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Correlation Of Vitamin D Levels With Inflammatory Cytokines In Autoimmune Disorders

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ABSTRACT

Background: Vitamin D is a very important immunomodulator and it is also considered to play an important role in control of immune responses. Its low levels in autoimmune diseases are associated with increased inflammation, which is usually further augmented by the increased pro-inflammatory cytokines. The link between vitamin D and the levels of inflammatory cytokines may reveal the way the disease advances and what means may be used to treat the patient.

Objectives: Aim of Study to determine the correlation of vitamin D and inflammatory cytokines in autoimmune patients.

Study design: A cross-sectional study.

Place and duration of study: Department of Physiology, Central Park Medical College, Lahore, Pakistan from March 2024 to October 2024.

Methods: Cross-sectional study was carried out among the patients with autoimmune disorders. The levels of serum vitamin D .and the concentration of cytokines (IL-6, TNF-alpha, IL-10) were determined. The relationship between cytokine levels and vitamin D insufficiency was determined using statistical analysis (selection of vitamin D insufficiency and association of any correlation and t-tests).

Results: They have analyzed a total of 100 patients with a mean of 40.6 years of age (SD = 12.4). Low concentration of vitamin D was associated positively with various pro-inflammatory cytokines such as IL-6, TNF-a, and IL-1-b ($p < 0.01$). On the contrary, the cytokine levels were lower in patients with high levels of vitamin D. The information indicated that insufficiency of vitamin D increases inflammation in autoimmune diseases.

Conclusion: Human autoimmune disorders are demonstrated to have elevated inflammatory cytokines in the condition of vitamin D deficiency. It is possible that supplementation can control inflammation and control the course of disease but more study needs to be conducted to determine effective doses in terms of clinical practice.

Keywords: *Vitamin D, cytokines, autoimmune disorders, inflammation.*

1. INTRODUCTION

Autoimmune diseases such as rheumatoid arthritis (RA), lupus, and multiple sclerosis (MS) entail the dysregulation of the immune system concerning directing itself against the self-tissue. Pathogenesis of autoimmune projects the interaction of genetic effect, the environmental element, and the immunological

component of which inflammatory cytokines are the key factors in the exacerbation and course of the disease [1]. Vitamin D is one of the regulatory factors, which affects immune response and has been developed as an important modulator in the pathophysiology of

autoimmunity. The active vitamin D, which is, 1,25-dihydroxyvitamin D, is reported to have an impact on the regulation of the immune system as it impacts the innate as well as adaptive immune response [2]. This has been highly contributed by its effect on immune cells, T cells, B cells, dendritic cells and macrophages all which exert vitamin D receptor (VDR) and activate vitamin D through 1a hydroxylase enzyme. Vitamin D deficiency has been associated with various autoimmune diseases and it is believed that low vitamin D levels could put people at risk of immune dysregulation and require elevated levels of pro-inflammatory cytokines [3]. An important role in inflammatory processes underlying the pathology of autoimmune diseases belongs to cytokines: IL-6, TNF-alpha (TNF-alpha), and IL-1beta (IL-1 beta). High levels of these cytokines commonly correspond to the activity of a disease. The importance of Vitamin D in inhibiting these cytokines implies that its inadequacy will prompt inflammation through an escalation of the condition, thus deteriorating the efficacy of the disease in autoimmune disorders [4]. Various studies have suggested that supplementing vitamin D would be effective in decreasing the level of inflammatory cytokines as well as clinical outcome, which implies that vitamin D may be useful in treating auto immune diseases [5]. But even as the cases are increasingly supported by the immunomodulatory capacity of vitamin D, it is advised that the study be continued on the particular relationship between vitamin D and various inflammatory cytokines involved in autoimmune diseases [6]. In this study article, the correlation between the level of vitamin D and the inflammatory cytokines (IL-6, TNF- alpha and IL-1- b extension) would be examined among the autoimmune disorder patients. We also want to explore the idea that the deficiency of vitamin D might be related with an enhanced disease activity and the possible modification of these inflammatory processes by supplementation [7]. This study is going to give meaningful insights of how vitamin D is a regulator of inflammation in autoimmune prevalence in assisting to determine its potential as a therapeutic target. Moreover, the knowledge on the connections between vitamin D and cytokines could be used in revising the ways of treating autoimmune disorders at the clinical level in more prolific ways [8,9].

2. METHODS:

The cross-sectional study was carried out at Department of Physiology, Central Park Medical College, Lahore, Pakistan from March 2024 to October 2024. This study targeted patients with autoimmune disorders, such as rheumatoid arthritis, lupus, and multiple sclerosis. All the patients were collected with blood samples in order to determine levels of vitamin D in serum and inflammatory cytokines (IL-6, TNF-a, IL-1 beta). An in-depth clinical evaluation of disease activity was done with Years of disease activity (DAS-28, SLEDAI, EDSS). The Institutional Review Board granted ethical permission, and all the participants had signed an informed consent. Statistical analysis was done based on SPSS 24.0 software. In order to perform the correlation analysis of the relationship between the levels of vitamin D and the levels of cytokines, descriptive statistics were applied, such as means, standard deviations, and correlation analysis. Independent t-tests were used to compare the groups and $p < 0.05$ was used to determine significance.

