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THE ROLE OF VITAMIN D IN MULTISYSTEM SARCOIDOSIS

ULOGA VITAMINA D U SARKOIDOZI

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Summary: Recently published data indicate that vitamin D abnormalities are common in sarcoidosis patients. The purpose of this study was to compare serum vitamin 25(OH)D levels among sarcoidosis patients with different clinical courses of the disease. The study also included the first observations on cognitive functions (i.e. depression and fatigue syndrome) in relation to vitamin D deficiency in sarcoidosis patients. At the Biochemical Laboratory of the Clinical Center of Serbia, Belgrade, vitamin D25(OH)D was measured using the Elecsys® Vitamin D total test. A total of 226 patients with biopsy-positive sarcoidosis were analyzed. The average median value of serum vitamin D was 9.47 μg/L, suggesting severe deficiency. Statistically significant correlation was found in patients with chronic disease and low levels of serum vitamin 25(OH)D (Chi-Square=6.044; df=2; p=0.014). The patient group with vitamin D serum levels higher than 20 μg/L showed higher levels of the mean forced vital capacity (FVC) by 380 mL, and forced expiratory volume in one second (FEV1) by 220 mL, when compared to the patient group with lower serum vitamin D. A statistically significant role was established for serum vitamin 25(OH)D levels as the predictor of fatigue (R^2=0.878; p=0.038 (β=0.216)) and depression in patients with sarcoidosis (R^2=0.80; p=0.000 (β=0.391)). The insufficiency of 25(OH)D seems to be an important factor in predicting the course of chronic disease, significant lung function impairments and cognitive failures such as fatigue and depression. The fact that the majority of the analyzed sarcoidosis patients had totally deficient serum 25(OH)D levels made this finding even more notable.

Keywords: vitamin D, deficiency, sarcoidosis

Kratak sadr`aj: Nedavno objavljena istraživanja kod obolelih od sarkoidoze govore o čestim abnormalnim vrednostima vitamina D. Cilj ove studije bio je da se uporedi nivo vitamina 25(OH)D kod obolelih od sarkoidoze sa različitim kliničkim tokom bolesti. Takođe, ova studija predstavlja prva zapažanja o vezi između kognitivnih funkcija (odnosno osećaja depresije i zamora) i deficita vitamina D kod obolelih od sarkoidoze. U Biohemijskoj laboratoriji Kliničkog centra Srbije vitamin D – 25(OH)D meren je korišćenjem testa Elecsys® Vitamin D. Analizirano je 226 bolesnika sa sarkoidozom potvrđenom biopsijom. Prosečna srednja vrednost vitamina D u serumu bila je 9,47 mg/L, što ukazuje na ozbiljan nedostatak. Statistički značajna korelacija nađena je kod pacijenata sa hroničnom formom bolesti i niskim nivoom vitamina 25(OH)D u serumu (Xi-kvadrat=6,044; df=2; p=0,014). Grupa pacijenata sa nivoom vitamina D u serumu većim od 20 mg/L pokazuje veći nivo srednjeg forsiranog vitalnog kapaciteta (FVC) za 380 mL i forsiranog ekspiratornog volumena u prvoj sekundi (FEV1) za 220 mL u odnosu na grupu pacijenata sa nižim nivoom D vitamina. Utvrđeno je da nivo vitamina 25(OH)D u serumu ima statistički značajnu ulogu kao prediktor zamora i depresije kod obolelih od sarkoidoze. Insuficijencija 25(OH)D vitamina pokazala se kao važan faktor u predviđanju toka hronične bolesti, značajnih oštećenja plućne funkcije i kognitivnih poremećaja kao što su zamor i depresija. Činjenica da većina ana liziranih bolesnika sa sarkoidozom ima potpuni nedostatak 25(OH)D u serumu učinila je takav nalaz još bitnijim.

