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ASSOCIATION BETWEEN VITAMIN D DEFICIENCIES IN SARCOIDOSIS WITH DISEASE ACTIVITY, COURSE OF DISEASE AND STAGES OF LUNG INVOLVEMENTS

POVEZANOST DEFICIJENCIJE VITAMINA D U SARKOIDOZI SA TEŽINOM I TOKOM OBOLJENJA, KAO I OŠTEĆENJEM PLUĆA

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Summary

Background: Despite negative association between 25-hydroxy vitamin D and incidence of many chronic respiratory diseases, this feature was not well studied in sarcoidosis. Current study investigated the association between 25-hydroxy vitamin D deficiency with sarcoidosis chronicity, disease activity, extra-pulmonary skin manifestations, urine calcium level and pulmonary function status in Iranian sarcoidosis patients. Results of this study along with future studies, will supply more effective programs for sarcoidosis treatment.
Methods: Eighty sarcoidosis patients in two groups of insufficient serum level and sufficient serum level of 25-hydroxy vitamin D were studied. Course of sarcoidosis was defined as

Kratak sadržaj

Uvod: Uprkos negativnoj povezanosti između 25-hidroksi vitamina D i učestalosti brojnih hroničnih respiratornih oboljenja, ovaj uticaj još uvek nije ispitivan u sarkoidozi. Ova istraživanja izučavaju vezu između deficijencije 25-hidroksi vitamina D sa stepenom hroničnosti kod sarkoidoze, aktivnosti oboljenja, ekstra pulmonalnih kožnih manifestacija, nivoa kalcijuma u urinu i statusa pulmonalne funkcije kod Iranskih pacijenata sa sarkoidozom. Rezultati ovih izučavanja sa budućim istraživanjima mogu ukazati na mnogo bolji uspeh u tretmanu sarkoidoze.
Metode: Proučavano je osamdeset pacijenata sa sarkoidozom podeljenih u dve grupe u odnosu na insuficijentni i zadovoljavajući nivo 25-hidroksi vitamina D. Stepen sarkoi-

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acute and chronic sarcoidosis. Pulmonary function test (PFT) was assessed by spirometry. Skin involvements were defined as biopsy proven skin sarcoidosis. 24-hour urine calcium level was used to specify the disease activity. Stages of lung involvements were obtained by CT-scan and chest X-ray. The statistical analyses were evaluated using Statistical Package for the Social Sciences.

Results: A significant negative correlation was obtained between vitamin D deficiency in sarcoidosis patients and disease chronic course and stages two to four of lung involvements. Considering other parameters of the disease and vitamin D deficiency, no significant correlation was detected.

Conclusions: In conclusion, results of the current study implies in the role of vitamin 25(OH)D deficiencies in predicting the course of chronic sarcoidosis. Furthermore, it was concluded that vitamin 25(OH)D deficiency can direct pulmonary sarcoidosis toward stage 2–4 of lung involvements.

Keywords: vitamin D (D014807), hypercalciuria (D053565), sarcoidosis (D012507)

doze je definisan kao akutna i hronična sarkoidoza. Pulmonalni fnkcionalni test (PFT) je izveden spirometrijom. Uključenost kože je definisana biopsijom. Nivo kalcijuma u 24-urinu je korišćen za dokazivanje stepena aktivnosti oboljenja. Stepen uključenosti promena na plućima je dobijen primenom CT-skenera i snimanjem pluća rendgenski. Za statističku procenu rezultata korišćen je statistički program Social Sciences (SPSS).

Rezultati: Dobijena je značajno negativna korelacija između deficijencije vitamina D kod pacijenata sa sarkoidozom i hroničnog toka bolesti i stupnjeva u dva do četiri plućna stepena. Nije nađena značajna korelacija između drugih parametara oboljenja i deficijencije vitamina D.

Zaključak: Može se zaključiti da dobijeni rezultati ukazuju na ulogu deficijencije vitamina 25(OH)D u predviđanju toka hronične sarkoidoze. Takođe, može se zaključiti da deficijencija vitamina 25(OH)D može ukazati na pulmonalnu sarkoidozu sa uključenjem pluća stepena 2–4.

