Vitamin D Levels in Autoimmune Bullous Diseases

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ABSTRACT

Introduction: Vitamin D deficiency has been implicated in a number of medical conditions including autoimmune disorders. The immunobullous diseases represent a group of conditions characterised by antibody mediated autoimmune response against structural elements of the skin resulting in blistering of the skin and mucosa. Study aimed to determine the vitamin D levels in patients with autoimmune bullous diseases and compare with that of normal healthy controls. To correlate the vitamin D levels with the severity of the disease.

Material and methods: Vitamin D levels in thirty cases of autoimmune bullous disease has been studied and compared with that of forty healthy controls. Correlation of vitamin D levels with the severity of the disease was assessed.

Results: Twenty female and ten male patients were included in the study. 86.67% of the patients had moderate to severe skin involvement and 70% had moderate to severe mucosal lesions. The mean Vitamin D levels in patients was 21.37 with a SD of 8.01 while that of controls was 53.97 with a SD of 19.95. There was no association with the severity of disease and Vitamin D levels.

Conclusion: Deficiency of Vitamin D is noted in autoimmune bullous disease. Severity of the disease showed no relation with serum Vitamin D levels.

Keywords: Immunobullous Disease, 1, 25 Dihydroxy Vitamin D, Pemphigus Vulgaris, Bullous Pemphigoid.

INTRODUCTION

The decrease of rickets after food fortification with vitamin D led physicians to believe that vitamin D related health problems had come to an end. But unfortunately rickets appears to be the tip of an iceberg. Low vitamin D levels as an environmental factor, has been linked to many autoimmune disorders such as type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis etc.[1] The discovery of Vitamin D receptors [VDRs] in most cells of the body and the presence of enzymes that synthesize the active form of vitamin D , namely 1,25 dihydroxy vitamin D in non- renal sites like skin have led to a renewed interest in its functions.[2] Non classical immunomodulatory and antiproliferative responses triggered by active 1,25 dihydroxy vitamin D were first reported more than a quarter of a century ago and might have a significant role in human physiology beyond skeletal and calcium homeostasis.[3] Pemphigus vulgaris and bullous pemphigoid are autoimmune blistering disorders of the skin. The diverse immune modulatory potentials of 1,25 – dihydroxy vitamin D, the high prevalence of vitamin D deficiency in autoimmune disease and insufficient data about the vitamin D status in autoimmune bullous disease patients, intrigued us to perform this study.

Objectives

To determine the vitamin D levels in patients with autoimmune bullous diseases and compare with that of normal healthy controls.

To correlate the vitamin D levels with the severity of the disease.

MATERIAL AND METHODS

This study was conducted in the department of Dermatology of a tertiary care centre in Kerala for a period of 2 years from August 2015 to July 2017. Approval from the institutional ethics committee was obtained prior to the study. Thirty newly diagnosed and histopathologically confirmed cases of immunobullous disease were included in this study. All the patients were examined by one expert physician to minimise observer bias resulting from interindividual variations. The extent of involvement of skin and mucosae were measured and scored as zero to three. Forty healthy volunteers without any significant cutaneous or autoimmune conditions were recruited as controls. Informed written consent was obtained from the subjects. The patients and controls were interviewed regarding medical history and intake of drugs and supplements. Blood samples were collected in the morning after 12 to 14 hours of fasting, from antecubital vein and centrifuged at 3000 rpm for 10 minutes at 4 degree celsius. The separated plasma was submitted for biochemical analysis. Serum concentration of 1, 25 dihydroxy vitamin D was measured by using ELISA method.

STATISTICAL ANALYSIS

Data was analysed using SPSS software. Methods used for analysis included t-test, one-way analysis of variance (ANOVA). *P* value was estimated and a value of less than 0.05 was considered significant. Multiple regression analysis was also used to assess the association with independent variables.

RESULTS

Thirty patients with immunobullous disease were included in the study, of which twenty were females and ten males.

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Controls included thirteen females and twenty seven males. Of the thirty patients, sixteen were diagnosed as pemphigus vulgaris, nine as bullous pemphigoid, four as pemphigus foliaceus and one patient had mucus membrane pemphigoid. Severe disease was noted in thirteen patients, moderate in fifteen and mild in two. So 93.3% of the patients had moderate to severe disease. Moderate to severe skin involvement was noted in 86.67% and moderate to severe mucosal involvement in 70% of the patients. The mean vitamin D levels in patients was 21.37 with a SD of 8.01 whereas in the control group, mean value was 53.97 with a SD of 19.95. This difference was significant with a P value < 0.001. In terms of gender the mean vitamin D levels in female patients was 22.70 with a SD of 8.96, while in controls it was 52.92 with a SD of 16.35. In male patients the mean vitamin D level was 18.70 with a SD 5.03 whereas in controls it was 54.48 with a SD 21.75. Both these were significant with a P value < 0.001. Among patients there was no significant difference of vitamin D levels between males (mean 18.7) and females (mean 22.7). The P value = 0.13.

