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Pardis Rahmani *et al*, Cognizance Journal of Multidisciplinary Studies, Vol.4, Issue.4, Apr 2024, pg. 304-315
(An Open Accessible, Multidisciplinary, Fully Refereed and Peer Reviewed Journal)
ISSN: 0976-7797
Impact Factor: 4.843
Index Copernicus Value (ICV) = 77.57

Serum 25(OH)D Levels and Mitral Valve Calcification in Patients with Severe Rheumatic Mitral Stenosis

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DOI: 10.47760/cognizance.2024.v04i04.022

Abstract:

Background: Rheumatic heart disease (RHD) imposes a significant burden on patients and the health system, especially in the developing countries. Recently, the role of vitamin D deficiency in increasing the severity of valve involvement and calcification in patients with RHD has been suggested. However, its role in the severe stenosis of the mitral valve is unknown. The aim of this study was to determine the relationship between serum levels of 25(OH)D and mitral involvement severity scores in patients with severe mitral stenosis (MS).

Materials and Methods: In this cross-sectional study conducted in Shahid Madani Heart Center, Tabriz, Iran, 104 patients with severe rheumatic MS were reviewed, in the absence of other underlying diseases. Trans-esophageal Echocardiography was performed for all patients, and mitral valve Wilkins score and mitral valve area were calculated. Blood samples were taken from patients and levels of 25(OH)D, total calcium, phosphorus, and i-PTH were measured.

Results: Eighty eight cases were female and 16 were male. Eighty-one patients had mild to moderate mitral calcification and in 23 patients with mitral valve was severely calcified. Furthermore, 54 were vitamin D deficient, while 35 had insufficient vitamin D levels, and only 15 had normal blood levels of vitamin D. In addition high serum iPTH levels were present in 83 patients (80%). The levels of 25(OH)D,

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calcium, phosphorous, and iPTH with total Wilkins score, calcification score and mitral valve area were not significantly correlated ($p>0.05$ for all above).
Conclusions: Although no correlation was found between the severity of mitral valve involvement, and vitamin D and iPTH levels, vitamin D deficiency and secondary hyperparathyroidism tend to be common among patients with severe rheumatic MS, which may play a role in the progression of the disease.
Keywords: Calcium, Rheumatic Heart Disease, Severe Mitral Stenosis, Vitamin D.

Introduction

Rheumatic heart disease (RHD) is developed by overreaction of immune system to streptococcus A infection and is characterized by involvement of different parts of the human heart specially valve endocardium (1,2). Although nowadays this illness is not common in the developed countries, it still imposes a lot of burden on the developing countries health system (2). Vitamin D is thought to alter endothelial function and thus can play a role in atherosclerosis and RHD processes. This effect is shown to be mediated by vitamin D receptor (VDR) and vascular endothelial growth factor (VEGF) which intervene in different parts of endothelial function (3,4). Since calcifying nanoparticles (CNPs) are able to act as nucleation centers and promote calcification, they should receive special attention, especially in situations where they can be prevented, such as nanostructured drugs (5). some nanosystems for various applications such as food and beverage fortification and therapeutic agents. In order to support the great potential of nanotechnology in vitamin D delivery, it would be important to conduct more extensive and comprehensive studies (6,7). Vitamin D deficiency increases the risk of cancer and infection disease (8). Lifestyle, dietary factors and genetic variants in other genes affecting vitamin D pathways, such as vitamin D-binding proteins and enzymes involved in vitamin D activation (9). Knowing the fact that both vitamin D deficiency and RHD are very common among Iranian people, we tested the hypothesis that a correlation between these two might be present.