Inclusion Criteria:

Patients having an autoimmune disease and aged between 18 to 65 years who will have a stable condition of the disease and must provide informed consent.

Exclusion Criteria:

The study excluded patients with any other chronic illness, being pregnant, taking vitamin D pills, or having active infection.

Ethical Approvals Statement:

The Institutional Review Board (IRB) authorized the study with all the procedures being consistent with the ethical standards of the Declaration of Helsinki. All the participants gave an informed consent, which guaranteed confidentiality and voluntary participation.

Data Collection:

The samples were taken in the form of blood samples and patient medical records. The vitamin D and inflammation cytokine serum levels were determined by the usual laboratory tests. The physicians who attributed to clinical assessments to determine the disease activity and severity were trained.

Statistical Analysis:

The SPSS 24.0 was used to carry out statistical analysis. The demographic and clinical variables of the patients were summarized and described using descriptive statistics. The correlation of vitamin D and inflammatory cytokines was determined with Pearson correlation test. Group comparisons were adopted in an independent t-test. Statistically significant was taken when the p-value was less than 0.05.

3. RESULTS:

One hundred patients (mean age: 40.6 +/- 12.4 years) participated in the study. 35 percent of them were reported to be patients with rheumatoid arthritis, 30 percent had lupus, and 35percent had multiple sclerosis. Most significantly, the serum vitamin D levels were lower when there were more inflammatory cytokines, such as IL-6, TNF-alpha, and IL-1 beta. The relationship between 25-H VD and high levels of cytokines were significant ($p < 0.01$) demonstrating that the deficiency in vitamin D could worsen the immune response in autoimmune diseases. Moreover, the patients with low vitamin D levels had shown a higher disease activity score, which is in line with the increased inflammation. The tendency was especially observed in patients with rheumatoid arthritis, where the interrelation between the lack of vitamin D and the excessive TNF-o and IL-6 concentrations turned out to be particularly significant ($p < 0.05$). Data indicate that the lack of vitamin D can be one of the factors underlying the aggravation of the disease and the increased level of inflammation in autoimmune conditions. Besides, the outcomes highlight the use of vitamin D supplementation as therapeutic modality in reducing inflammation and adverse effects on these patients.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Value
Total Participants (N)	100
Mean Age (Years)	40.6 ± 12.4
Gender Distribution	60% Female, 40% Male
Autoimmune Disease Types	- Rheumatoid Arthritis (35%) - Lupus (30%) - Multiple Sclerosis (35%)
Disease Activity (Mean DAS-28, SLEDAI, EDSS)	5.2 ± 2.1
Vitamin D Deficiency (≤ 20 ng/mL)	45%
Vitamin D Insufficiency (21–30 ng/mL)	30%
Normal Vitamin D (≥ 30 ng/mL)	25%

Table 2: Serum Vitamin D and Cytokine Levels in Autoimmune Disorders

Cytokine	Mean Level (pg./mL) ± SD	Vitamin D Deficiency Group (≤ 20 ng/mL)	Vitamin D Insufficiency Group (21–30 ng/mL)	Normal Vitamin D Group (≥ 30 ng/mL)
IL-6	25.6 ± 8.4	32.7 ± 10.4	24.5 ± 6.7	18.2 ± 4.5
TNF-α	18.3 ± 6.2	22.6 ± 5.1	16.7 ± 4.8	13.1 ± 3.9
IL-1β	12.5 ± 4.1	16.2 ± 5.2	12.0 ± 3.6	9.7 ± 2.8

Table 3: Correlation between Vitamin D Levels and Cytokine Concentrations

Cytokine	Correlation with Vitamin D	p-value
IL-6	-0.68	< 0.01
TNF-α	-0.61	< 0.01
IL-1β	-0.54	< 0.01

Table 4: Disease Activity Scores and Vitamin D Levels

Disease Activity Measure	Vitamin D Deficiency (≤ 20 ng/mL)	Vitamin D Insufficiency (21–30 ng/mL)	Normal Vitamin D (≥ 30 ng/mL)
Rheumatoid Arthritis DAS-28	6.8 ± 1.9	5.2 ± 1.5	4.3 ± 1.3
Lupus SLEDAI	11.2 ± 4.3	8.7 ± 3.2	6.1 ± 2.4
Multiple Sclerosis EDSS	4.2 ± 1.6	3.5 ± 1.2	2.8 ± 1.0

Table 5: Comparison of Cytokine Levels and Disease Activity by Vitamin D Status

Cytokine	Vitamin D Deficiency (≤ 20 ng/mL)	Vitamin D Insufficiency (21–30 ng/mL)	Normal Vitamin D (≥ 30 ng/mL)	p-value
IL-6	32.7 ± 10.4	24.5 ± 6.7	18.2 ± 4.5	< 0.01
TNF-α	22.6 ± 5.1	16.7 ± 4.8	13.1 ± 3.9	< 0.01
IL-1β	16.2 ± 5.2	12.0 ± 3.6	9.7 ± 2.8	< 0.01
DAS-28	6.8 ± 1.9	5.2 ± 1.5	4.3 ± 1.3	< 0.05
SLEDAI	11.2 ± 4.3	8.7 ± 3.2	6.1 ± 2.4	< 0.05
EDSS	4.2 ± 1.6	3.5 ± 1.2	2.8 ± 1.0	< 0.05

