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Association of serum level of 25-hydroxy vitamin D with clinical activity and pulmonary involvement severity in patients with sarcoidosis

Asociación del nivel sérico de 25-hidroxivitamina D con la actividad clínica y la gravedad de la afectación pulmonar en pacientes con sarcoidosis

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Abstract

We determined the role of measuring 25-hydroxy vitamin D to predict clinical activity and severity of pulmonary involvement in sarcoidosis. 61 consecutive patients with sarcoidosis were assessed. The serum level of 25 hydroxyvitamin D was measured using the chemiluminescent immunoassay. Sarcoid clinical activity classification (SCAC) was used to assess the clinical condition of the disease. The patients were also followed for 6 months. 14.8 % suffered severe 25-hydroxy vitamin D deficiency and 26.2 % had mild to moderate 25-hydroxy vitamin D deficiency. Serum phosphorus level was negatively associated with SCAC. There was also significant relationship between SCAC and pulmonary stages. The serum level of 25-hydroxy vitamin D was not associated with clinical activity. Within a 6-month follow-up time, clinical improvement of disease was overall achieved in 32 out of 61 patients leading success rate 52.5 %. Advanced age and stage 3-4 of pulmonary defects were main predictors for lack of 6-month clinical improvement in sarcoidosis patients. There is no relation between serum level of 25-hydroxy vitamin D and two indices of clinical activity of sarcoidosis and the severity of pulmonary involvement. The assessment of serum phosphorus and serum creatinine can be assessed to determine disease severity.

Resumen

Determinamos el papel de la medición de la 25-hidroxivitamina D para predecir la actividad clínica y la gravedad de la afectación pulmonar en la sarcoidosis. Se evaluaron 61 pacientes consecutivos con sarcoidosis. El nivel sérico de 25-hidroxivitamina D se midió mediante inmunoensayo quimio luminiscente. Se utilizó la Clasificación de Actividad Clínica de la Sarcoidosis (CACS) para evaluar la condición clínica de la enfermedad. Los pacientes fueron seguidos durante 6 meses. El 14.8 % presentó una deficiencia severa de 25-hidroxivitamina D y el 26.2 % tuvo una deficiencia leve a moderada de 25-hidroxivitamina D. El nivel de fósforo sérico se asoció negativamente con la CACS. También se observó una relación significativa entre la CACS y los estadios pulmonares. El nivel sérico de 25-hidroxivitamina D no se asoció con la actividad clínica. Durante el período de seguimiento de 6 meses, se logró una mejora clínica general en 32 de los 61 pacientes, alcanzando una tasa de éxito del 52.5 %. La edad avanzada y los estadios 3-4 de defectos pulmonares fueron los principales predictores de la falta de mejora clínica a los 6 meses en los pacientes con sarcoidosis. No existe relación entre el nivel sérico de 25-hidroxivitamina D y los dos índices de actividad clínica de la sarcoidosis ni con la gravedad de la afectación pulmonar. La evaluación del fósforo sérico y la creatinina sérica puede ser útil para determinar la gravedad de la enfermedad.

Introduction

Vitamin D and its metabolites have critical roles in immunomodulation and thus in preventing serious complications related to vitamin D deficiency. Besides the critical role of vitamin D in supporting natural health in human, inflammatory reactions can alter its metabolisms leading vitamin D deficiency[1,2]. In this regard, it has been revealed that inflammation can alter vitamin D production pathway and thus can result in alteration of the levels of its metabolites such as 1,25-dihydroxyvitamin D or in 25-hydroxyvitamin D deficiency[3,4]. Thus, it seems that any disorder with inflammation basis can impair Vitamin D deficiency and lead to poor prognosis of the disease.