Ključne reči: vitamin D (D014807), hiperkalciurija (D053565), sarkoidoza (D012507)

Introduction

Sarcoidosis is a multi-organization disease characterized by granuloma formation and enhanced immune operation activities (1, 2). Several studies have advocated that the innate immune failure in responding to persistent antigens causes Granuloma formation of sarcoidosis (1–3). Sarcoidosis disease occurs in winter and in regions with increased latitude in which lack of sun-exposure leads to vitamin D deficiency (4, 5). Vitamin D pro hormone plays many potential roles in immune regulatory structure (5, 3). As explained in third national health and nutrition survey, vitamin D deficiency is associated with sarcoidosis prevalence (6). Indeed, sarcoidosis treatment with corticosteroids leads to osteoporosis, which so physicians include calcium and vitamin D (CAD) supplements in line with routine treatment. But, some concerning issues about sarcoidosis insist. In this light, hypercalcemia is a known feature of sarcoidosis in 5 to 11% of cases (7, 8). Activated macrophages in the sarcoidosis granuloma are responsible for overproduction of vitamin D3 active form.

Overproduction of active form of vitamin D3 (calcitriol or 1,25-dihydroxy vitamin D (1,25(OH)2D)), provides hypercalcemia, hypercalciuria and osteoarticular manifestations (9–12). In addition, hyperparathyroidism can cause hypercalcemia (1). In such cases although vitamin D serum level deficiency insists, but 1,25(OH)2D normal serum level remains a prime obstacle in efficiency of 1,25(OH)2D evaluation (10, 13, 14). Most sarcoidosis patients exhibit normal levels of 1,25(OH)2D. But, these patients represent low levels of 25-(OH)D (15, 16). As a result, measuring Vitamin D-25 as the major circulating form of vitamin D is the most efficient administrator to test the adequacy of vitamin D level (1, 17).

Objectives

Negative association was reported between 25-hydroxy vitamin D, active sarcoidosis, sarcoidosis chronicity and pulmonary function status in sarcoidosis patients, in recent studies (1, 4, 5, 18). But, correlation of 25-(OH)D status with sarcoidosis factors has not been yet studied in Iranian sarcoidosis population. The purpose of this non-experimental designed survey was to investigate association of 25-hydroxy vitamin D deficiency with sarcoidosis chronicity, active form of disease, skin extra-pulmonary manifestations, urine calcium and pulmonary function status in a group of Iranian sarcoidosis patients at referral respiratory hospital of Iran. Since this study is the first study of its kind, the results will be more effective treatment of Iranian patients by considering the level of 25(OH)D.

Material and Methods

Study Design

This correlational descriptive study was conducted at the sarcoidosis clinic of Masih Daneshvari Hospital, Tehran. To figure the possible correlations between vitamin D status and other limits in sarcoidosis patients, this study was conducted between November 2013 and November 2016. Thereby, the study was approved by the Ethics Committee of Shahid Beheshti medical sciences university (SBMU 1.REC.1393.71). An expert methodologist estimated the study population size due to statistics guidelines (19, 20).

Inclusion and exclusion criteria

Inclusion criteria: Greater than 18 years old sarcoidosis patients with biopsy-proven disease and no co existing chronic respiratory disease.

Exclusion criteria: The smoker or tuberculosis patient. Disease with vitamin D levels changing properties.

Study subjects

Forty sarcoidosis patients with 25(OH)D 50 nmol/L or less were selected as experimental group which was comprised of two subgroups: deficient group with 25(OH)D ≤ 25 nmol/L and insufficient group with 27.5 25(OH)D 0 nmol/L (6). To cut difficulties of two unequal groups' analyses, 40 unknown sarcoidosis patients with 25(OH)D > 50 nmol/L defined as enough vitamin D were included in the control group. Groups were selected without considering the exact result of vitamin D level or other required clinical and para clinical parameters data such as the amount of CD4/CD8 T cell ratio, Angiotensin-converting enzyme blood levels and the radiological stage of the disease. All patients signed the written consent forms in regard of human rights and patient's privacy. On the same day of disease diagnosis, the blood samples, 24-hour urine, CT-scan and chest X-ray (CXR) were got. The patients without parenchymal lesions were defined as stage 0–1 of the lung disease and the patients with parenchymal lesions were classified in stage 2–4 of the lung disease. Patients underwent primary tests such as parathyroid test. Pulmonary function test (PFT) was performed by spirometer (Spiro lab II, Italy) on the basis of the European Respiratory Society criteria (18). Forced expiratory volume in the 1st second (FEV1); forced vital capacity (FVC) and the FEV1/FVC were expressed as a percentage of the reference values and milliliters (mm) (21). The primary demographic data, such as age, gender, smoking status, course of disease and the time of diagnosis were also recorded in the sarcoidosis clinic forms. Extra-pulmonary skin involvements were characterized by dermatologist. Sarcoidosis patients were registered in the national sarcoidosis patient's registry scheme (http://nritldrer.ir/#/Sarcoidosis/). Finally, patients received relevant to the involved organ and disease severity steroid treatment or oral non-steroidal anti-inflammatory drugs. Vitamin D supplementations were prescribed with vitamin D deficiency.