Klju~nere~i: vitamin D, nedostatak, sarkoidoza

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Introduction

Sarcoidosis is a multisystem granulomatous disease characterized by non-caseating granulomas infiltrating the affected organs. The disease predominantly involves the lungs, lymph nodes and skin, organs that are the entry points for many immunologically active factors. The cause of the disease and the prognosis are unknown. The diagnosis is usually made on the basis of clinical presentation and radiological imaging and definitely confirmed by histologic evidence of non-caseating granulomas in the absence of other possible causes of sarcoid-like granulomas (1).

There are some important reflections associated with vitamin D in sarcoidosis; the observations are not due merely to secondary osteoporosis or calcium metabolism disorders, as would be expected, but to immune response in general, thus leading inevitably to the discussion on vitamin D and its role not only in bone health issues in sarcoidosis but beyond. Recently, many effects of vitamin D have been shown to occur outside the feedback control of the osseous – endocrine loop; these effects are also independent from serum calcium, phosphorus or PTH levels (2).

The relation of vitamin D and human health has been attracting much interest of late. The number of publications reveals the vitamin D deficiency has been associated with many non-skeletal conditions such as cancer, autoimmune diseases, metabolic syndrome, cardiovascular diseases and respiratory disorders (3, 4). Large prospective clinical studies of autoimmune diseases like RA (5) and type I diabetes (6) propose an important role for vitamin D as a regulating factor in autoimmune diseases; on the contrary, up to date, this role of vitamin 25(OH)D has not been well studied in sarcoidosis.

The purpose of this study was to compare serum vitamin 25(OH)D levels among our sarcoidosis patients with different clinical courses of the disease in relation to vitamin 25(OH)D levels among cases. The study also included the first observations on the neuropsychological functions (i.e. feeling of depression and the fatigue syndrome) in the light of vitamin D deficiency in sarcoidosis patients.

Vitamin D in sarcoidosis – historical glimpse

Vitamin D was discovered as a dietary constituent (from cod liver oil) that helped in protecting against and healing the bone disease known as rickets (3–6). In humans and other mammals vitamin D is also made in the skin by exposure to sunshine, hence its nickname »the sunshine vitamin«. Vitamin D insufficiency related to chronic diseases has become a worldwide problem (7–11).

The relationship between vitamin D and sarcoidosis was first recognized by Harrell and Fisher in 1939 (12). They described the occurrence of hypercalcemia in 6 of 11 patients with sarcoidosis. More than seven decades ago, these authors made three important observations:

1. Hypercalcemia is a feature of sarcoidosis
2. Consuming a vitamin D rich diet results in worsening hypercalcemia
3. Vitamin D might be related to calcium abnormality in sarcoidosis.

Twenty years later, Henneman et al. (13) observed that the clinical manifestation of hypercalcemia in sarcoidosis is a form of vitamin D intoxication, and thus established that the hormone is produced at an extrarenal site. Despite the normal physiological conditions under which the synthesis of calcitriol occurs entirely in the kidney, Singer and Adams (14) showed that it is the calcitriol [1,25(OH)2D] which causes hypercalcemia in sarcoidosis and that macrophages from patients with active sarcoidosis are the synthetic source of the hormone.

Vitamin D and sarcoidosis – novel observations

Recently published data indicate that in sarcoidosis patients vitamin D abnormalities are common. The majority of patients with sarcoidosis have symptoms associated with vitamin D deficiency such as: symptomatic osteomalacia with bone pain, the sensation of fatigue and exhaustion (15, 16). A recent review by Burke and co-workers (17) evaluated the levels of vitamin D in patients with sarcoidosis. They found that 49% of patients had vitamin D levels below 10 ng/mL. Although most of the patient population was vitamin D deficient, 71% of patients had normal values of the active form of vitamin 1,25(OH)2D. In patients with sarcoidosis (most of them) there are normal serum levels of active calcitriol but low levels of inactive vitamin 25(OH)D (18).

