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Original Article

Vitamin-D Deficiency and Hashimoto's Thyroiditis-Myth or Reality

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ABSTRACT

Objective: To determine the comparison between vitamin D deficiency and Autoimmune Thyroid Disease, especially Hashimoto's Thyroiditis.

Study Design: Cross-sectional Study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital, Rawalpindi Pakistan, from June 2022 to July 2023.

Methodology: In this study, 400 subjects of both genders, between the age of 20-70 years, were enrolled. All the patients who reported for thyroid evaluation at medical Outpatient Department, Combined Military Hospital, Rawalpindi were included in this research. Individuals with renal or hepatic diseases, primary hyperparathyroidism, metabolic bone diseases, epilepsy, subacute thyroiditis, transitory thyroid dysfunction with negative thyroid autoantibodies, and missing lab data were excluded. All the individuals were tested for serum vitamin D, phosphorus, parathyroid hormone, calcium, thyroid function tests including antithyroid antibodies. Vitamin D deficiency and insufficiency were indicated as serum 25(OH)D level <25nmol/L and 25-75nmol/L, respectively.

Results: When compared to 110(27.5%) individuals without autoimmune thyroid disease, 290(72.5%) /patients with Autoimmune Thyroid Disease had a higher rate of vitamin D insufficiency (85.3% vs. 55.5%, p=0.001). There was a significant inverse correlation between serum vitamin D levels and serum thyroid-stimulating hormone levels when gender, BMI, age, and sample season were taken into consideration.

Conclusion: Deficiency of vitamin D has a strong correlation with Hashimoto's Thyroiditis and Autoimmune Thyroid diseases. High blood serum levels of Thyroid stimulating hormone have an independent correlation with decreased levels of vitamin D.

Keywords: Autoimmune Thyroid Diseases, Hashimoto's Thyroiditis, Vitamin-D Deficiency.

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INTRODUCTION

Vitamin D, a steroid molecule, controls the expression of several genes and is primarily synthesized in the skin.[1] The majority of the cells and tissues in the human body consist of the vitamin D receptor (VDR). It works by interacting with the vitamin D receptor and activating the genes that respond to the VDR. The major functions of vitamin D, in addition to providing skeletal strength, are to control the homeostasis of phosphorus and calcium and bone metabolism.[2] Commonly, the variations in vitamin D levels are defined as; levels of serum vitamin D lower than 50nmol//L (20ng/ml) as vitamin D deficiency and levels of vitamin D between 50-72.5nmol/L (20-29ng/ml) as vitamin D insufficiency.[3] Based on recent research, Vitamin D insufficiency and deficiency, which is widespread across the globe, also have some additional significant impacts other than skeletal actions, such as infections, metabolic disorders, cancers, and cardiovascular disorders.[4,5] Low Vitamin D levels are believed to cause Autoimmune Thyroid Disorders (AITD) such as Grave's disease and Hashimoto's Thyroiditis; however, all of the findings have been conflicting so far.[6]

While clinical evidence has demonstrated that taking vitamin D supplements can avert or conceal these autoimmune illnesses, epidemiological investigations have found a strong connection between decreased levels of 25(OH)D in the serum with a greater incidence of a number of autoimmune disorders, such as type 1 diabetes mellitus (T1DM), systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), and inflammatory bowel disorder (IBD).

As vitamin D insufficiency is connected to elevated levels of anti-thyroid antibodies, enhanced thyroid volume, aberrant thyroid activity, and higher concentrations of thyroid stimulating hormone (TSH), certain research revealed low levels of 25(OH)D in

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blood serum of people with AITD.[7] According to other studies, there is either no link or a very weak one between decreased vitamin D amounts and thyroid autoimmunity.[8,9] Coupling vitamin D treatment with cyclosporine successfully stopped the development of drug induced autoimmune thyroiditis in animal studies, whereas BALB/c mice having a deficiency of vitamin D acquired chronic hyperthyroidism.[10] This research will provide evidence-based support to demonstrate if there is an absolute correlation between vitamin D deficiency and Hashimoto's disease or if it is all a myth.

METHODOLOGY

This cross-sectional study was performed at the Department of Medicine, CMH Rawalpindi Pakistan, from 1st June 2022 to 31st July 2023. The Institutional Review Board (IRB) authorized this study, and ethical approval was obtained (reference number 474) Prior to being included in the research, all participants were provided with a description of the study's methodology and were asked for their informed verbal and written consent. Sample size was calculated using the World Health Organization sample size calculator by keeping in view the prevalence of vitamin D deficiency 31.2% reported in Pakistan.[11] Additionally, a non-probability and consecutive sampling approach was applied for the sampling process.

Inclusion Criteria: All individuals who reported for thyroid evaluation irrespective of gender were included in this study.

Exclusion Criteria: All the patients with multiple conditions that can affect vitamin D metabolism, such as renal or hepatic diseases, primary hyper-parathyroidism, metabolic bone disorder, and patients of epilepsy who were prescribed anticonvulsants, gastrointestinal disorders including celiac disease, crohn's disease or those on steroids, were excluded from this study. Patients with subacute thyroiditis or non-thyroidal illness, temporary thyroid malfunction with negative thyroid autoantibodies, and missing lab data were also excluded from this research.