The mean vitamin D levels in various groups according to the severity of the disease was 15.50 in mild, 20.67 in moderate and 23.08 in the severe group. There was no significant difference among the groups, $P = 0.425$.

DISCUSSION

This study shows that serum vitamin D is significantly lower in newly diagnosed immunobullous disease patients who did not use any medication compared to healthy controls. Joshi et al. in their study of 30 patients in North Indian population with pemphigus vulgaris demonstrated deficient vitamin D levels (11.1 +/- 5.8 ng/ml).[4] Marzano et al. in their study on 67 patients found that pemphigus vulgaris and bullous pemphigoid patients with active disease had lower 25 OH vitamin D levels and higher prevalence of severe hypovitaminosis D as compared with matched control subjects.[5] Immune cells can synthesize the active form of vitamin D3 and express the vitamin D receptor (VDR) which mediates the genomic function of the vitamin.[6] Vitamin D can down regulate the adaptive immune system to lower the incidence of autoimmune disease while boost the innate immune system to fight infections.[7] El Komy et al in their study on 34 pemphigus vulgaris patients and 20 healthy controls concluded that there was a statistically significant difference between both groups regarding suboptimal vitamin D levels (P = 0.007).[8] Epidermal expression of 1,25 OH 2D connects the environment to the immune system via expansion of CD4 + CD25+ regulatory T cells and down – regulating cutaneous immune responses.[9] Considering that vitamin D has modulatory effects on B lymphocyte proliferation and immunoglobulin synthesis, its deficiency may increase autoantibody production in autoimmune bullous diseases.[5] Moreover, calcitriol acts directly on suppressing autoimmune responses by inhibiting Th1 cytokines.[10] In contrast, the effects of vitamin D on Th2 cells are conflicting since it seems to inhibit Th2 cell differentiation, but enhances the secretion of Th2 derived cytokines like IL 4 and IL 5. Finally vitamin D can induce an increase in T regulatory cells and a decrease in expression of IL 17, dampening autoimmune response and inflammation.[5] In our study there was no significant association between severity of disease and the vitamin D levels. Moravvej H et al. in their study on 52 patients with pemphigus observed that patients with more severe disease are likely to have lower vitamin D levels.[11] Marzano et al in their study found out that severity score was inversely associated with vitamin D level regardless of age and there was an increased prevalence of vertebral fractures in spite of not reduced bone mineral density.[5]

Stefan Tukaj in his minireview emphasised the need for further research and clinical trials involving the pemphigus and pemphigoid patients as there are limited number of epidemiological and experimental studies on vitamin D

Gender		Case	Control	Total
Female	N	20	13	33
	Mean	22.70	52.92	34.61
	SD	8.96	16.35	19.31
Male	N	10	27	37
	Mean	18,70	54.48	44.81
	SD	5.03	21.75	24.64
Total	N	30	40	70
	Mean	21.37	53.97	40.00
	SD	8.01	19.95	22.72

Vitamin D levels based on gender among cases and controls.

Severity	N	Mean	SD
Mild	2	15.50	0.707
Moderate	15	20.67	7.168
Severe	13	23.08	9.260

Vitamin D levels based on severity in cases.

Source	Sum of squares	df	Mean Square	F	Significance
Corrected model	18356.562	4	4589.141	17.279	0.000
Intercept	12590.614	1	12590.614	47.405	0.000
Age	5.449	1	5.449	0.021	0.887
Sex	22.630	1	22.630	0.085	0.771
Group	12753.592	1	12753.592	48.019	0.000
Error	17263.785	65	265.597		
Total	147606.748	70			
Corrected total	35620.348	69			

Multivariate analysis of vitamin D with independent factors.

involvement in the autoimmune bullous diseases.[12]

CONCLUSION

The present study shows that autoimmune bullous diseases have increased prevalence of hypovitaminosis D. There was no significant relation between the vitamin D level and the severity of disease. An optimal level of vitamin D might be important in preventing the incidence and exacerbation of autoimmune bullous disease. Causality cannot be concluded from this study. Further studies are needed to determine the possible causative role of hypovitaminosis D, the exact effects of vitamin D and the possible therapeutic implications in autoimmune bullous disease.

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