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EVALUATION OF 25- HYDROXY VITAMIN D LEVELS IN RHEUMATOID ARTHRITIS AND CORRELATION WITH DISEASE ACTIVITY

Biochemistry

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ABSTRACT

Introduction: Vitamin D has anti-inflammatory, antiproliferative and immunomodulatory action and its deficiency is associated with many autoimmune disorders like RA, IDDM

Aims & Objectives: Estimate serum 25 hydroxyl vitamin D in patients diagnosed with RA and find out correlation between serum vitamin D levels and disease severity in RA.

Materials and Methods: Hospital based cross-sectional study conducted on 50 cases of RA and 50 controls. RA cases were diagnosed according to the 2010 ACR-EULAR classification criteria. Disease activity was measured in patients of RA according to DAS-28. Serum 25- Hydroxy vitamin D was assayed by direct competitive chemiluminescence immunoassay.

Results: Average age was 45.96±12.39 years in cases. RA was almost two times more in females as compared to males. Significant positive correlation was seen between age and RA score in cases. Maximum numbers of cases were in moderate category of disease activity. Vitamin D levels were lower in RA cases as compared to controls and this difference was statistically very significant & Highly Significant Negative correlation was seen between Vitamin D and RA score in cases.

Conclusion: RA is more in females and cases had significantly lower serum vitamin D levels and it may be one of the causes leading to the worsening of RA. As the inflammatory burden increases in RA, the levels of vitamin D are reduced.

KEYWORDS

25- Hydroxy vitamin D, Rheumatoid Arthritis, Autoimmune Disease

INTRODUCTION:

Vitamin D is a steroid hormone that is involved in the metabolism of bone and calcium.[1] Deficiency of vitamin D in India is very common.[2] Rheumatoid arthritis (RA) is most prevalent autoimmune disorder[3], occurs between 30 and 50 years. Women are influenced about three times more than men. Extensiveness of the disease increases with age.[4] The cause of the disease could be ascribable to genetic and non-genetic factors as vitamin D.[5,6] In RA, the first event is the activation of antigen-dependent T cells triggering an immune response essentially of the Th1 type.[3] The role of Vitamin D as anti-inflammatory, antiproliferative and immunomodulatory hormone[7]; and the rationale for relating vitamin D deficiency and RA is supported by following facts: Identification of Vitamin D receptors on macrophages, chondrocytes, and synovial cells in joints of RA patients[8], on antigen-presenting cells and activated T-B lymphocytes[9] and on the primary lymphoid organs.[10] Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated by Vitamin D. Vitamin D causes downregulation of antigen-presenting cells, inhibition of T-cell proliferation, and decreased production of helper T cell-1, cytokines, IL-2.[7] It restrains antibody secretion and production in the β-cells.[11] Vitamin D deficiency has been related to the prevalence of some autoimmune diseases like IDDM, SLE, RA.[12] There is an inverse relationship between disease activity and the concentration of vitamin D.[13]

The relationship between the severity of RA and levels of Vitamin D is a subject of immense interest and therapeutic implications, hence the study was undertaken to estimate serum 25 hydroxyl vitamin D in patients diagnosed with RA and to find out correlation between serum vitamin D levels and disease severity in RA.

MATERIAL AND METHODS:

Hospital based cross-sectional study was conducted for one year in the department of biochemistry in collaboration with department of orthopedics, MMIMSR, Mullana, Ambala, Haryana, India. Hundred subjects of either sex in age group 25-75 years were included. Two groups were made. Group 1: 50 patients that were diagnosed with RA as cases and Group 2: 50 age and sex matched healthy volunteers as controls.

RA cases were diagnosed according to the 2010 ACR-EULAR classification criteria.[14] Subjects who were on the supplementation of vitamin D as a part on any treatment, with any type of renal diseases or on calcium supplements were excluded from the study.

Disease activity was measured in patients of RA according to disease activity score (DAS-28).[15]

Formula: DAS28 = $0.56 \times \sqrt{(28TJC)} + 0.28 \times \sqrt{(28SJC)} + 0.70 \times \ln(ESR) + 0.014 \times PtGA$

DAS-28 score > 5.1= high activity; 3.2 - 5.1= moderate activity and < 3.2 = low activity.

Serum vitamin D [25(OH)D] was assayed by direct competitive chemiluminescence immunoassay (CLIA).[16] Reference range: 30 - 100ng/mL. Below 20 ng/ml= vitamin D deficient; Between 20 - 30 ng/ml= vitamin D insufficient and between 30-100 ng/ml= sufficient of vitamin D.

RESULTS:

In cases the average age was 45.96±12.39 years, ratio of females and males was 16:9 and average RA was 4.26±0.71. In controls average age was 39.44±8.43 years, ratio of females and male was 18:7. Vitamin D levels were lower in cases as compared to controls and this difference was statistically Very significant. (Table 1) We found out the Severity of the Disease Activity on the basis of DAS28 score in cases. Maximum were in moderate category. (Table 2) On comparing vitamin D levels and RA score in male and female cases, Vitamin D was lower in females as compared to males and RA score was almost similar in both and difference was not statistically significant. (Table 3) The Correlation between the age and vitamin D levels in cases and controls was not significant. (Table 4) Significant positive correlation was seen between the age and RA score in cases. (Table 5) A Highly Significant Negative correlation was seen between Vitamin D and RA score in cases. (Table 5; Fig 1)