The role of vitamin 1,25(OH)2D in sarcoidosis

The raised levels of calcitriol in sarcoidosis may represent a favorable response, thus emphasizing the immunoregulatory properties of vitamin 1,25(OH)2D (19).

High affinity receptors for calcitriol–vitamin D receptors (VDRs) are present on dendritic cells, lymphocytes and macrophages – the key immune effector cells in sarcoidosis. Calcitriol has been shown to downregulate the activation and proliferation of lymphocytes through inhibition of interleukin-2 (IL-2) and interferon-gamma (IFN-γ) (20). Cytokines such as IFN-α are also produced by dendritic cells at the site of inflammation. The expression of IFN-γ is downregulated by vitamin D which may have a task to decrease inflammation in patients with autoimmune disease (21). The same may be possible in patients

with sarcoidosis; however, these mechanisms have not been completely elucidated yet in sarcoidosis.

The vitamin 1,25(OH)2D is released by the sarcoid granulomas, the sites of autonomous conversion of vitamin 25(OH)D to vitamin 1,25(OH)2D. The level of calcitriol is positively correlated with the disease activity (21, 22). Elevated levels of vitamin 1, 25(OH)2D downregulate dendritic cells leading to attenuation of the immune response. Severe vitamin D deficiency is thought to sensitize the antigen-presenting capacity of dendritic cells (21). High activity of dendritic cells could direct the immune response toward endogenous body molecules thus leading to autoimmune diseases such as systemic lupus erythematosus (21) or even sarcoidosis (18).

Vitamin 25(OH)D in sarcoidosis

There is another possible condition in the pathogenesis of sarcoidosis related to vitamin D activity: granuloma formation is the result of a defect in innate immunity that fails to overcome an infection like mycobacterial infection; so instead of the appearance of granulomatous caseating tuberculosis, the body forms another granulomatous response – non-caseating sarcoidosis. This defect has been linked to vitamin D deficiency according to Richmond and Drake (24).

Vitamin D-25 is the major circulating form of vitamin D and the form that is measured to evaluate the adequacy of vitamin D intake (4). There are several reasons for this: first, 25(OH)D is the best available clinical indicator of vitamin D status (25). Normal or elevated 1,25(OH)2D (calcitriol) is present in patients with vitamin D deficiency due to secondary HPT (26). Vitamin D produced in the skin or ingested is rapidly converted to 25(OH)D (26). Only a very small fraction of the 25(OH)D is converted to 1,25(OH)2D, so despite being the active metabolite, calcitriol does not reflect the body stores of vitamin D (26). What is very important is that vitamin 25(OH)D has a much longer half-life compared to 1,25(OH)2D (3 weeks vs. 3–4 hours) (27). Besides, vitamin 25(OH)D is a very stable metabolite in serum (25).

There is no standard definition of vitamin D deficiency, but some reports suggest that a level of the inactive form of vitamin 25(OH)D below 25 nanograms per milliliter (ng/mL) indicates deficiency (4, 20).

Methods and Study Design

A total of 226 patients with biopsy -positive sarcoidosis were included in the study. The very day the blood samples for vitamin 25(OH)D analyses were obtained, the information about the disease: course, duration and the time of diagnosis, were recorded as well. A high serum chitotriosidase level besides the clinical and radiological parameters was considered as an attribute of active sarcoidosis. An elevated 24 hour/urine calcium level was also considered as a parameter of active disease.

In order to analyze the potential influence of vitamin D and the possible correlation of low concentrations of vitamin 25(OH)D with the lung function parameters, on the same day spirometry was performed at the Department for Lung Function Investigation, Clinical Center of Serbia, Belgrade. All measures were expressed as a percentage of the reference values. The European Respiratory Society criteria for bronchial obstruction were used to assess patients with obstructive lung function impairments (28).