It is now suggested that the synthesis of Vitamin D can be impaired in sarcoidosis through granulomatous inflammation as a main diagnostic marker of the disease[5]. In patients with sarcoidosis, the hydroxylation of vitamin D occurs outside the kidneys as the main site of metabolites hydroxylation[6]. In fact, vitamin D hydroxylation in these patients occurs inside the immune cells found in the granulomas. This event leads to increase in 25-hydroxy vitamin D or its active form of 1,25-dihydroxy vitamin D production leading increase in calcium concentration in both plasma and the urine[4-6]. It seems that the increase in the level of both inactive and active vitamin D metabolites may help to predict sarcoidosis-related complications such as hypercalcemia or hypercalciuria, or even its clinical activity, extension of its pulmonary involvement and even its poor prognosis[7].

Internal physicians may diagnose sarcoidosis de novo or provide proper management of its exacerbations, recurrences, and/or acute complications. Mediastinal and pulmonary localizations can be found in 90 % of all patients with sarcoidosis, however in about half the cases, the disease is not severe and is reversible without treatment. In the other half of cases, early or late respiratory complications can be seen. Early complications include sub-acute respiratory insufficiency by interstitial lung disease or by bronchial airway obstruction. Among late complications, the most frequent is pulmonary fibrosis that in its severe condition, pulmonary fibrosis can cause respiratory failure and death[8-10].

Several studies focused on the association of increased level of 1,25-dihydroxy vitamin D and clinical features of sarcoidosis. However, the role of 25-hydroxy vitamin D as a predictive marker for sarcoidosis clinical condition or its prognosis remains controversy. Although some studies could demonstrate a significant negative correlation was found between 25-(OH) D and disease activity of sarcoidosis measured by somatostatin receptor scintigraphy[11,12], but some other studies could not reveal this clinical association[11,13].

Hence, the present study aimed to determine the role of measuring 25-hydroxy vitamin D to predict clinical activity and severity of pulmonary involvement in sarcoidosis.

Materials and methods

Study population. In a prospective case-series study, 84 consecutive patients with sarcoidosis referred to Shariati Hospital within a 6 months' period from January 2014 to July 2014 were included into the study. The inclusion criteria were based on Löfgren[14] characteristics including enlargement of the lymph nodes near the inner border of the lungs as hilar lymphadenopathy as on X-Ray, tender red nodules as erythema nodosum, and arthritis involved the lower extremities.

The *exclusion criteria* were history of using vitamin

D supplements during the last 6 months, daily calcium use more than 1000 mg, history of diseases affecting calcium metabolism (malignancies, thyroid or parathyroid disorders, gastrointestinal diseases, active renal disease, pregnancy, use of thiazides), prolonged sedentary positions, or use of corticosteroids within the last 3 months. Considering exclusion criteria, 61 patients met the criteria that were finally included. The baseline data were collected by interviewing and physical examination at first visit of the patients by a single resident.

Study measurements, Baseline laboratory parameters including plasma levels of calcium, phosphorus, creatinine, erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) were assessed on admission. The serum level of 25 hydroxyvitamin D was measured using a direct competitive chemiluminescent immunoassay. The patients also underwent pulmonary functional test by using spirometry to assess the parameters of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. Also, to assess the condition of pulmonary involvement and its severity, chest radiography was done and the development of lung defects was classified by the standard staging method as Stage 0 (No intrathoracic involvement), Stage I (Bilateral hilar adenopathy), Stage II (Pulmonary parenchyma involved), Stage III (Pulmonary infiltrates with fibrosis, and Stage 4 (end-stage lung disease with pulmonary fibrosis and honeycombing)[15]. Also, sarcoid clinical activity classification (SCAC) was used to assess the clinical condition of the disease as: 1) acute onset, no immunosuppressive therapy, 2) acute onset, one period of treatment (< 12 months), 3) acute onset, several periods of immunosuppressive therapy or long-lasting treatment (> 12 months), 4) sub-acute onset, no immunosuppressive therapy, 5) sub-acute onset, one period of immunosuppressive treatment (< 12 months), and 6) sub-acute onset, several periods of immunosuppressive therapy or long-lasting treatment (> 12 months).

