 practically healthy persons who took part in epidemiological study in Lviv region which was conducted in May and June 2010-2012.

All patients underwent clinical and biochemical blood test. The levels of rheumatoid factor (RF) and C-reactive protein (CRP) were measured by immunoturbidimetric assay. Anti-cyclic citrullinated peptide antibodies (A-CCP) were determined by flow cytometry. Erythrocyte sedimentation rate (ESR) was measured by Westergren method. DAS28-ESR was calculated using a formula that includes ESR value and the number of swollen and painful joints by the 28/28 scale (DAS28) (13, 14). The level of 25(OH)D in the serum was measured using electroluminescence method. The optimal vitamin D supply was defined when serum 25(OH)D level was 30-50 ng/ml, vitamin D insufficiency and deficiency were noted for 25(OH)D levels between 20-30 ng/ml and for 25(OH)D levels lower than 20 ng/ml, respectively (15).

This study was performed according to the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Lviv Regional Clinical Hospital and State Institution "D. F. Chebotarev Institute of Gerontology" NAMS Ukraine. Each participant provided written informed consent.

Statistical analyzes were performed using software "Statistica 7.0" and SPSS version 17. The results are presented as the mean and standard deviation (M ± SD). The test for normality of distribution of the sampling was carried out by the Kolmogorov-Smirnov test. The subgroup differences were assessed by one-way ANOVA test adjusted by Scheffe. Univariable and multifactor linear regression models were used to determine the associations between 25(OH)D and outcome measures (markers of diseases activity) before and after adjustment for a age, sex and body mass index (BMI). Confidence interval (95% CI) was determined separately for each of these parameters. Receive operating characteristic (ROC) curves were used to determine the optimal vitamin D cutoff points for identifying disease activity. Youden's index (J) was used to determine the optimal cutoff point. P value less than 0.05 was considered statistically significant.

RESULTS

The evaluation of serum 25(OH)D levels in patients with RA found that 54.8% of patients had vitamin D deficiency, 37.6% revealed vitamin D insufficiency, and up to 14.0% had severe vitamin D deficiency [serum 25(OH)D levels < 10 ng/ml]. No significant difference was noted in serum 25(OH)D levels of RA patients and controls. RA patients had significantly lower body weight and BMI compared to controls. 74.2% of patients with RA declared an intake of calcium and vitamin D supplements (tab. 1). Table 2 provides clinical and laboratory characteristics of patients with RA in relation to the disease activity.

Tab. 1. General characteristics of studied groups

Variable	Patients with RA, n = 93	Control group, n = 93	P-value
Age [years]	53.41 ± 11.33	51.37 ± 12.71	–
Height [cm]	162.87 ± 8.42	163.15 ± 7.34	–
Weight [kg]	70.15 ± 15.15	75.16 ± 13.25	0.02
BMI [kg/m^2]	26.54 ± 5.78	28.20 ± 4.43	0.03
Number of patients taking vitamin D supplements [%]	74.2	0	0.001
25(OH)D [ng/ml]	19.18 ± 9.18	18.87 ± 8.91	–

Tab. 2. Clinical and laboratory characteristics of patients with RA, depending on disease activity

Variable	Disease activity, degree		
	I (n = 18)	II (n = 48)	III (n = 27)
Age [years]	48.44 ± 10.34	54.46 ± 10.21	54.85 ± 13.22
Disease duration [years]	8.67 ± 4.55	9.22 ± 6.72	7.40 ± 5.46
Duration of morning stiffness [min]	83.33 ± 65.00	177.36 ± 125.17	193.13 ± 127.83
Number of painful joints	48.78 ± 9.56	49.14 ± 12.0	53.23 ± 9.55
Number of swollen joints	36.40 ± 17.35	40.98 ± 15.99	41.67 ± 13.69
Mean dose of methotrexate [mg]	12.72 ± 2.93	11.16 ± 2.59	12.12 ± 2.86
Mean dose of prednisolone [mg]	7.25 ± 4.84	9.12 ± 3.74	11.70 ± 6.07*
ESR [mm/h]	12.83 ± 7.03	23.77 ± 9.44***	45.37 ± 12.79***
CRP [mg/l]	422 ± 3.67	16.76 ± 23.86**	69.60 ± 101.64**
DAS28-ESR	6.13 ± 0.61	6.71 ± 0.70*	6.89 ± 1.03**
Hb [gl]	127.28 ± 14.38	122.73 ± 16.46**	110.52 ± 16.50**

The significant difference of values compared with patients who had I degree of RA activity (*p < 0.05, **p < 0.01, ***p < 0.001).

Patients with the first degree of RA activity had significantly higher serum 25(OH)D levels compared to those with the III degree of RA (22.6 ± 9.7 vs. 16.5 ± 9.3 ng/ml; p < 0.05), and did not significantly differ from patients with the II degree of RA activity (19.4 ± 8.6 ng/ml; p > 0.05). The risk of a high RA activity appeared significantly increased when the level of 25(OH)D was lower than 20 ng/ml [OR = 3.00 (95% CI = 1.01-8.86; p < 0.05)].

Table 3 shows the clinical and laboratory characteristics in relation to 25(OH)D levels. 25(OH)D levels were significantly associated with number of painful and swollen joints, DAS28-ESR, CRP and ESR, Hb. There was no effect of 25(OH)D level on A-CCP and RF levels. Taking into account that age, gender and BMI of patients affect the vitamin D level the multifactor linear regression model was used to study the effect of serum 25(OH)D on the RA activity with the adjustment of the above mentioned parameters (age, gender and BMI). As shown in table 3, associations between serum 25(OH)D level and clinical and biochemical data of RA activity increased after adjustment for age, gender and BMI.