As to our knowledge, the possible role of vitamin 25(OH)D in neuropsychological functioning in sarcoidosis patients was analyzed for the first time in this study. On the same day the blood samples were taken for analyzing the vitamin 25(OH)D serum levels, patients completed two different questionnaires: one for evaluating the sensation of fatigue – Fatigue Assessment Scale (FAS), the other for evaluating the feeling of depression – Center for Epidemiologic Studies – Depression Scale (CES-D). Both questionnaires have already been used in the studies on cognitive functioning in sarcoidosis patients, and have been validated in sarcoidosis.

FAS is a 10 items questionnaire to assert fatigue; five questions reflecting physical fatigue and five questions for mental fatigue. The response scale is a 5-point scale (1–never to 5–always). Scores on the FAS can range from 10 to 50. A score of 22 and beyond indicates fatigue (29).

The full CES-D is a 20 items self-report scale designed to measure the presence and degree of depressive symptomatology in broad-based survey research populations. The rating scale ranged from 1 – seldom or never, to 4 – almost always. A total score of 16 or higher indicates depression (30, 31).

At the Biochemical Laboratory of the Clinical Center of Serbia, Belgrade, vitamin D -25(OH)D was measured using the Elecsys® Vitamin D total test. The test is based on the electro-chemo-luminescence method (ECLIA). The commercial reagents used were produced by Roche Diagnostics–Elecsys ® Vitamin D total (REF 05894913190), Roche Diagnostics GmH, Mannheim, Germany. Following the reference values, serum vitamin 25(OH)D levels were defined as:

A) Severe deficiency: a serum level of vitamin 25(OH)D<10 μg/L;
B) Insufficiency: a serum level of vitamin 25(OH)D 10 mg/L – 30 μg/L
C) Sufficient: a serum level of vitamin 25(OH)D >30 μg/L
D) Toxicity: a serum level of vitamin 25(OH)D >100 μg/L.

Patients

Two hundred twenty-six patients with biopsy-positive sarcoidosis were analyzed; 163 female/63 male, mean age 48 ± 11 years. Considering the stage of lung disease the patients were divided into a group without parenchymal lesions, stage 0–1 of the lung disease (140 patients) and a group with parenchymal lesions, stage 2– 4 of the lung disease (85 patients). In the analyzed group 57 (25.2%) were patients with acute sarcoidosis and 168 (63.7%) patients with chronic disease.

Acute sarcoidosis was defined as a form of the disease that persisted for less than 2 years; the type of the disease that sometimes has an abrupt onset (with symptoms like erythema nodosum, polyarthralgia and bilateral hilar adenopathy and occasionally diffuse parenchyma infiltration) but tends to remit spontaneously.

Chronic sarcoidosis we defined as a form of the disease with both symptoms and signs of sarcoidosis activity and parameters of the activity unremitting for more than two years. For these patients, therapy only relieves the symptoms and rarely leads to resolution of the structural abnormalities.

The statistical analyses were done using SPSS, version 15 (Statistical Package for Social Science), Chicago, IL.

Results

Vitamin 25(OH)D serum levels did not show a normal distribution in the analyzed group of sarcoidosis patients. The median value was 9.47 µg/L, the percentiles ranging from 4.49 µg/L (25th percentile) to 16.00 µg/L (75th percentile), thus suggesting severe deficiency; 52% (117 patients) had vitamin 25(OH)D under 10 µg/L.

No statistical significance was found in the differences between the vitamin 25(OH)D serum levels of female and male patients (Chi-Square=2.647; df=2; p=0.266). Considering the age of our sarcoidosis patient group, no statistical significance was found between the patients' age and the levels of vitamin 25(OH)D (Chi-Square=0.4; df=2; p=0.919) *(Table I)*.

No statistical significance was found when analyzing the stage of the lung disease (parenchymal versus non-parenchymal lesions) (Chi-Square=2.253; df=2; p=0.324).

The mean duration of sarcoidosis in our patient group was 7.21±6.74 years, ranging from 32 years (in one patient) to one year (in 22 patients). In a majority of our patients (41–18%), the diagnosis of sarcoidosis was established in May *(Figure 1)*.