Follow-up. The patients were also followed for 6 months to assess the rate of improvement following treatment and also probable remission.

Statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t test, ANOVA test or non-parametric Mann-Whitney U test or Kruskal-Wallis test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. Categorical variables were, on the other hand, compared using chi-square test or Fisher's exact test when more than 20 % of cells with expected count of less than 5 were observed. The multivariate regression models were used to determine major predictors of the disease improvement after 6 months of following-up. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

General findings, in total, 61 patients were assessed with the average age 40.92±9.09 years (ranged 21 to 56 years) that 63.9 % were female. Regarding clinical symptoms, 6.6 % complained dry cough, 8.2 % had peripheral arthritis, 4.9 % were found to have erythema nodosum, and lymphadenopathy was shown in 3.2 %. Among all participants, 36.1 % had SCAC-1, 11.5 % had SCAC-2, 14.8 % had SCAC-3, 14.8 %

had SCAC-4, 16.4 % had SCAC-5, and 6.6 % had SCAC-6 (Figure 1). In this regard, acute form of the disease was revealed in 54.1 % and 63.9 % needed to immunosuppressive medication. With regard to staging pulmonary involvement, stage I was found in 55.7 %, stage II in 26.2 %, stage III in 13.1 %, and stage IV in 4.9% (Figure 2). Biopsy of pulmonary lesions was performed in 9.8 % demonstrating granuloma kaseosa. Also, 4 patients underwent CT scan that had normal findings in 3 patients and indicated paratracheal adenopathy in a patient. By considering cutoff < 10 ng mL^{-1} as severe deficiency and 10-25 ng mL^{-1} as mild to moderate deficiency of 25-hydroxy vitamin D, 14.8 % suffered severe 25-hydroxy vitamin D deficiency and 26.2 % had mild to moderate 25-hydroxy vitamin D deficiency. Mean serum level of calcium was 9.24±2.06 mg dL^{-1} and mean level of phosphorus was 3.49±0.79 mg dL^{-1}. Moreover, mean serum creatinine level was 1.06±0.26 mg dL^{-1} indicating renal failure in 6.6 %. Regarding pulmonary function test, mean FEV1 was 79.95±12.34 %, mean FVC was 77.03±17.64 %, and mean FEV1/FVC was 1.08±0.18. In this regard, 44.3 % had FEV1 lower than 80 % and 55.7 % had FVC lower than 80 % indicating pulmonary functional impairment.