Vitamin D-25(OH) serum level

Vitamin D-25(OH) serum level was assessed using the Elecsys® Vitamin D test by electro-chemoluminescence method (ECLIA). In this regard, Roche reagents (Roche Diagnostics GmH, Mannheim, Germany) were utilized. Following values was used to define different 25-OH-vitD serum levels:

A) Deficiency: 25(OH)D ≤ 25 nmol/L serum level.

B) Insufficiency: a serum level of 27.5 nmol/L – 50 nmol/L 25(OH)D.

C) Sufficient: a serum level of >52.5 nmol/L 25(OH)D.

Course of sarcoidosis

Lofgren syndrome as the acute form of sarcoidosis was defined as treatable disease in less than 2 years. Chronic sarcoidosis was defined as the form of the disease in which both symptoms and signs of disease remained stable and active for over two years despite the therapy. Patients were followed up for three years to pursue the disease symptom improvement and managing everyday tasks without complaints of disease.

Disease activity

24-hour urine calcium level was used to specify the active form of disease. The normal range of 24-hour urine calcium level was considered 100 to 300 mg/24h. The amounts above the greatest level were defined as hypercalciuria.

Statistical analysis

The statistical analyses were evaluated using Statistical Package for the Social Sciences (SPSS) (ver. 22.0; SPSS Inc. Chicago, IL, USA) software. Statistical analyses were conducted under international statistical reporting standards (22). So, descriptive variables like 25-OH-vitD serum level were expressed as mean (±standard deviation) or median (minimum–maximum). Categorical shifts were expressed as frequencies and percentages. Shapiro-Wilk Normality test for normality of distribution showed that 25-OH-vitD distribution was not normal. P value of < 0.05 was significant. After classifying patients into two groups due to vitamin D, correlation between vitamin D deficiencies with qualitative variables were tested using Pearson Chi-Square test and correlation between vitamin D deficiencies with quantitative variables were tested using two independent sample Mann-Whitney test.

Results

Normal distribution was only got in FEV1% variable by Shapiro-Wilk normality test. 80 biopsy proven sarcoidosis patients were studied during one year. Age and sex central Indices were approximately same in both groups. The mean age was 46.3 ± 8.1 with the range of 19–78 yrs. Most of patients were in the 40–50-year old age group. Regarding the sex item, female patients were predominant (n=48, 60%) (*Table I*). Suggesting vitamin D level; 53% of men and 48% of women patients had vitamin 25(OH)D deficiencies. Considering the sex of patients, no statistical significance correlation was found between the vita-

min 25(OH)D serum levels of male and female patients in Chi-Square test (p=0.812). So, no statistical significance correlation was found between the age of patients and vitamin 25(OH)D serum levels (p=0.328).

On the basis of seasonal distribution, spring was the most referred season with the frequency of 26.25%. The mean of disease treatment duration in the patients was 1.31±1.01 years, ranging from two months (in one patient) to two years (in 21 patients). May was the most common month for establishing the disease in our clinic. None of the patients showed primary hyperparathyroidism. 37 (46.2%) patients were overweight according to the Body Mass Index (BMI > 25). Most of the patients showed high levels of ACE (63.7±45). Overall, the most commonly involved organ was the respiratory tract (51 cases; 63.75%) with wheezing and crackle as the common pulmonary abnormalities. The prevalence of joint manifestations in patients was 41.7% and Joint manifestation was a dominant feature of the patients with a diagnosis of Lofgren syndrome (87.2%).

Vitamin D serum level and clinical information

The value of serum level 25(OH)D in our study was measured at the moment of referring to the clinic, thus mostly in the mid-spring. The mean value was 54.32 nmol/L, the percentiles ranging from 5 nmol/L to 145 nmol/L. No statistical significant correlation was detected considering the vitamin D levels and duration of sarcoidosis treatment (p=0.061).

Skin manifestations of disease were reported in 30 (37.5%) patients. Arthritis, arthralgia and joint swelling were seen in 16 cases (20%). No statistical significant correlation was obtained between vitamin D levels and categorical variable skin manifestations of disease (independent sample Mann-Whitney test) (p=0.706).

