Original Research

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Correlation Between Vitamin D3 Levels, Autoantibodies, and Antibody-Related Diseases in Patients with Hashimoto's Thyroiditis

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Abstract

Objective: Hashimoto's thyroiditis (HT) is a common autoantibodies condition that impact on the thyroid gland. In this disorder, several autoantibodies play an essential role in the dysfunction of the thyroid, including the metabolism of 1,25-dihydroxyvitamin D3 (1,25 VitD3)-XP, and leading to contributed to the development of related autoimmune diseases. The aim of current study to explore the important correlation between 1,25 VitD3 deficiency and specific types of autoantibodies in the patients.

Materials and Methods: The current involved 150 male's patients, aged 25-50 years, who were compared with same numbers and aged of as healthy controls. Various biomarkers to thyroid gland were measured, including thyroid -stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3). In additionally, anti-thyroid peroxidase (TPO), thyroglobulin (TG), TSH receptor antibodies (TRAbs) and 1,25VitD3 were measured. These biomarkers were measured by the electrochemiluminescence immunoassay technique (ECL). Furthermore, the level of antibodies against VitD3, extractable nuclear antigens m immunoglobulin G4 related disease (IgG4-RD), and glycoprotein 120 were assessed by IDS-system.

Results: This study indicated that blood group B was most commonly associated with HT. Moreover, the concentration of the 1,25 VitD3 was significantly lower in the patient group compared to the control, with level of 3.5 ± 0.1, 35.9 ± 0.3 ng/mL, respectively. Furthermore, an inverse positive correlation in the increased concentrations of TRAbs, TG, and TPO (r=-0.98, -0.66, -0.75) autoantibodies and the low levels of 1,25 VitD3 were detected. Likewise, a strong direct correlation (r=+0.98) was observed in the increased concentrations of both anti-TSH and anti-VitD3. Finally, IgG4-RD had a significantly positive association with the concentrations of 1,25 VitD3-XP, and TSH in patients with a highly significant difference ($p<0.001$).

Conclusion: The findings suggested a significant positive correlation between increased levels of autoantibodies, antibody-related diseases, and low 1,25 VitD3 levels.

Keywords: Hashimoto's thyroiditis**,** autoantibodies**,** TSH-receptor antibodies, hypothyroidism, anti-TPO, anti-vitamin D3

Introduction

Overriding etiological factors contributing to thyroid dysfunction are autoimmune thyroid diseases, also called autoimmune thyroiditis (1). Hypothyroidism develops due to an abnormality in the immune system, where thyroid tissues become the focal aspect of autoimmune attack. Autoantibodies play a critical role in the pathogenicity of autoimmune illness as they selectively target particular proteins within the thyroid gland, activating of inflammation, resulting in functional impairment (2,3). Numerous investigations in recent years have highlighted the complications of these autoimmune mechanisms as well as their impacts on people predisposed to thyroid-related autoimmune reactions (4,5). Hashimoto's thyroiditis (HT) is one of these conditions. It is a condition in which the body attacks its thyroid gland (6). This usually occurs in people with hypothyroidism, which means that their bodies cannot produce the required hormones to maintain iodine levels (7). Therefore, individuals with HT may initially experience an overactive thyroid, a condition where damaged gland cells release hormones into the bloodstream (8). However,

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as the disease progresses, it mainly displays low thyroid levels and probably a swollen thyroid gland (goiter) (9).

In this situation, the body's defense system gradually destroys thyroid cells, making it difficult for the thyroid gland to produce sufficient hormones to meet the body's needs (10). Such an autoimmune response negatively affects the gland tissues and lowers thyroid hormone levels, triggered by autoantibodies that target the gland's own tissue and eventually destroy it. There are autoantibodies that attack thyroid hormones in HT. These include anti-thyroglobulin antibodies (anti-TG) and thyroid peroxidase antibodies (anti-TPO) (11,12). Additionally, autoantibodies against TSH receptors, known as TRAbs, block the thyroid-stimulating hormone (TSH) hormone receptors on the thyroid gland tissue, resulting in diminished hormone production as seen in HT (13,14). Accordingly, Vitamin D3, or cholecalciferol, is crucial for modifying how our body fights off illness (15). It helps control the immune system, affecting both natural and acquired defenses (16). Furthermore, Vitamin D3 plays a crucial role in different parts of immune system including macrophages and thymocytes which important to different against pathogen in the different types of cellular and humoral immunity. This function is essential for regulate the system of immunity (17). There were several Studies suggested a positive correlation between lower concentration of Vitamin D3 in the bloodstream and HT (18).

As a result, low level of Vitamin D3 may lead to trigger the autoimmune condition, the previous condition occurred by stimulated the inflammatory immune response against the tissue of thyroid gland and more one type of immune cells including B-cells and T-cells were breakdown of tolerance and lead to autoimmune. Recently studies have revealed positive correlation between Vitamin D and autoantibodies, as well as autoimmune thyroid such as HT (19-22).