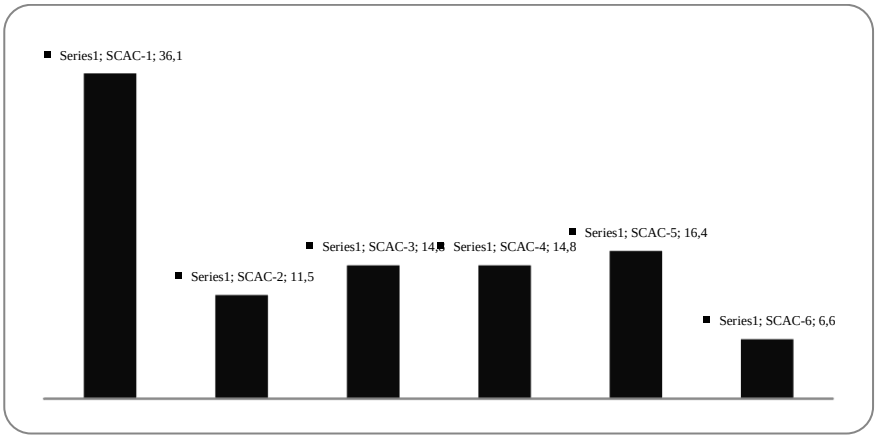

Figure 1 Sarcoid clinical activity According to SCAC classification

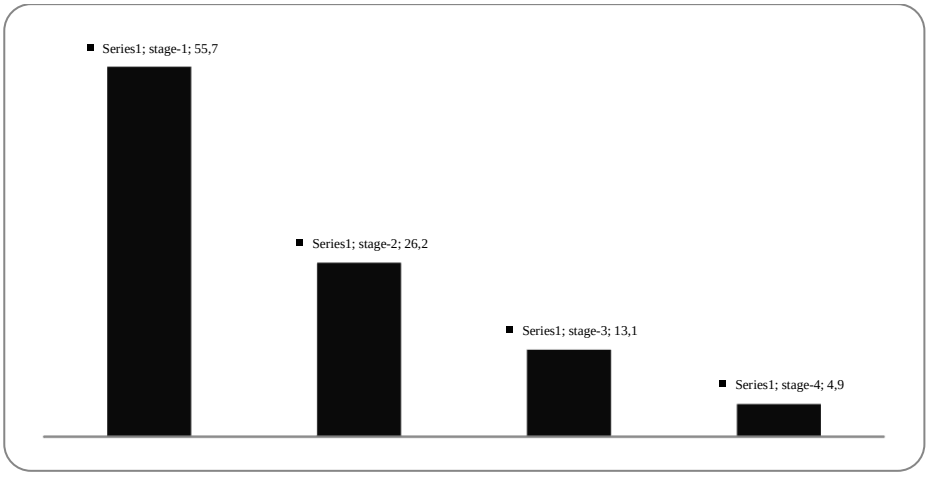

Figure 2 Stage of Pulmonary involvement in Sarcoidosis patients

Determinants of SCAC, among all baseline characteristics, only serum phosphorus level was negatively associated with SCAC (beta = -0.343, p = 0.010), however no relationship was revealed between SCAC and other biochemical markers such as serum calcium and creatinine levels as well as 24 h urine calcium level. Also, strong correlations were found between SCAC and two pulmonary function parameters of FEV1 (beta = -0.516, p < 0.001) and FVC (beta = -0.420, p < 0.001). There was also significant relationship between SCAC and pulmonary stages that mean SCAC was 2.35± .48 in stage I, 2.81±1.64 in stage II, 4.12±1.89 in stage III, and 5.00±1.73 in stage IV with a significant difference (p = 0.005) (Figure 3).

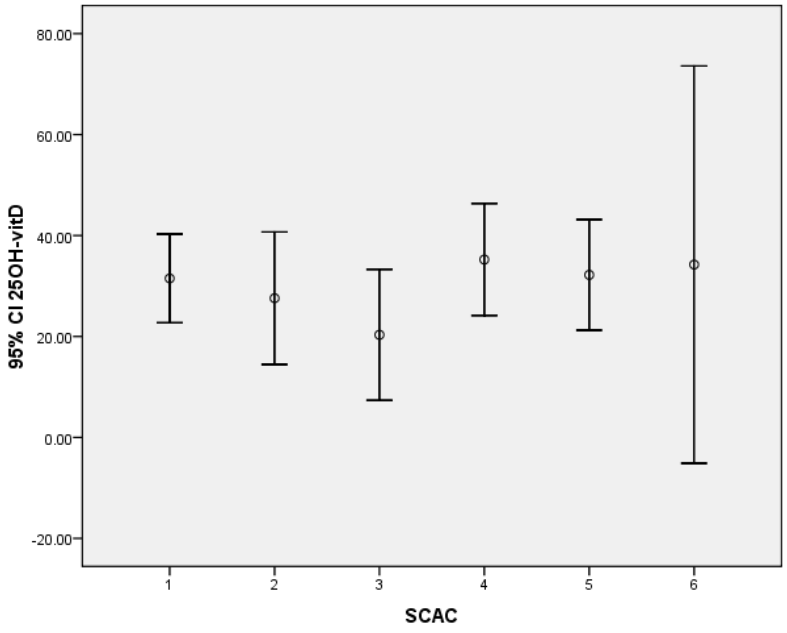

Figure 3 Mean 25-hydroxyvitamin D in different SCAC classes in Sarcoidosis patients