When analyzing the season when the diagnosis of sarcoidosis was established (the months of the year) no statistical correlation was found considering the level of vitamin D in the analyzed group (Chi-Square=30.062; df=22; p=0.117). No statistical significance was found considering the vitamin D levels and duration of sarcoidosis (Chi-Square=5.539, df=2; p=0.063 (Kruskal Wallis Test)).

Statistically significant was the correlation between the calcium urine levels (24 hour urine) and serum vitamin D in our sarcoidosis patients (Chi-Square=6.759; df=2; p=0.034). The majority of patients with high levels of calcium in the 24 h urine sample were patients with the absolute vitamin 25 (OH)D deficiencies.

When analyzing the course of sarcoidosis (acute vs. chronic) in the light of vitamin 25(OH)D deficiency, a statistically significant correlation was found in patients with chronic disease and low levels of serum vitamin 25(OH)D (Chi-Square=6.044; df=2; p=0.014) *(Table II)*.

After adjustment for age, gender, height, body mass index, ethnicity and smoking history, the mean FVC was 380 µL and FEV1 was 220 mL higher in patients with vitamin D levels above 20 µg/L, com-

Table I Vitamin 25(OH)D subgroups in patients with sarcoidosis

Vitamin 25(OH)D				
Gender	Sufficient	Relative deficiency	Severe deficiency	
Male	7	4	52	63
Female	9	16	138	163
Total	16	20	190	226

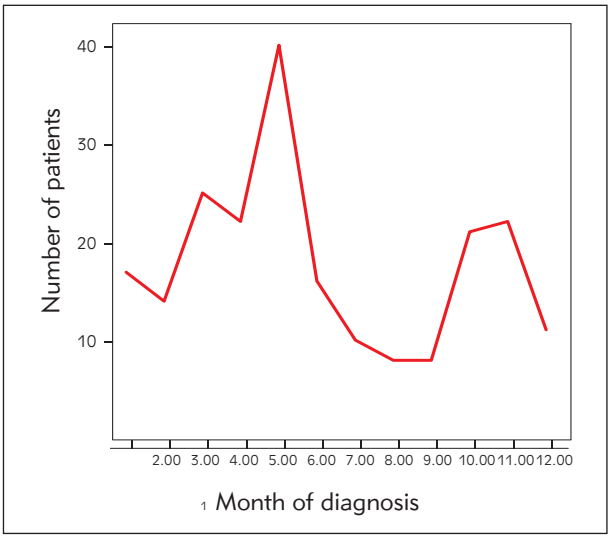

Figure 1 Months of the diagnosis in sarcoidosis patient group.

Table II Course of sarcoidosis and vitamin 25(OH)D levels

	25(OH)D		
Course of sarcoidosis	Vitamin 25(OH)D <20 μg/L	Vitamin 25(OH)D ≥20 μg/L	Total
Acute	42	15	57
Chronic	148	20	168
Total	190	36	226

pared to the group with serum vitamin 25(OH)D lower than 20 μg/L. However, the difference was not statistically significant.

Multiple linear regression analysis – forward method for fatigue assessment (dependent variable) revealed a statistically significant role of serum vitamin 25(OH)D levels to predict the sensation of fatigue (R^2=0.878; p=0.038 (β=0.216)). Multiple linear regression analysis – forward method was also used to assess the feeling of depression in relation to vitamin 25(OH)D. The analyses revealed a statistically significant role of vitamin 25(OH)D in predicting depression in patients with sarcoidosis (R^2=0.80; p=0.000 (β=0.391)).

Discussion

The incidence of sarcoidosis varies throughout the world. The highest annual incidence is found in northern Europe with 5–40 cases per 100,000 people, while the lowest is recorded in Japan (1). Sarcoidosis occurs most frequently in the winter months when vitamin D levels are low. Further on, sarcoidosis is more prevalent in areas that are farther from the Equator (32, 33).