With respect to CT-scan chest X-ray (CXR) results, patients were classified into a group with lymph node involvement, (stage 0–1 of the lung disease) (38.7%) and a group with parenchymal lesions, (stage 2–4 of the lung disease) (61.3%). When analyzing the lung involvements of sarcoidosis (parenchymal vs. non-parenchymal) in the light of vitamin 25(OH)D deficiency, a statistically significant negative correlation was found in patients with parenchymal lung involvements of sarcoidosis and low levels of serum vitamin 25(OH)D (Pearson Chi-Square= 4.266; df=1; p=0.039). 72% of sarcoidosis patients with vitamin D deficiency showed parenchymal involvement. This proportion was 50% in sarcoidosis patients with enough vitamin D serum level. In contrast, no statistically significant correlation was obtained between the patients' lymph node involvement and the levels of vitamin 25(OH)D (Mann-Whitney test; p=0.243).

Table I Vitamin 25(OH)D level (nmol/L) and course of sarcoidosis.

	25(OH)D		Total
Course of sarcoidosis	25(OH)D>50	25(OH)D>50	
47	29 (72.5%)	18 (45.0%)	Acute
33	11 (27.5%)	22 (55.0%)	Chronic
80	40	40	Total

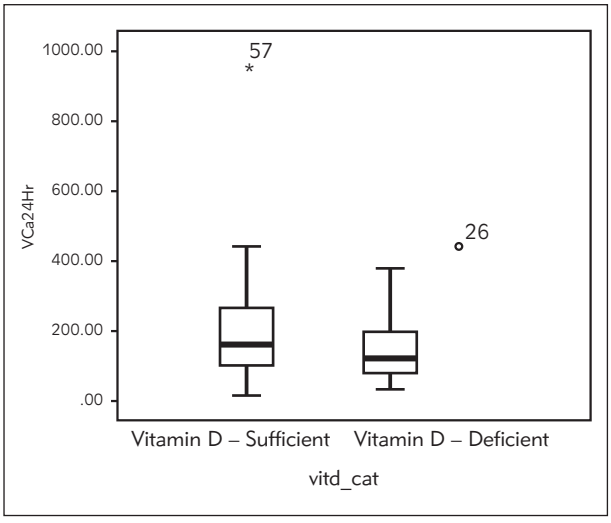

Figure 1 24 hr. urine calcium level (mg/24hrs) box plot based on level of vitamin D.

Studied sarcoidosis patients were contained of 47 (58.8%) acute sarcoidosis patients and 33 (41.3%) chronic sarcoidosis patients. About, 55% of sarcoidosis patients with vitamin D deficiency showed chronic disease. Only 28% of sarcoidosis patients with sufficient vitamin D serum level showed chronic disease. Considering the course of sarcoidosis (acute vs. chronic), a significant positive correlation was found in patients with chronic disease, in the light of vitamin 25(OH)D deficiency (Pearson Chi-Square=4.142; DF=1; p=0.012) (*Table I*).

The mean urinary calcium level was 189.7 ± 111.9 mg/24hr with the range of 19–789 mg/24hr. 18.9% of patients showed hypercalciuria. Absolute vitamin 25(OH)D deficiencies were identified in patients with high levels of calcium in the 24 hr urine sample. No significant correlation was obtained between the continuous variable urinary calcium level (24 hour urine) and serum levels of vitamin D in current study (Spearman correlation test) (p=0.053) (*Figure I*).

Considering the correlation between vitamin D serum levels and the continuous variable pulmonary

function FEV1 and FVC, no statistically significant correlation was obtained in current study (Spearman correlation test) (p=0.289, p=0.084). However, FVC in patients with vitamin D levels above 50 nmol/L included a mean of 340 mL higher than patients with ≤50 nmol/L serum vitamin 25(OH)D. In this case FEV1was 220 mL higher. Nevertheless, no statistically significant differences was obtained between the volumes of FEV1 and FVC in patients with vitamin D levels above 50 nmol/L and the patients with serum vitamin 25(OH)D ≤50 nmol/L.

Discussion

Ever since the first study was tested on the relationship between chronic respiratory diseases and vitamin D as a regulatory factor, many studies were conducted worldwide on this issue (23). But, the association of vitamin D deficiency with different features of sarcoidosis is not still well-studied (1). The purpose of this study was to investigate the relation between vitamin 25(OH)D serum level with Course of sarcoidosis, Status of Pulmonary function, Skin extrapulmonary involvement, Lung involvement stage and Disease activity among sarcoidosis cases of Iran.

The highest annual incidence of sarcoidosis is found in northern Europe with 5–40 cases per 100,000 people (8, 22). Sarcoidosis incidence in Iran is not obvious. Based on the registry organization of Iranian Sarcoidosis patients in Referral Masih daneshvari hospital, Tehran, the incidence of sarcoidosis in Iran is almost 1–2 cases per 100,000 people. Vitamin D deficiency is considered playing an important role in sarcoidosis development (23). In people living in regions with far areas from the Equator, lack of sun-exposure leads to vitamin D deficiency. Vitamin D deficiency and chronic course of sarcoidosis occur with a higher incidence in dark-pigmented individuals and African-Americans living in the Southern United States (2, 8). Iran is a country with low latitude (32° 00' N) and white skinned population. This confirms higher incidence of acute course of sarcoidosis among the studied patients.