Tab. 3. The associations between clinical and biochemical variables (depended variables) and serum 25(OH)D level (independent variable) in patients with RA, β (95% CI)

Variable	Univariable	Multivariable*
Disease activity	-0.22 (-0.03; -0.00)	-0.23 (-0.03; 0.00)
Number of painful joints	-0.21 (-0.18; 0.00)	-0.27 (-0.21; -0.02)
Number of swollen joints	-0.20 (-0.28; +0.07)	-0.28 (-0.35; -0.04)
DAS28-ESR	-0.33 (-0.05; -0.01)	-0.40 (-0.06; -0.02)
CRP [mg/l]	-0.23 (-0.72; +0.00)	-0.28 (-0.83; -0.03)
ESR [mm/h]	-0.26 (-0.78; -0.10)	-0.27 (-0.84; -0.07)
Hemoglobin [g/l]	0.28 (0.15; 0.90)	0.22 (0.02; 0.80)

*adjusted for age, gender and BMI patients

The 25(OH)D threshold level value for prognosis of the third degree of RA activity was calculated using ROC-analysis and Youden's index applied for. Figure 1 presents a results of the ROC analysis. The area under the ROC-curve (AUROC) was 0.67 (95% CI = 0.513-0.83; p = 0.05). According to the results, Youden's index corresponded to 19.7 ng/ml, i.e. the 25(OH)D levels in RA patients of 19.7 ng/ml or lower can be considered as a reliable predictor of high activity of rheumatoid arthritis.

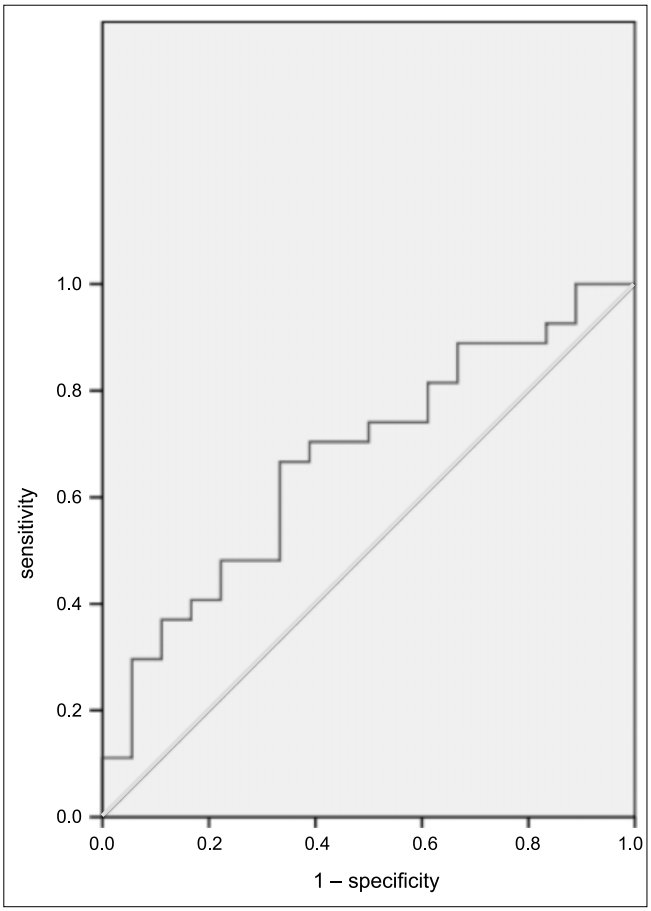

Fig. 1. ROC-curve to determine the optimal threshold value of serum 25(OH)D level in prognosis of the III degree of RA activity (J = 19.66 ng/ml)

DISCUSSION

Our study revealed that vitamin D deficiency and insufficiency are highly prevalent in patients suffering from RA. It was found that 54.8 and 37.6% of patients included to our study had vitamin D deficiency and insufficiency, respectively. Further, the mean serum 25(OH)D levels in RA group appeared very similar in healthy controls, extending the vitamin D deficiency problem for general population living in Ukraine, or at least in Lviv area. Our findings are in contrast to other studies that documented significantly reduced 25(OH)D levels in the course of RA, compared to healthy controls (16-18). In our study conditions healthy controls were not strictly matched to RA patients; controls had higher body weight and BMI and did not use supplements. The before mentioned factors most likely underlie the lack of significant difference in 25(OH)D levels between study groups.

Patel et al. found the correlation between serum 25(OH)D level in patients with early inflammatory arthritis and levels of CRP, DAS28, HAQ and the number of painful joints (19). The study in Finland among 143 women with RA showed the lowest serum 25(OH)D level in patients with the highest disease activity (20). Haque et al., found that only during the exacerbation of RA (DAS28 above 2.6 points) there was a negative correlation between serum 25(OH)D level and markers of disease activity (DAS28, the intensity of pain syndrome and the HAQ index) (21).

Azzeh et al. considered serum 25(OH)D level as a good predictor of RA disease activity in Saudi patients. They found that the corresponding values of vitamin D for high disease activity (DAS28 > 5.1) and low disease activity (DAS28 $\leq$ 3.2) are $\leq$ 12.3 ng/ml and $\geq$ 17.9 ng/ml, respectively (22). In our study serum 25(OH)D level 19.7 ng/ml or lower was considered as a predictor level of high activity of rheumatoid arthritis.

CONCLUSIONS

1. In patients with rheumatoid arthritis vitamin D deficiency and insufficiency are highly prevalent (54.8 and 37.6%, respectively).
2. Negative relationship between serum 25(OH)D and biochemical and clinical variables of RA activity was determined.
3. Vitamin D deficiency can be regarded as a reliable predictor of high activity of rheumatoid arthritis [AUROC = 0.67 (95% CI = 0.513-0.83; p = 0.05)].

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