However, the autoantibodies against self-antigen such as (nuclear and extracted nuclear antigens) were had role to attracted the tissue of gland and cause the goiter and block the receptors of received the TSH. Consequently, these autoantibodies and other types were contributed the HT with high significant (23).

Furthermore, immunoglobulin (Ig) G4 is the least prevalent groups the four subtypes of IgG, and have multifunction in autoimmune and related disease. in the allergic disease, IgG4 is play an immune inhibitory role, and prevent anaphylactic reaction to immunogens. However, in the various autoimmune disease can have a pathogenic role by neutralizing their immunogens. glycoprotein 120 (gp120), and IgG-related diseases were played medically important roles in dysregulation of immune response and metabolic process (24).

This study investigated the potential link between Vitamin D3 deficiency and two types of antibodies, which are autoantibodies and antibody-related disease, in individuals with HT.

Materials and Methods

Study Population

This study involved a cohort of 150 males, aged 25 to 50 years, who had received a pre-diagnosis for HT. Additionally, we included a control group of 150 healthy males of the same age and ethnicity. Some of the autoantibodies that were measured in the serum of patients and controls were anti-TG, anti-TPO, anti-vitamin D3, extractable nuclear antigen (ENA), IgG4-related disease (IgG4-RD), thyroid-stimulating hormone receptor antibodies (TRAbs), and gp120. We also used thyroid hormones such as thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), and 1,25-dihydroxyvitamin D3 (1,25 VitD3) (biologically active). The research protocol was approved by the Amara Medical Institute Ethics Committee (decision no: 8/18/6, date: 05.10.2023). All participants have approved on the contribution in the current study.

Study Period

We conducted this study from October to December 2023. In the meantime, we extracted 5 mL of venous blood from the study donor and collected it into gel tubes. To separate the serum, the blood samples underwent centrifugation; thus, the serum levels of FT3, FT4, TSH, anti-TPO 1,25 VitD3 XP, anti-TG, anti-VitD3, TRAbs, IgG4-RD, anti-gp120, and anti-ENA were assessed.

Assessing Serum Autoantibodies and Thyroid Hormone Levels

The electrochemiluminescence immunoassay technique evaluated and formulated the levels of TSH, FT3, FT4, anti-TG, anti-TPO, and TRAbs in both the patient and the control groups, immediately after blood collection. We used the Cobas instrument for analysis and a Roche (Roche Diagnostics GmbH, 2020) kit for the assay.

Estimation of Anti-VitD3 Levels

The serum levels of anti-VitD3 antibodies were determined using ELISA kits from Sunlong Biotech, China. To obtain results, the ELISA analyzer, from Thermo-Scientific Comp, USA, was used as per the manufacturer's instructions.

Measurement of IgG4-RD, 1,25 VitD3 XP, Anti-gp120, and Anti-ENA Concentrations

We used the IDS-iSYS from Immunodiagnostic Systems Ltd., UK, to gauge the serum concentrations of anti-ENA,

IgG4-RD, and anti-gp120. We used kits from the same source for the analysis and calculated the results according to the manufacturer's recommended procedures.

Statistical Analysis

We used the SPSS Statistics 28 (1 New Orchard Road, Armonk, New York, 10504-1722, USA) software to analyze the data and verify the variables in this study. We set the threshold of statistical significance at less than 0.05. Also, independent t-tests, matrix plots, and percentile frequencies were considered to interpret outcomes. We tested all patients and control results using standard Glass' and Cohen's tests, ensuring a value greater than 1.

Results

Figure 1 demonstrates the distribution of ABO blood groups in patients. Notably, groups A and B represent significant proportions, comprising 34.7% and 36.7%, respectively. Furthermore, group B manifests an elevated prevalence in patients, constituting 27.3% of the total. In contrast, the AB group has a percentage as low as 1.3%.

Figure 2 shows the age distribution of the patients. The group of 46-50-years-old ones experienced a higher incidence among patients compared to the other groups, with 112 (74.6%). Additionally, those at the age range of 36-45 years scored 25 (16.7%). Finally, patients under 35 years old totaled 13 (8.7%).

Figure 3 demonstrates the mean concentrations of free thyroid hormones and TSH in the patient group compared to those of control group. The concentration of both free thyroid hormones was lower in the serum of patients (FT3=0.5 ± 0.3 pmol/L, FT4=3.4 ± 0.1 pmol/L) compared to control (4.0 ± 0.04, 15.4 ± 1.1 pmol/L, respectively) with a statistically significant difference ($p<0.001$). Moreover, the concentration of TSH in the serum of patients was significantly higher (89.9 ± 0.8 mIU/L) compared to that of control group 2.6 ± 0.06 mIU/L. A significant difference in 1,25 VitD3 levels was observed between the patient group, with concentration of 3.5 ± 0.3 ng/ mL and 35.9 ± 1.3 ng/mL, respectively ($p<0.001$). The serum autoantibody levels are shown in Table 1. Notably, patients exhibited a substantially higher levels of TPO and TG concentrations in the serum, measuring 132.3 ± 5.5 AU/mL and 152.3 ± 4.7 AU/mL, respectively, compared to the control values of 14.2 ± 1.0 and 12.9 ± 0.9 AU/mL ($p<0.001$).