The diagnosis of majority of our sarcoidosis patients was established in May, however, on average, patients are involved for over 3 months before diagnosis. Due to poverty, many Iranian patients postpone visiting health care providers. Duration of sarcoidosis diagnosis is there for extended in Iran. Based on this, we may conclude that sarcoidosis occurred in our patients in January to February, when vitamin D serum levels are insufficient.

Study of vitamin D was tested on 25(OH)D serum level in our study. Current study design was based on earlier studies represented that free 25(OH)D showed higher correlation with the actual vitamin D deficient states than 25(OH)D (23). Similar to some earlier studies, female patients were predominant sex group and most of patients belonged to the age group 40–50 (n=48, 60%) (1, 20). Joint manifestations proportion were higher than previous reports (14%–36%) (24). In current study 87.2% of patients with a diagnosis of Lofgren's syndrome showed joint manifestations under the study by Moore (80%) (24).

With correlation between the stage of the lung disease and parenchymal lung involvement with the low levels of vitamin 25(OH)D, statistical significant associations were detected (p=0.039). This is at odd with a former study which studied 226 sarcoidosis patients with no correlation found between stage of the lung disease and vitamin 25(OH)D serum levels (1). This variation may be due to different studied populations in two studies. 226 studied patients in mentioned study were Serbians with a high incidence of chronic course of sarcoidosis and high prevalence of vitamin D deficiency on the basis of long latitude of their country.

Current study showed that existence of respiratory involvements of stage 0–1 is not correlated with vitamin D deficiency in sarcoidosis patients. A significant negative correlation was detected between stages 2–4 of lung involvements in sarcoidosis patients with 25(OH)D deficiency. This shows that Vitamin D deficiency has an important immune modulatory impression on lung impairments in a sarcoidosis patient.

Current study results showed that sarcoidosis patients with acute course of disease possessed higher level of vitamin D serum level comparing to the sarcoidosis patients with chronic course of disease. So, results of the current study implies in the role of vitamin 25(OH)D deficiencies in leading the course of sarcoidosis to chronicity. This confirmed an earlier study on 25(OH)D deficiencies correlation with course of chronic sarcoidosis and data from 86 sarcoidosis patients with 29.5% of acute patients with 25(OH)D deficiency and 64.2% of chronic patients with 25(OH)D deficiencies (5).

Results of current study on pulmonary functioning statues were following an earlier study (1, 6). This implies in that 25(OH)D deficiencies may have relation with pulmonary function reduction (↓ FVC). Since this issue was not showed in current study, future studies on this field are recommended.

As showed earlier, hypercalcemia and hypercalciuria occur in 10% and 30% of the sarcoidosis patients (13, 14, 25). In current study, Absolute vitamin 25(OH)D deficiencies were recognized in patients with hypercalciuria. Hence, we suggest that active sarcoidosis occurs in patients with deficient serum level of vitamin 25(OH)D. Our study confirms an earlier work which showed that 25(OH)D deficiencies was a potential risk factor in emerging active type of sarcoidosis (1). Patients with hypercalciuria are recommended avoiding the sunlight and consuming

supplementations of vitamin D. We monitor urine calcium level of sarcoidosis patients to prevent renal failure in the patients.

Current study was tested on a sample size of patients that can affect the generalization of the results.

Conclusion

In conclusion, results of the current study implies in the role of vitamin 25(OH)D deficiencies in predicting the course of chronic sarcoidosis. Vitamin 25) OH) D deficiency can lead the stage of lung involvement in pulmonary sarcoidosis toward stage 2-4. But, since no correlations between vitamin 25(OH)D deficiency and calcium level in urine (disease activity) or pulmonary function status were observed, further researches in these fields are recommended.

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Footnotes

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Author declaration

Authors certify that the manuscript represents a valid work and neither this manuscript nor one with substantially similar content under named authorship has been published or is being considered for publication elsewhere. The study was performed at the Masih Daneshvari referral respiratory hospital of Tehran, Iran. Authors have participated in the research and the shaping of the manuscript.

Conflict of interests

Authors have no conflicts of interest to declare. Authors give consent to submission and publication of the work. Authors disclose no relationship to any organization or industrial manufacture in any material of discussed.

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