The role of 25-hydroxy vitamin D, the mean level of 25-hydroxy vitamin D in women was significantly lower than in men (25.81±14.37 versus 38.12±20.28, p = 0.017), however its level was not associated with age (beta = 0.006, p = 0.965). The level of 25-hydroxy vitamin D was 32.88±18.70 in stage I of pulmonary involvement, 27.35±14.42 in stage II, 26.83±17.85 in stage III, and 25.00±24.27 in stage IV with no significant difference (p = 0.634) (Figure 4). A significant correlation was also indicated between the level of 25-hydroxy vitamin D and serum phosphorus level (beta = -0.280, p = 0.036). In this regard, serum level of 25-hydroxy vitamin D was not correlated with other factors including serum calcium level, urinary calcium level, serum creatinine, and pulmonary functional indices.

Serum creatinine level, the serum level of creatinine was higher in men than in women (1.21±0.28 mg dL^{-1} versus 0.98±0.28 mg dL^{-1}, p = 0.005). However, no significant association was found between serum creatinine level and patients' age, SCAC biomarker, 25-hydroxy vitamin D, and serum phosphorus level. There was a significant association of serum creatinine level with serum calcium level (beta = 0.408, p

= 0.002), but not with 24h urinary calcium level (beta = 0.161, p = 0.233). Also, no association was observed between serum creatinine level ad two parameters of FEV1 (beta = -0.158, p = 249) and FVC (beta = -0.257, p = 0.058). we interestingly found an association between serum creatinine level and higher stage of pulmonary development that mean serum creatinine level was 1.01 ± 0.27 mg dL^{-1} in stage I, 1.04±0.27 mg dL^{-1} in stage II, 1.20±0.33 in stage III, and 1.60±0.57 in stage IV (p = 0.023).

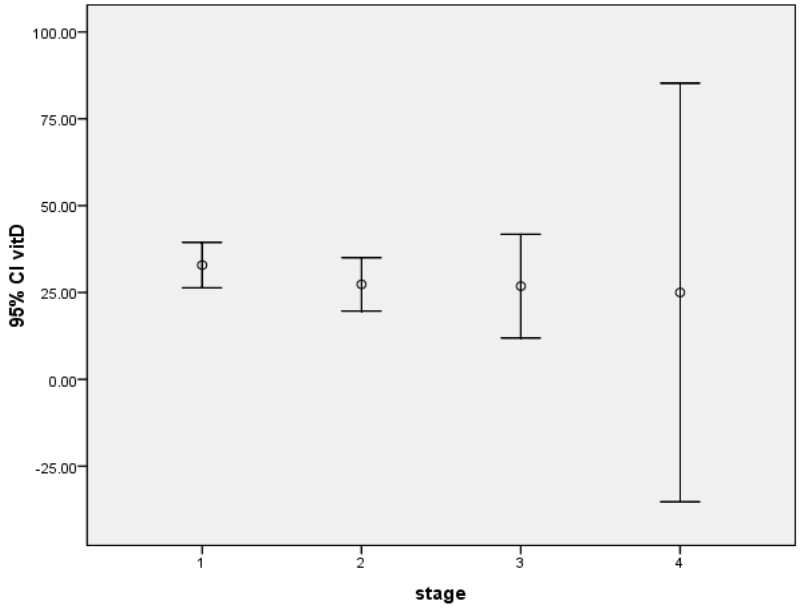

Figure 4 Mean 25-hydroxyvitamin D in different pulmonary stages in Sarcoidosis patients

Follow-up results: Within a 6-month follow-up time, the improvement of disease condition was 58.8 % in stage I, 50.0 % in stage II, 37.5 % in stage III, and 33.3 % in stage IV. In total, clinical improvement of disease was overall achieved in 32 out of 61 patients leading success rate 52.5 %. Of those with improper clinical improvement, 19.7 % had vital organs dysfunction that was mild in all followed-up patients. Within this period, 19.7 % required continuing immunosuppressive medication. In the multivariate logistic regression analysis, advanced age and stage 3-4 of pulmonary defects were main predictors for lack of 6-month clinical improvement in sarcoidosis patients.