Materials and Methods

In the current study, 104 patients with the diagnosis of severe MS (mitral valve area (MVA)<1.5cm^2) were recruited consecutively from the outpatient cardiology clinic of Tabriz University of Medical Sciences between March 2019 and March 2020. All patients underwent trans-esophageal echocardiography and MVA and Wilkins score (and its subtypes) were calculated. Additionally, five mL of venous blood samples were collected after 12-hour overnight fasting and serum 25(OH)D, intact parathyroid hormone (iPTH), total calcium and phosphorus levels were measured. To reduce the difference caused by seasonal change, we measured 25(OH)D levels twice a year when possible and the mean level was included in the analysis. Vitamin D deficiency and insufficiency were defined as levels <20 pg/ml and between 20 and 40 pg/ml, respectively. Besides, normal limits of iPTH levels were defined as 10 to 65 pg/ml and higher levels were considered as hyperparathyroidism.
Statistical analysis was performed using SPSS software version 18.0 (SPSS, Inc., USA). Normality of variables distribution was evaluated using the Kolmogorov-Smirnov test. Variables not normally distributed were analyzed using nonparametric tests. Categorical and normally

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distributed quantitative variables were displayed as numbers (percentages) and means ± SD, respectively. Non-normally distributed quantitative variables were presented as median (interquartile range). Between groups comparisons were made by $\chi 2$, independent-sample t test, and one-way analysis of variance (ANOVA), as appropriate. Correlations between variables were analyzed by Pearson correlation test or Spearman rank correlation analysis. $P < 0.05$ was considered statistically significant.

Results

In this study, 104 people (88 females and 16 males) with severe mitral stenosis were included. Mean age was 49±10.8 years. Serum calcium, phosphorus, intact parathyroid hormone (i-PTH) and 25(OH)D levels were measured and recorded. They are shown in Table 1. Mitral valve area (MVA) which was calculated by 3D planimetery, was compared to calcium, phosphorus, iPTH, and 25(OH)D levels quantitatively using Pearson and Spearman bivariate correlations. Direct correlation between MVA and calcium and phosphorus levels along with inverse correlation between MVA and iPTH and 25(OH)D levels depicted no significant correlations (Figure 1). To ensure, 25(OH)D levels were divided into 3 levels: deficiency, insufficiency and normal. Fifty four patients (51.9%) had vitamin D deficiency, 35 patients (33.7%) had vitamin D insufficiency and only 15 patients (14.4%) had normal vitamin D levels. Then we investigated the correlation between qualitative vitamin D levels and MVA using kruskal-wallis method which was also insignificant (Figure 2). In addition, considering the normal values of iPTH between 10 and 65 pg/ml, 83 patients (79.8%) had levels above this limit.

On the other hand, Wilkins score was calculated using leaflet motility, valve thickness, subvalvular thickening and valvular calcification severity scores. The number of patients with each score is shown in Table 2. Correlation between total Wilkins score and markers of calcium metabolism was investigated using Pearson and Spearman bivariate correlations. Although calcium, phosphorus and 25(OH)D levels were reversely and iPTH levels were directly correlated to Wilkins score, none of these were statistically significant (Figure 3).

Calcification severity was divided into two groups: scores 1 & 2 were defined as mild to moderate calcification and scores 3 & 4 were defined as severe calcification. As, it is shown in Table 3, no significant difference in 25(OH)D levels is noted between these two groups.

Table 1. Values of calcium metabolism variables

	unit	***Mean/Median***
Calcium	mg/dl	10.1±0.9
Phosphorus	mg/dl	3.8±0.6
25(OH)D	pg/ml	18.5 (3,114)
iPTH	pg/ml	94.6 (10,250)