Table 1: Levels of 25-hydroxyvitamin D in the cases and control groups

Parameter	Group	Minimum	Maximum	Mean ± SD	p- value	Significance
25(OH)D level (ng/ml)	Cases (n=50)	4.20	28.73	9.65±5.93	<0.001**	HS
	Controls (n=50)	30.15	66.64	40.12±9.12		
HS= Highly Significant as p<0.001						

Table 2: Severity of the Disease Activity on the basis of RA Score (DAS28 score) in cases

Severity of disease activity (DAS 28 Score)	Number of cases (%)	DAS 28 Score Mean± SD
Low (< 3.2)	03 (6.0%)	2.77± 0.37
Moderate (3.2 - 5.1)	39 (78.0%)	4.15± 0.45
High (> 5.1)	08 (16.0%)	5.37± 0.18

Table 3: 25-hydroxyvitamin D levels and RA Score in male and female cases

Parameter	Gender	Mean ± SD	p-value	Significance
25(OH)D level (ng/ml)	Males (n=18)	27.29±18.22	0.33	NS
	Females (n=32)	23.75±16.59		
RA Score	Males (n=18)	4.29±0.77	0.57	NS
	Females (n=32)	4.25±0.69		
Non Significant as p>0.05				

Table 4: Pearson's correlation of Age and Vitamin D in cases and controls

Pairs of parameter	Cases			Controls		
	p	r	Significance	p	r	Significance
Age and Vitamin D	0.54	0.08	NS	0.31	0.14	NS
NS=Non Significant as p>0.05						

Table 5: Pearson's correlation of Age and RA score; Vitamin D and RA Score in cases

Pairs of parameters	p	r	Significance
Age and RA Score	0.01*	0.93	S
Vitamin D and RA Score	0.000***	-0.70	HS
S= Significant as p<0.05; HS=Highly Significant as p<0.001			

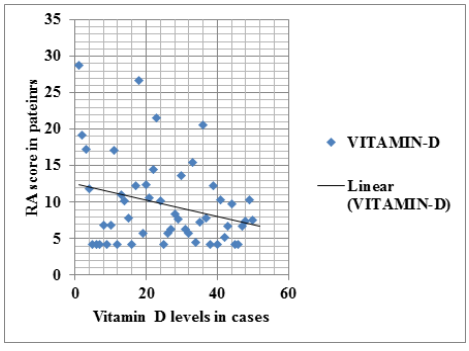

Figure 1: Correlation between vitamin D levels of the patients and their RA score.

DISCUSSION:

RA is most prevalent autoimmune, chronic inflammatory disease.[7] In this study, mean age was 45.96±12.39 years in cases and 39.44±8.43 years in controls. RA was almost two times more in females as compared to males and the average RA score was 4.26±0.71. Significant positive correlation was seen between age and RA score in cases. In a study by Narendra et al[7] and Aisha Yassin et al[17] mean age of cases was 44.92 ± 13.06 years and 31.1±6.2 years respectively; mean age controls was 44.02 ± 11.65 years and 28.05±6.18 years respectively similar to our study. Women comprised 85% of the study participants[17]. Satyajeet et al[18] evaluated Indians and reported that RA mostly affected female patients. Study revealed that the incidence of RA is two to three times higher in women than men. The onset of RA, in both women and men, is highest among those in their sixties.[4]Bunim JJ et al[19] and Sherif R et al[20] concluded that RA with Vitamin D deficiency was more in older age (30-50 years) and female gender.

Vitamin D levels were lower in RA cases as compared to controls and this difference was statistically very significant & Highly Significant Negative correlation was seen between Vitamin D and RA score in cases. Aisha Yassin et al[17] concluded that vitamin D levels were significantly lower in patients as compared to controls and there was significantly inverse correlation between vitamin D levels and RA which is similar to present study. Merlino et al concluded that greater intake of vitamin D might be associated with lower risk of RA.[21] In a study from Morocco, reduced levels of vitamin D were observed in all patients of RA. Authors attributed the above findings to the deficiency of vitamin D leading to decrease stimulation of T helper cell response leading to increased production of pro-inflammatory cytokines, Interferon gamma, TNF-alpha.[22] Lin J et al[23] and Sherif R et al[20] concluded that the RA patients had lower vitamin D values than healthy controls. There was a negative association between serum vitamin D and RA disease activity.

There have been various studies that have assessed the relationship between levels of vitamin D and RA activity. Rossini et al[24] found an inverse association between vitamin D levels and disease activity in RA. Maximum numbers of cases were in moderate category of disease activity on the basis of DAS28 score. Haque UJ[25] concluded that in cases with moderate to high disease activity, vitamin D deficiency was associated with higher DAS scores, pain and disability. Brance M L et al[26] and Gopinath et al[27] found that low levels of Vitamin D were associated with moderate-high disease activity suggesting the importance of optimal Vitamin D levels in RA patients.

CONCLUSION:

It is thus concluded that in RA patients serum vitamin D levels are significantly lower than in healthy control and vitamin D deficiency may be one of the causes leading to the worsening of RA. As the inflammatory burden increases in RA, the levels of vitamin D are reduced. The inadequate vitamin D status in RA, along with considerably strong association with disease activity in RA cases indicates the need for proper evaluation of vitamin D status in RA. It was seen that the incidence of RA in female patients was higher than in men. It is further suggested that vitamin D supplementation in this group may reduce RA activity and for this a long term follow up study is required in order to assess the level of serum vitamin D from the beginning of the course of disease, also before and after therapy in order to monitor the effect of the type and intensity of treatment on the level of vitamin D.

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