Discussion

Reviewing the literature with the terms of "25-hydroxy vitamin D" and "sarcoidosis" in journal databases including PubMed and IS achieved 52 articles that among them a few studies mainly focused the role of 25-hydroxy vitamin D to assess and predict severity of clinical and pulmonary conditions in sarcoidosis. In our observation, we first show that 14.8 % of patients suffered severe 25-hydroxy vitamin D deficiency and 26.2 % had mild to moderate 25-hydroxy vitamin D deficiency. Despite high prevalence of 25-hydroxy vitamin D deficiency in the study pop-

ulation, 25-hydroxy vitamin D deficiency could not be related to pulmonary dysfunction or abnormal clinical condition or requiring immunosuppressive medication. However, clinical condition of the disease was associated with pulmonary function parameters, serum phosphorus level, and also stages of pulmonary defects severity, in fact, the development of pulmonary impairment was associated with higher need to repeated immunosuppressive drugs. Moreover, lowering level of serum phosphorus, but not lowering calcium or 25-hydroxy vitamin D levels could predict SCAC index. We also showed a strong association between pulmonary involvement stating and increased level of creatinine in sarcoidosis. In total, it can be concluded that the two indices of low serum phosphorus level and high serum creatinine level could predict disease clinical activity (SCAC) and pulmonary impairment severity (staging), respectively.

As previously shown, a few studies assessed relation between 25-hydroxy vitamin D level and prognosis of sarcoidosis. Some studies such as Bolland et al. study[15], those patients with serum level of 25-hydroxy vitamin D< 50 nmol L^{-1} had similar clinical skeletal health status when compared with other individuals. Also, Berlin et al.[16] showed that serum level of 25-hydroxy vitamin D was not associated with clinical activity of the disease and granuloma defects in defected tissues. Thus, it can be concluded that the measurement of 25-hydroxy vitamin D has no effective role in predicting patients' prognosis or expansion of pulmonary involvement, however because of the central role of low serum phosphorus and also high serum creatinine level to predict clinical activity of disease and pulmonary involvement severity, these two biomarkers can be considered more than 25-hydroxy vitamin D or other metabolites of vitamin D.

In conclusion, there is no relation between serum level of 25-hydroxy vitamin D and two indices of clinical activity of sarcoidosis and the severity of pulmonary involvement. According to the role of decreased level of serum phosphorus to predict clinical activity level of the disease and also elevated level of serum creatinine to predict pulmonary involvement severity, the assessment of these markers for new scoring of disease severity is recommended.

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Conflicts of interest

The authors declare that there are no conflicts of interest**.**

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Ethical considerations

The study guaranteed respect for the privacy and confidentiality of the information obtained.

Limitations in the research

There were no limitations when conducting the research.

Authors' contribution to the article

Keivan Goharimoghadam, conceptualization and ideas, data curation, research, methodology, project management, resources, supervision, writing of the original draft. *Ali Majidinejad*, conceptualization and ideas, research, supervision, writing of the original draft, writing, revision, and final editing.

Permissions for publication

The work was previously approved by the scientific committee of the Tehran University of Medical Sciences before being submitted to this journal. The authors, after a thorough review of the paper, have decided to proceed with the publication.

Access to data

The data and information of this research are present in the article.

Use of artificial intelligence

We assume that the entire document was written based on ethical and professional criteria, and AI was not used to make the figures or text.