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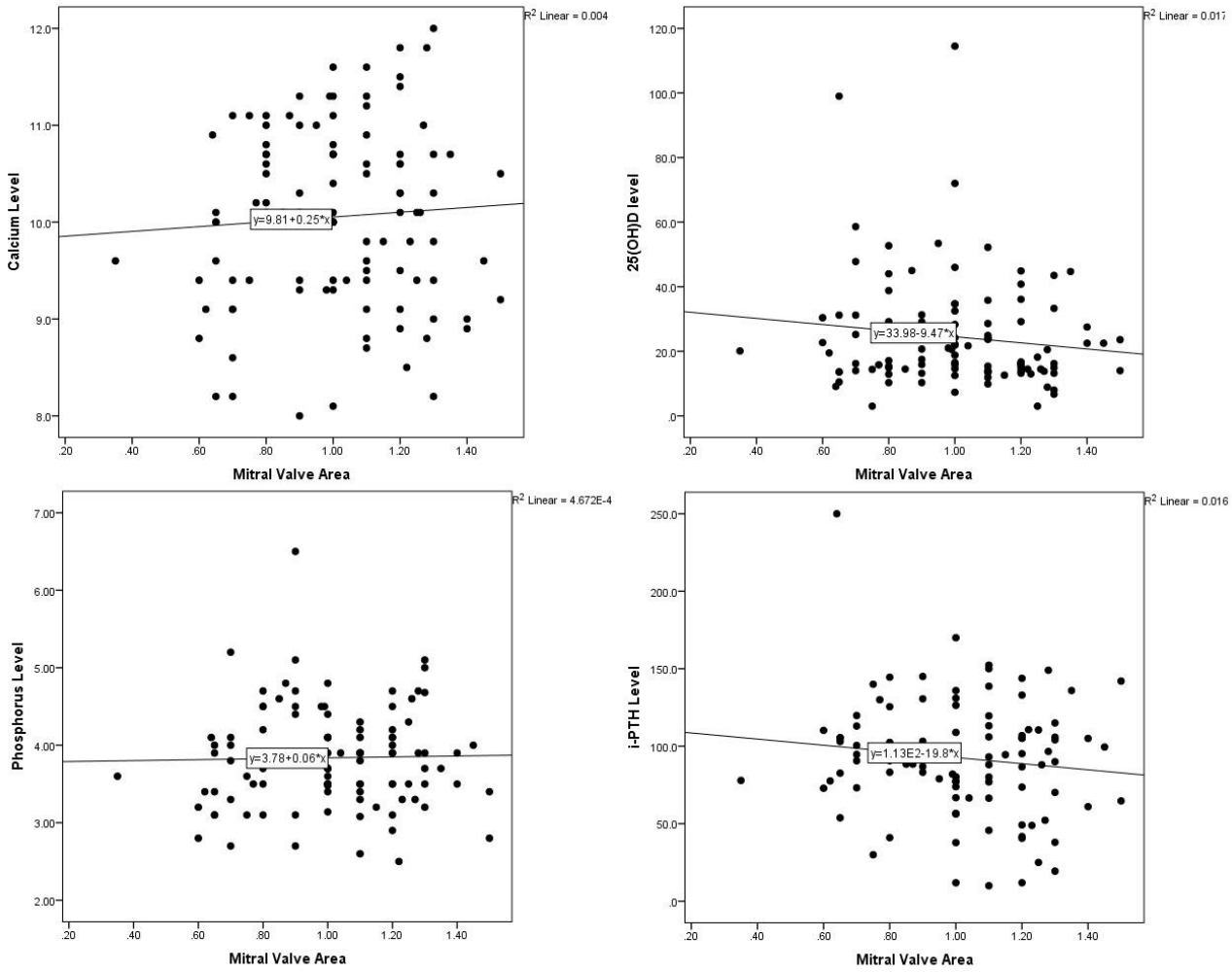

Figure 1. Correlation between mitral valve area (cm^2) and markers of calcium metabolism. No significant correlation is noted. (p=0.53 for calcium, p=0.27 for 25(OH)D, p=0.83 for phosphorus, p=0.41 for iPTH).