Vitamin D deficiency and the risk of developing sarcoidosis

Sarcoidosis is common in dark pigmented individuals and is particularly high in African- Americans living in the Southern United States, who have a higher incidence of vitamin D deficiency (34, 35). In this population sarcoidosis is found to be a serious multisystem disease with a chronic course. These populations are evidently the same populations who are at higher risk for developing SLE with a more severe clinical course of disease (36).

In a majority of our patients the diagnosis of sarcoidosis was established in May (18%), however, the following circumstances must be considered. The diagnosis of sarcoidosis can be problematic (37). On average, patients have symptoms for more than 3 months before diagnosis and require three or more encounters with health care providers before the diagnosis can be established (38). Patients with sarcoidosis presenting with pulmonary symptoms often experience a delay in the diagnosis of sarcoidosis, as these symptoms are nonspecific, and alternative diagnoses such as asthma or bronchitis are often considered, thus causing the diagnostic postponement (39).

In keeping with the previous reflections, we might conclude that sarcoidosis in our patients occurred most frequently in February, one of the winter months when vitamin D levels are low.

The exact incidence of sarcoidosis is precisely known only for the countries with a central register. In Serbia it varies from 16 to 20/100 000, counted on the basis of the register of the Serbian Association of Sarcoidosis (http://www.wasog.org/sarcoidosis_O_world.htm), almost the same as in some parts of the United States of similar latitude (40). The clinical form of sarcoidosis in our patient group was predominantly chronic disease (63.7%) with low serum vitamin 25(OH)D levels; patients with serum 25(OH)D under 10 μg/L (117 patients) all had chronic disease.

The majority of patients with high levels of calcium in the 24 h urine sample were patients with the severe vitamin 25(OH)D deficiencies. The correlation was statistically significant, demonstrating two facts: a) patients with hypercalciuria have active sarcoidosis; so the active form of the disease is evidently related to low vitamin 25(OH)D levels; b) on the other hand, the majority of patients with hypercalciuria have active sarcoidosis and they are strongly recommended to avoid sunlight, and the supplementation of vitamin D or dietary intake are also not suggested. How to restore low vitamin 25(OH)D levels is a clinically serious problem in this group of patients. The issue becomes even more severe when we consider the fact that patients with a chronic course of sarcoidosis all have 25(OH)D levels beyond 10 μg/mL. These patients need continuous corticosteroid therapy, which in morbostatic doses can lead to weight gain. Previous studies confirmed the body mass index (BMI) >25 found in our sarcoidosis patient group in more than 30% of patients (41). Obesity has been associated with low serum levels of vitamin D. The logic explanation for such an observation is probably the life style of the individuals with BMI >25 (sedentary, indoors, not exposed to sunlight in order to hide the overweight). Besides, there is the fact that vitamin D is a fat-soluble vitamin that is taken up by adipose tissues (42–46).

Relationship of vitamin D status and lung function in patients with sarcoidosis

A few studies have investigated the relationship of vitamin D and lung function in patients with COPD. Two small studies of adults and children with asthma have found positive associations between serum 25(OH)D concentrations and FEV1 (47, 48).

In the Third Nutrition Survey (NHANES III) strong positive relations between serum 25(OH)D intake and FEV1 (forced expiratory volume in one second) and

FVC (forced vital capacity) were reported (49). In our patient group 73% of chronic sarcoidosis patients have been found to have bronchial obstruction (50). Although in sarcoidosis the exact mechanism of bronchial obstruction is not completely explained and the mechanism of the obstruction definitely differs from the one in COPD, in our analyzed group we found patients with serum vitamin 25(OH)D under 20 mg/L had FVC 380 mL lower compared to patients with a 25(OH)D level of 20 μg/mL; also, the FEV1, suggesting bronchial obstruction, was 220 mL lower in the same group of patients with low vitamin 25(OH)D under 20 mg/L. Almost no difference was noticed in the flows of the small airways. There is evidently a certain relationship between the serum concentrations of vitamin 25(OH)D, FEV1 and FVC. This is the first study on this issue in sarcoidosis. Further studies are necessary to determine whether supplementation with vitamin D, when possible, is of any benefit in these patients.