After the informed consent was taken, all the individuals were advised serum vitamin D levels, antithyroid antibodies, and thyroid function tests. For Hashimoto's disease, the relevant antibodies were the Thyroid peroxidase antibodies (TPO-Ab). Additionally, these individuals had their parathyroid hormone (PTH), phosphorus, and calcium levels assessed. All the aforementioned tests were performed on an Automated chemistry and immunoassay analyzer. A serum vitamin D amount of 75-250nmol/L is deemed sufficient; however, vitamin D amounts between 25-75nmol/L are deemed insufficient, and vitamin D amounts lower than 25nmol/L are considered deficient. Antithyroid antibody levels less than 20 AU/ml in patients are considered as negative, but levels more than 20 AU/ml are considered as positive for the disease. In the thyroid profile, the reference ranges of Serum total T3, Serum TSH, and Serum Free T4 (>20 years) are (1.23-3.28) nmol/L, (0.44.5) mIU/L, (10.3-34.7) pmol/L, respectively. A patient is considered to have Hashimoto's disease if their anti-thyroglobulin antibody level is greater than 4 IU/mL and the symptoms of hypothyroidism are present. The reference ranges of plasma Parathyroid hormone, serum inorganic phosphorus (Adults), and serum total calcium are (1.7-9.2) pmol/L, (0.81-1.45) mmol/L, and (2.1-2.57) mmol/L, respectively. All the cases were reviewed.

Statistical Package for Social Sciences version 26 (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA) was employed for the data analysis in this research. Mean and standard deviation were used to represent quantitative variables. Qualitative variables were recorded in the form of frequency and percentage. The Chi Square test and Fischer exact test were used for qualitative variables, whereas the independent samples t-test was used to examine quantitative variables across categories. A *p*-value <0.05 was indicated as statistically significant for all the standard tests employed in this research.

RESULTS

About 400 patients were employed in the present study. The mean age of the patients was 44.95±5.72 years. Of the total patients, 84(21%) were male, and 316(79%) were females. The body mass index (BMI) mean in present study was 23.65±4.23 kg/m2. Moreover, out of the total count, 290(72.5%) individuals had insufficient vitamin D levels, 110(27.5%) individuals had sufficient vitamin D levels, and nobody was deficient. Table-I compares the clinical characteristics of the vitamin D sufficiency and insufficiency categories. The majority of females 245(84.5%) had insufficient vitamin D. Individuals having insufficiency of vitamin D had lesser PTH levels, BMI, and Free T3 as compared to that of the sufficient vitamin D category (*p*-values <0.05). Additionally, there were no variations in the amounts of serum phosphorus, calcium, TPO-AB, and Free T4

(*p*-value >0.05). The frequency of thyroid peroxidase antibody positivity and TSH levels were considerably greater in vitamin D insufficiency patients than in vitamin D sufficiency patients. Out of 400 patients, 220(55.0%) patients had AITD, and 180(45.0%) patients did not have AITD. In Table-II, the baseline features of individuals with AITD and those without AITD are compared. Statistically notable variations were seen in Gender (*p*<0.001), Age (*p*=0.017), BMI (*p*-value <0.001), vitamin D insufficiency (*p*=0.001), PTH (*p*-value <0.001), total T3 (*p*-value <0.001), Free T4 (*p*-value <0.011) TSH (*p*-value=0.008) and serum calcium (*p*-value=0.028) of both AITD and non-AITD categories. Serum Phosphorus levels and TPO-Ab were the same in both AITD and non-AITD groups (*p*-values >0.05).

Table-I: The Characteristics Based on Vitamin D Insufficiency (n=400)

Study Parameters	Vitamin D insufficiency (n=290)	Vitamin D sufficiency (n=110)	*p*-value
Age	45.46±5.37	43.59±6.41	0.003
Gender			
Male Female	45(15.5%) 245(84.5%)	39(35.5%) 71(64.5%)	<0.001
BMI (kg/m2)	21.99±3.20	24.40±2.15	0.001
PTH (pmol/)	1.79±1.67	5.34±2.50	<0.001
Total T3 (nmol/l)	1.41±0.26	2.13±0.52	0.001
Free T4(pmol/L)	20.48±4.28	20.70±7.89	0.632
TSH (mIU/l)	4.60±1.62	3.09±1.04	0.008
Calcium (mmol/L)	2.12±0.41	2.29±0.54	0.305
Phosphorus (mmol/L)	1.29±0.23	1.62±0.23	0.162
TPO-Ab (mIU/L)	269.0±643.0	199.8±496.2	0.117
Prevalence of TPO- Ab positivity n(%)	138(47.6%)	39(35.5%)	0.029

Table-II: The Characteristics Based on the Presence of Autoimmune Thyroid Disease (AITD)