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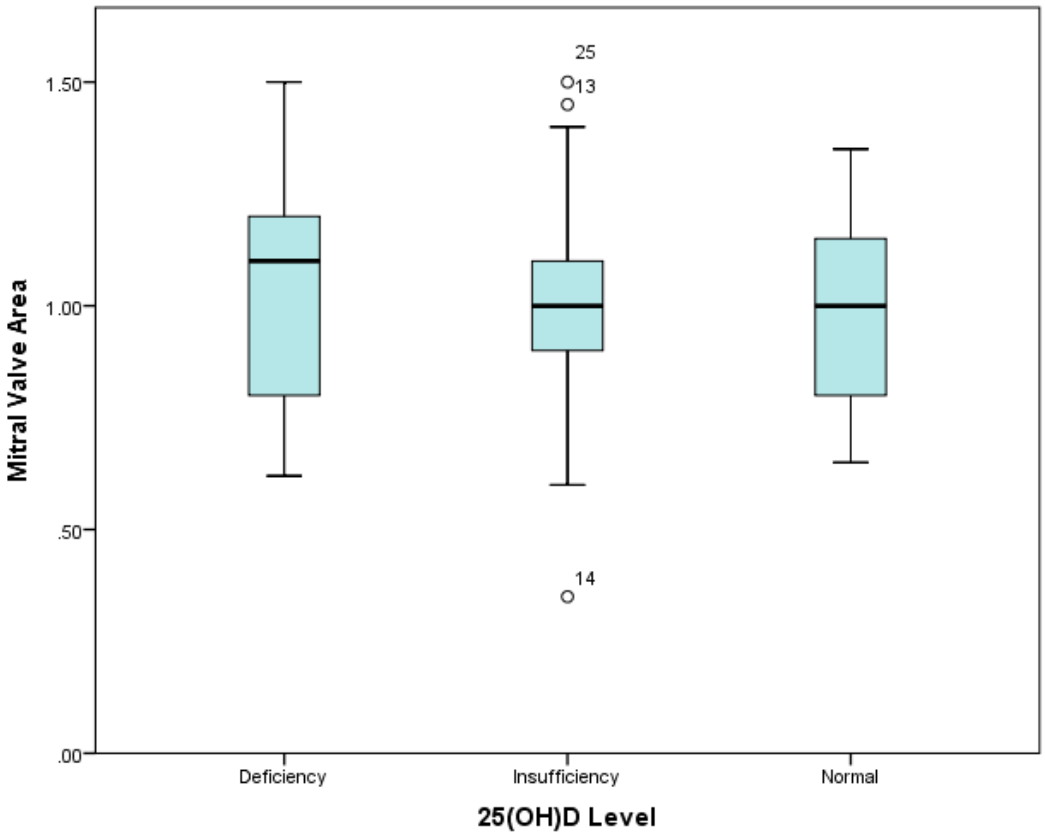

Figure 2. Boxplot comparing MVA between different levels of 25(OH)D, (p=0.67).

Table 2. Frequency of each Wilkins score subtype

	1	2	3	4
leaflet motility	1	86	14	3
Valve thickness	3	82	19	-
subvalvular thickening	3	30	53	18
Valvular calcification	3	78	18	5