Cited Literature

1. Peelen E, Knippenberg S, Muris AH, Thewissen M, Smolders J, Tervaert JW, et al. Effects of vitamin D on the peripheral adaptive immune system: a review. Autoimmun Rev 2011;10(12):733-43. DOI: https://doi.org/10.1016/j.autrev.2011.05.002. PMID: 21621002.
2. Wöbke TK, Sorg BL, Steinhilber D. Vitamin D in inflammatory diseases. Front Physiol 2014;5:244. DOI: https://doi.org/10.3389/fphys.2014.00244
3. Ao T, Kikuta J, Ishii M. The effects of vitamin D on immune system and inflammatory diseases. Biomolecules 2021;11(11):1624. DOI: https://doi.org/10.3390/biom11111624. PMID: 34827621; PMCID: PMC8615708.
4. Bishop E, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus 2020;5(1):e10405. DOI: https://doi.org/10.1002/jbm4.10405. PMID: 32904944; PMCID: PMC7461279.
5. Gwadera Ł, Białas AJ, Kumor-Kisielewska A, Miłkowska-Dymanowska J, Majewski S, Piotrowski WJ. Calcium, phosphate, and vitamin D status in patients with sarcoidosis-associations with disease activity and symptoms. J Clin Med 2023;12(14):4745. DOI: https://doi.org/10.3390/jcm12144745. PMID: 37510860; PMCID: PMC10381487.
6. Adams JS, Sharma OP, Gacad MA, Singer FR. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest 1983;72(5):1856-60. DOI: https://doi.org/10.1172/JCI111147. PMID: 6688814; PMC ID: PMC370476.
7. Burke RR, Rybicki BA, Rao DS. Calcium and vitamin D in sarcoidosis: how to assess and manage. Semin Respir Crit Care Med 2010;31(4):474-84. DOI: https://doi.org/10.1055/s-0030-1262215. PMID: 20665397; PMCID: PMC4876288.
8. Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J 2021;58(6):2004079. DOI: https://doi.org/10.1183/13993003.04079-2020. PMID: 34140301.

9. Judson MA. The clinical features of sarcoidosis: A comprehensive review. Clin Rev Allergy Immunol 2015;49(1):63-78. DOI: https://doi.org/10.1007/s12016-014-8450-y. PMID: 25274450.
10. Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU. Pulmonary sarcoidosis. Lancet Respir Med 2018;6(5):389-402. DOI: https://doi.org/10.1016/S2213-2600(18)30064-X. PMID: 29625772.
11. Kiani A, Abedini A, Adcock IM, Mirenayat MS, Taghavi K, Mortaz E, et al. association between vitamin D deficiencies in sarcoidosis with disease activity, course of disease and stages of lung involvements. J Med Biochem 2018;37(2):103-9. DOI: https://doi.org/10.1515/jomb-2017-0041. P MID: 30581345; PMCID: PMC6294100.
12. Kavathia D, Buckley JD, Rao D, Rybicki B, Burke R. Elevated 1, 25-dihydroxyvitamin D levels are associated with protracted treatment in sarcoidosis. Respir Med 2010;104(4):564-70. DOI: https://doi.org/10.1016/j.rmed.2009.12.004. PMID: 2007 1158; PMCID: PMC4778713.
13. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. Mayo Clin Proc Innov Qual Outcomes 2019; 3(3):358-75. DOI: https://doi.org/10.1016/j.mayocpiqo.2019.04.006. PMID: 31485575; PMCID: PMC6713839.
14. Lofgren S. Primary pulmonary sarcoidosis. II. Clinical course and prognosis. Acta Med Scand. 1953;145(6):465-74. PMID: 13079661.
15. Bolland MJ, Wilsher ML, Grey A, Horne AM, Fenwick S, Gamble GD, et al. Randomised controlled trial of vitamin D supplementation in sarcoidosis. BMJ Open 2013;3(10):e003562. DOI: https://doi.org/10.1136/bmjopen-2013-003562. PMID: 24157819; PMCID: PMC3808783.
16. Berlin JL, Shantha GP, Yeager H, Thomas-Hemak L. Serum vitamin D levels may not reflect tissue-level vitamin D in sarcoidosis. BMJ Case Rep 2014;2014:bcr2014203759. DOI: https://doi.org/10.1136/bcr-2014-203759. PMID: 24663253; PM CID: PMC3975517.