4. DISCUSSION:

The natural connection between inflammatory cytokine and vitamin D has been of great importance over the past few years in understanding the importance of autoimmune disorders. The purpose of the study described was to determine the association between serum vitamin D, whose level is tested, and inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta), in patients with autoimmune illnesses; rheumatoid arthritis, lupus, and multiple sclerosis [10]. The results of our study support the accumulating evidence that low blood vitamin D concentration is related to increased pro-inflammatory cytokines, which can worsen the disease activity in such patients.Our study showed that autoimmune disorder patients with a deficiency of vitamin D (20 ng/mL) had significantly higher pro-inflammatory cytokines (IL-6, TNF-alpha and IL-1beta) than those with normal vitamin D level (30 ng/mL) [11,12]. They are also major mediators of the inflammatory cascade, and have been postulated to play a role in pathogenesis of autoimmune diseases. Past study has also demonstrated that vitamin D deficiency leads to amplified amounts of pro-inflammatory cytokines that facilitate the maintenance of inflammation and development of the disease. Indicatively, a report that was conducted by Boni glia et al [13]. showed that immunological supplementation of vitamin D in autoimmune diseases showed a reduction in the serum concentration of IL-6 and TNF-alpha. On the same note, Akbari et al. study of patients with rheumatoid arthritis revealed a correlation between low levels of vitamin D and higher concentrations of TNF-alpha implying that vitamin D deficiency may worsen the disease and inflammation [14]. Such findings indicate that vitamin D may be essential in regulating immune reactions in autoimmune diseases. The vitamin D receptors (VDR) are found in several immune system cells, such as T cells, B and macrophages and its active metabolite, 1,25-dihydroxyvitamin D, is able to directly modulate synthesis of cytokines produced by these cells. This brings out the possibility of vitamin D playing a role in immune response and cytokines synthesis which can control the progress of autoimmune diseases [15,16]. The area of vitamin D also regulating Th1 and Th17 cells which have a role in the inflammatory process has also been looked into in several studies. It is known that Th1 and Th17 cells are the contributors of autoimmune pathogenesis which produce pro-inflammatory cytokines. According to one study by Zemel et al [17]. it was shown that vitamin D may prevent Th1 and Th17

cells differentiation and favor regulatory T cells (Tregs), which may prevent the inflammation [18]. These findings can be supported by our study because patients who had low levels of vitamin D had an enhanced disease activity, which is usually related to enhanced Th1 cytokine and Th17 responses. Such results indicate that in addition to regulating the cytokine generation, vitamin D could also impact pro-inflammatory/ant-inflammatory immune response balance in autoimmune diseases [19]. Also, studies indicate that vitamin D influences the NF-dB and MAPK signaling pathways that are implicated in the secretion of inflammatory cytokines. Another finding in our study is that the correlation between low vitamin D and high IL-6, TNF-alpha, and IL-1 alpha was also high which confirms the study credence that vitamin D deficiency can compound inflammation through inflammatory pathways. Vitamin D can potentially help alleviate excess systemic inflammation present in a variety of autoimmune diseases, by dampening output of the pro-inflammatory cytokines, through modulation of these signaling pathways [20].

5. CONCLUSION:

This study note shows that there is a strong association between vitamin D deficiency and high concentration of inflammatory cytokines in autoimmune diseases. Having sufficient levels of vitamin D can support the reduction of inflammation and enhance the outcomes of a disease. These results indicate the possible therapeutic effect of vitamin D supplement in liquidating autoimmune diseases in patients.

6. LIMITATIONS:

This is a cross-sectional study and this restricts the potential of deriving causality. Moreover, the sample population was quite small and patients were not examined during a long time. Fluctuations in the severity of the disease and the regimen of its treatment in the participants might also influence the outcomes.

7. FUTURE FINDINGS:

Future studies should aim at conducting large scale longitudinal studies that can provide measures on the causal relationship that exists between vitamin D and the level of cytokine of the autoimmune illnesses. Determining the best dose and long-term outcome of supplementing vitamin D, will aid in the provision of better management modalities of these conditions.

Abbreviations:

IL-6 Interleukin-6

TNF-α Tumor Necrosis Factor-alpha

IL-1β Interleukin-1 beta

DAS-28 Disease Activity Score-28

SLEDAI Systemic Lupus Erythematosus Disease Activity Index

EDSS Expanded Disability Status Scale

VDR Vitamin D Receptor

1,25(OH)2D – 1,25-dihydroxyvitamin D

Th1 T-helper 1

Th17 T-helper 17

Tregs Regulatory T cells

NF-dB Nuclear Factor kappa B

MAPK Mitogen-Activated Protein Kinase

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Authors Contribution

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