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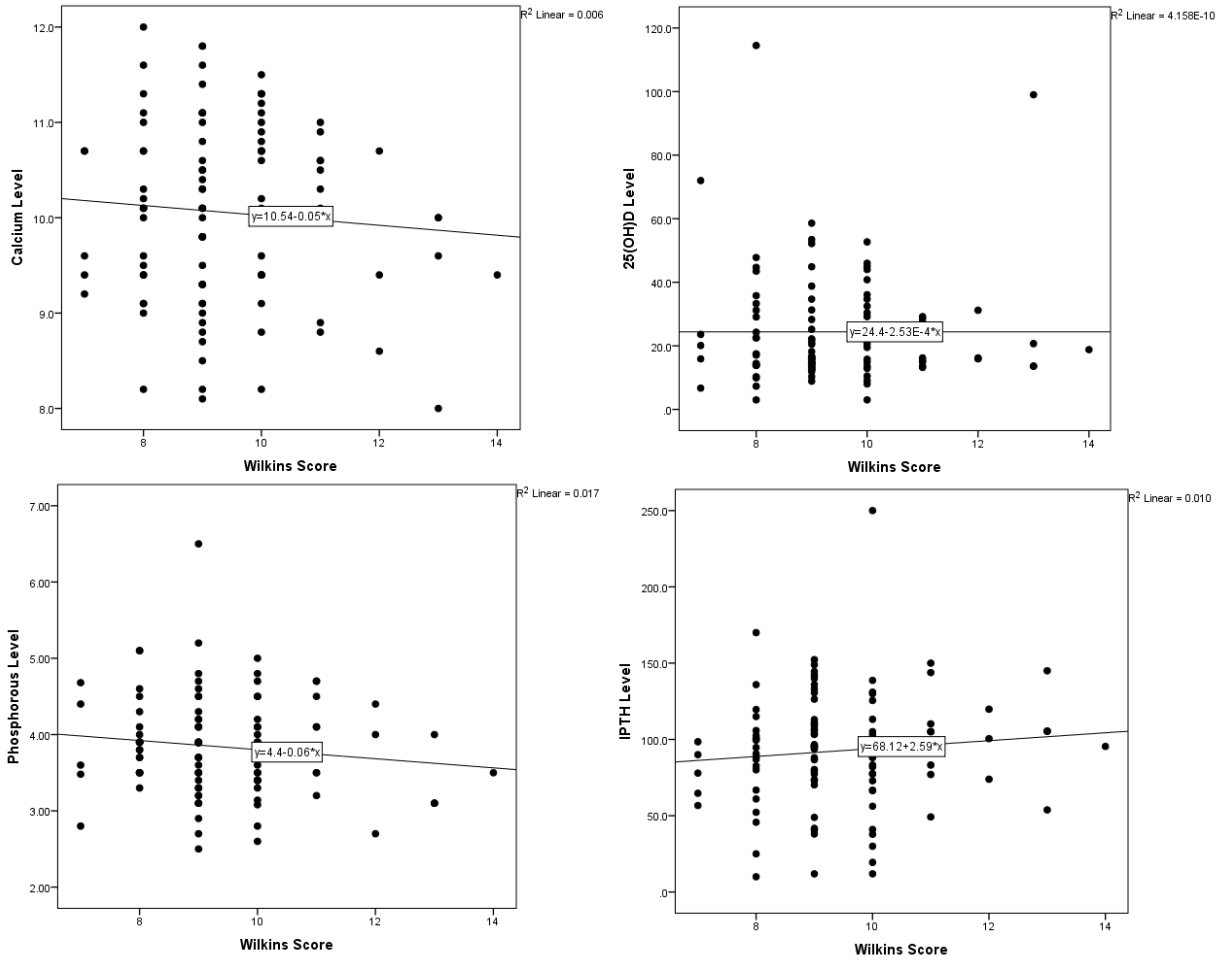

Figure 3. Correlation between Wilkins score and markers of calcium metabolism. No significant correlation is noted. (p=0.43 for calcium, p=0.79 for 25(OH)D, p=0.19 for phosphorus, p=0.39 for iPTH).

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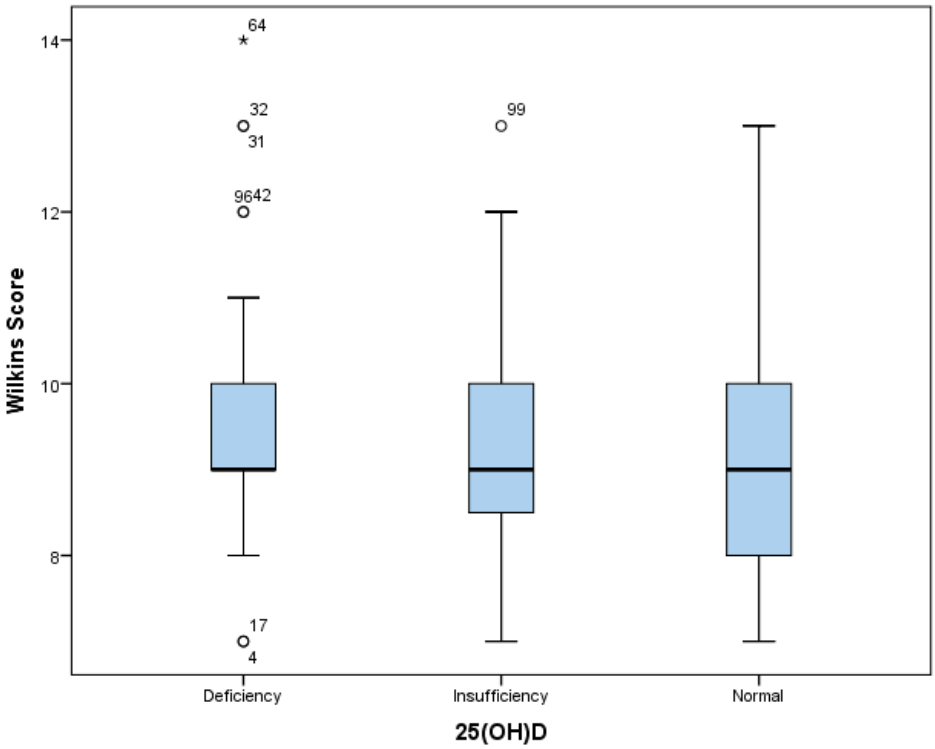

Figure 4. Boxplot comparing Wilkins score between different levels of 25(OH)D, (p=0.77).