	AITD (n=220)	Non-AITD (n=180)	*p*-value
Age (year)	44.64±4.85	48.6±9.93	0.017
Gender			
Male Female	22(10.0%) 198(90.0%)	62(34.4%) 118(65.6%)	<0.001
BMI (kg/m2)	21.92±2.15	23.55±2.48	<0.001
Vitamin D insufficiency	190(85.3%)	100(55.5%)	0.001
PTH (pmol/)	1.80±1.68	4.06±2.84	<0.001
Total T3 (nmol/l)	1.42±0.27	1.83±0.56	<0.001
Free T4(pmol/L)	23.15±9.44	16.17±7.89	0.011
TSH (mIU/l)	5.48±3.54	2.78±1.71	0.008
Calcium (mmol/L)	2.70±0.76	2.89±0.98	0.028
Phosphorus (mmol/L)	1.86±0.38	1.81±0.39	0.150
TPO-Ab (mIU/L)	273.63±75.64	269.21±71.37	0.548

DISCUSSION

Autoimmune Thyroid disease is the most prevalent medical condition that may result in both Grave's Disease and Hashimoto's Thyroiditis.[12,13] In the case of AITD, pathogenic thyroid autoantibodies are generated in addition to lymphocytic infiltration of the thyroid gland.[12] Pathogenesis of this disease is very complex and is a blend of multiple factors, including immunological, environmental, genetic, and hormonal, like the amounts of vitamin D.[14]

In the current investigation, the prevalence of thyroid autoantibody positivity and TSH levels was considerably greater in individuals with vitamin D insufficiency than in those with sufficient vitamin D. Patients with AITD, and in our case, with HT, had a noticeably greater frequency of vitamin D insufficiency than those without AITD. After adjusting for gender, BMI, age, and season of sampling, it was concluded that lower amounts of 25(OH)D were associated with greater TSH values.

A study by Evliyaoğlu *et al.,* (n=90) suggested the same results as the current study.

The mean vitamin D levels in Hashimoto's Thyroiditis individuals and controls, respectively, were 16.67±11.65 ng/mL and 20.99±9.86 ng/mL. When individuals with HT were compared to the healthy control category, their mean amounts of 25(OH) D were considerably lower (*p*=0.001). Moreover, vitamin D deficiencies, insufficiencies, and sufficiency were all prevalent in HT individuals, with an incidence of 64(71%), 16(17.7%), and 10(11.1%), correspondingly. And just in concurrence with our study, this research showed a significant connection between Hashimoto's Thyroiditis and the incidence of lower vitamin D levels.[15]

The same results were indicated by another research conducted by Kim *et al*. This investigation revealed a strong correlation between HT and lack of vitamin D, with the frequency of 25(OH)D insufficiency among individuals with AITD being substantially greater in patients which didn't have AITD (46.1% vs. 37.1%, *p*=0.011).[16]

Bozkurt *et al.,* findings revealed that levels of 25(OH)D in the blood serum of Hashimoto's Thyroiditis individuals were substantially reduced than the control individuals. The magnitude of deficiency of vitamin D related to volume of the thyroid, time of the condition, and antibody levels and all these parameters raised speculation that 25(OH)D

played an essential part in the onset of Hashimoto's Thyroiditis and its further development into hypothyroidism.[18] These findings supported the results of the current study.

However, unlike the current study, a study by Yasmeh *et al.,* (n=185) represented contradictory results. In comparison to a control group, individuals with HT did not have a greater frequency of vitamin D deficiency. Instead, vitamin D sufficiency rates were greater, and vitamin D insufficiency rates were lower in female HT individuals. Both the HT and control categories of men had mean 25(OH)D readings that were almost identical, and both were vitamin D deficient.[17]

Similarly, according to a recently published meta-analysis of twenty case-control studies, in contrast to controls, subjects with AITD had lower vitamin D amounts, and they were highly inclined to vitamin D deficiency. According to subgroup analysis, individuals with HT and GD also have a reduced amount of vitamin D and have a greater probability of having a deficiency of vitamin D.[19] The threshold for vitamin D deficiency was marked at a 25(OH)D value of 25–50nmol/L (10–20 ng/mL) in the research articles that were included this meta-analysis. Some researches showed no connection between thyroid autoimmune disease and the deficiency of vitamin D.[8,20]

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LIMITATIONS OF THE STUDY

The current research carries a number of limitations. Because research individuals were chosen from a population who came to a single teaching hospital and underwent sampling, there is a possibility of bias in the selection. This research only analyzed retrospective cross-sectional data. As a result, it was unable to establish a direct link between low vitamin D levels and AITD. Because patient sampling did not take place over just one season, fluctuations in blood collection may have had an impact on the outcomes. However, after making some corrections for sampling season, serum vitamin D levels were found to be adversely linked with TSH levels.

CONCLUSION

Autoimmune thyroid disease, especially Hashimoto thyroiditis, was found to be linked with vitamin D deficiency. After making some adjustments for gender, BMI, and age, there was indeed an inverse association between the vitamin D and TSH amounts. More controlled, randomized, and prospective studies are required to ascertain if insufficiency of vitamin D contributes to the etiology of HT or AITD and if taking supplements of vitamin D will be helpful for people with these disorders.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HR & ZW: Data acquisition, data analysis, critical review, approval of the final version to be published.

FAS & TBT: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ALK & I: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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