Vitamin D and neuropsychological functions in patients with sarcoidosis

Vitamin D and fatigue in sarcoidosis. »Fatigue is a common symptom and the symptom that has been with us forever...« were the words doctor Om Sharma used to start his editorial article on fatigue in sarcoidosis written for the European Respiratory Journal in 1999. As Samuel Butler stated: »Life is one long process of getting tired« (51). The occurence of fatigue in sarcoidosis is well known, but the exact incidence has not been established and varies from 30 to 70% depending on the age, sex, race of patients and organ involvement in the granulomatous process (52). The sensation of fatigue in sarcoidosis has been studied for years. Most of the recent studies explored the possible cause of exhaustion in sarcoidosis patients as well as the most reliable way of measuring it. However, very little is known about the relation between vitamin D and fatigue in sarcoidosis. As to our knowledge, this is the first modest observation on this topic.

There are many causes of fatigue in sarcoidosis such as: inflammation in general and metabolic derangement, myopathy, sleeping disorders, specific types of pain: chest pain, arthralgia, lack of exercise and psychological factors – a significant number of sarcoidosis patients were diagnosed with depression, a major symptom of which is fatigue (53).

In order to analyze the influence of serum 25(OH)D levels on the sensation of fatigue in our patient group we used multiple linear regression – forward method, with FAS score as a dependent variable. Three predictive models were available. The first one explains the fatigue in the light of high serum chitotriosidase, meaning the disease activity, which is important to support the previously mentioned fact of general inflammation leading to fatigue (R^2=844; p=0.000). The second model explains fatigue due to a chronic course of sarcoidosis and general inflammation (R^2=0.873; p=0.000), while the third model definitely best supports the theory of fatigue in relation to vitamin 25(OH)D serum levels (R^2=0.878; p=0.038).

Vitamin D and depression in sarcoidosis. In 1998 Landsdowne and Provost found that supplementation of vitamin D (400–800 IU per day) for five days during late winter had a significant positive effect on mood (54). A couple of years later Vieth et al. (55) demonstrated improved wellbeing after vitamin D supplementation for three months both when a low dose of 600 IU per day and a higher dose of 4000 IU per day was administered.

Receptors for vitamin D have been found in the brain and spinal cord (56), and it appears that vitamin D is significantly involved in a number of physiological actions in the brain, including modulation of acetylcholine and catecholamines, transmitters that are known to be involved in the regulation of emotional behavior (56).

In our sarcoidosis patient group we analyzed the feeling of depression in relation to serum vitamin D levels. Low serum vitamin D25(OH) was significantly associated with a high depression score. Multiple linear regression – forward method analysis was used (dependent variable CES-D score). The best explanation for depression in sarcoidosis was obtained in a model consisting of vitamin 25(OH)D and 24 hours urine calcium excretion, thus suggesting the following: calcium 24 hours urine levels are a reflection of the sarcoidosis activity. The vitamin 25(OH)D is the one, with its low levels, predicting the depressive mood besides the active disease in the analyzed group of sarcoidosis patients (R^2=0.800; p=0.000).

Conclusion

In conclusion, our results show that vitamin 25(OH)D deficiency is a great problem in sarcoidosis. Despite the autonomous production of the active calcitriol at the sites of granuloma formation, the insufficiency of 25(OH)D seems to be an important contributing factor in predicting the course of chronic disease, lung function impairments and cognitive failures such as fatigue and depression. The fact that the majority of the analyzed sarcoidosis patients had totally deficient serum 25(OH)D levels made this importance even more notable. Calcium metabolism disorders in sarcoidosis, however, make the problem even worse, for the supplementation and sunlight exposure can be acceptable only for patients with normal levels of serum or urine calcium.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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