Table 3. 25(OH)D levels based on mitral calcification severity

	number	***Mean±SD***
Mild to Moderate	81	24.1±6.9
Severe	23	25.4±19.3

Discussion

We studied the correlation between calcification and other parameters of severity of mitral valve involvement and vitamin D levels among patients with severe rheumatical MS. Our findings showed no statistically significant correlation. However, in our study vitamin D deficiency and

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insufficiency was found in about 85% of patients with severe MS, and this frequency is probably above the levels of general population, which is thought to be 54% to 62% among adults in Iran (10). In addition, iPTH levels above the normal limit were present in about 80% of patients and this finding demonstrated that most patients with severe MS are suffering from secondary hyperparathyroidism.

Yusuf et al, found a negative correlation between 25(OH)D levels and total wilkins and calcification scores. They demonstrated that by dividing patients into 3 groups based on calcification severity, this correlation still holds true (11). We used a similar method to show the results, however no statistically significant correlation was seen. This discrepancy can be a result of differences in patient selection. We enrolled only ones who were somehow at the end stage of their course of diseases and probably the possible effect of vitamin D deficiency had been omitted. In addition, because of the severity of MS in our cases, there was no patients with "no mitral calcification" in our study, and this could affect the results we discussed.

Yavuz et al, used a controlled study to assess this correlation so could directly compare the difference in vitamin D levels between MS patients and normal population. They showed significantly lower vitamin D levels among MS group as well as the negative correlation between vitamin D levels and total wilkins scores (12). Using controlled type study allowed them to conclude this correlation is present not only between patients with different severity of MS, but also between patients and normal subjects. This conclusion was not achieved by our study, but adding a control group would add the data whether these results is are also present among patients with severe MS or not (13-15).

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In patients who are making their first visit, specialists should be consulted to discuss various aspects of their health status (16,17). Their generality, including those that are unclear to the doctor, should be clarified after reviewing the records or conducting a physical examination (18). Scientifically and legally, medical consultation is an important step in planning treatment for patients with systemic problems (19-21).

Aortic calcification and stenosis and its correlation with vitamin D and iPTH levels have also been studied and they showed vitamin D deficiency may play a role in progression of aortic calcification and this effect could be via secondary hyperparathyroidism and elevated iPTH levels (21-24). Since about 40 years have passed since the publication of the "Charter of Patients' Rights" in the world (25,26), more attention has been paid to the role of protecting patients' rights in the medical and nursing professions, and many times, efforts have been made to make this role one of the legal duties (27,28). They should be placed. On the other hand, improving the rights of patients is necessary to determine the standards of clinical services in each country (29,30). Therefore, the existence of laws supporting the rights of the patient, in accordance with the cultural and social context and derived from the views of the people who somehow receive these rights or are responsible for observing them, is the primary and basic condition to guarantee the observance and promotion of the rights of the patients (31-35). Certain robots and technological advancements have demonstrated their potential in enhancing human health and augmenting our medical infrastructure (36-38). However, researchers should provide methods to measure the quality of health care services, because if it is not measured, health care services cannot be managed and improved (39-41).

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In our study most individuals had vitamin D deficiency and elevated levels of iPTH. Although there was no significant correlation between different severity scores and these levels, presence of vitamin d deficiency and hyperparathyroidism among most of the patients with severe MS is a remarkable clue of which calcium metabolism disorders could affect the disease progression.

Conclusion

Vitamin D deficiency and as a consequence, secondary hyperparathyroidism are prevalent among patients with severe MS and may play a role in progression of the disease. However, no correlation was found between severity scores and these levels. Controlled trials could demonstrate the effects of calcium metabolism on calcification of heart valves.

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