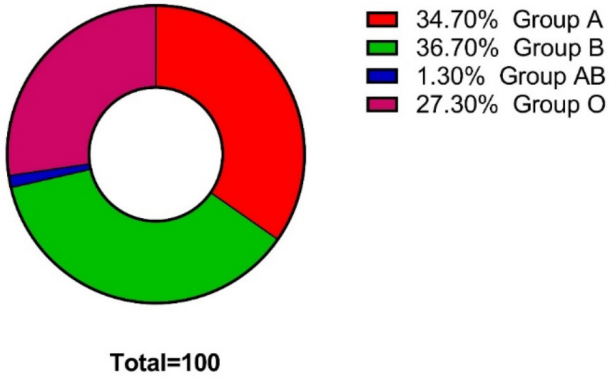

Figure 1. Distribution of the patients' according the blood groups, with the groups A, B, and 0 having higher percentages than the group AB.

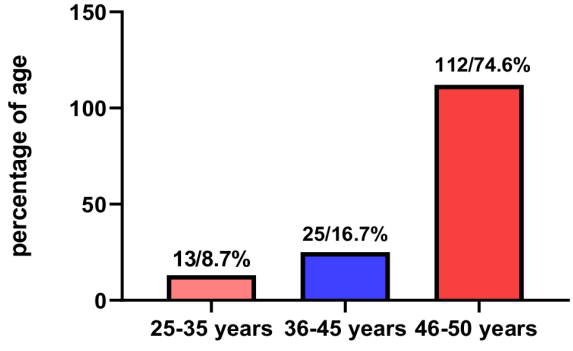

Figure 2. Age distribution of the patients in the current study.

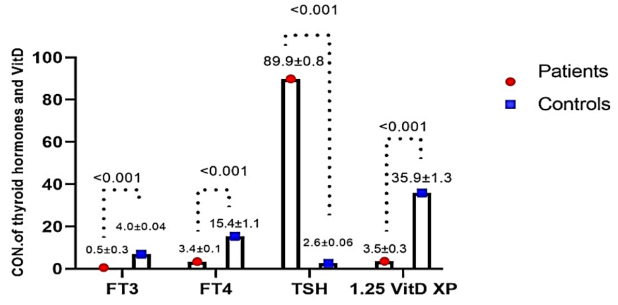

Figure 3. Thyroid function and 1,25 VitD3-XP levels in patients versus control. 1,25 VitD3: 1,25 vitamin D3

Table 1. Comparative concentration of autoantibodies in serum of patients versus control

Abs	Mean ± SE		p-value
	Patients	Controls	
TRAbs (AU/mL)	4.6 ± 0.08	0.4 ± 0.02	**<0.001**
Anti-TG (AU/mL)	152.3 ± 4.7	12.9 ± 0.9	**<0.001**
Anti-TPO (AU/mL)	132.3 ± 5.5	14.2 ± 1.0	**<0.001**
Anti-VitD3 (AU/mL)	4.7 ± 0.08	0.5 ± 0.02	**<0.001**
IgG4-RD (AU/mL)	25.4 ± 1.2	2.5 ± 0.6	**<0.001**
Anti-gp120 (AU/mL)	55.6 ± 5.6	10.5 ± 1.3	**<0.001**
Anti-ENA (AU/mL)	85.9 ± 4.6	10.6 ± 1.9	**<0.001**

TRAbs: TSH-receptor antibody test, TSH: Thyroid-stimulating hormone, Anti-TG: Anti-thyroglobulin antibody, Anti-TPO: Anti-thyroid peroxidase, Anti-VitD3: Anti vitamin D3, IgG4-RD: IgG4-related disease, Ig: Immunoglobulin, Anti-ENA: Anti-extractable nuclear antigen autoantibodies, Anti-gp120: Anti-glycoprotein 120, SE: Standard error

Furthermore, a significant difference was observed in the levels of TRAbs and anti-VitD3 antibodies (Table1). There were statistically significant differences in ENA, IgG4-RD, and anti-gp120 levels between the patient group and the control group ($p<0.001$).

Table 2 and Figure 4 shows a matrix plot of the correlation between TSH, VitD3, and autoantibodies (TRAbs, TG, TPO, and VitD3). The matrix plot analysis reveals a strong positive and direct correlation between levels autoantibodies and TSH. Specifically, the concentrations of TRABs exhibited a statistically significant positive association ($p<0.001$) compared to the other levels of antibodies, demonstrating a high correlation (r=+0.99). Additionally, anti-TPO, anti-TG, and VitD3 manifested a moderately positive correlation coefficient (r=+0.56, +0.75 and +0.66, respectively), with high statistical significance ($p<0.001$). Conversely, the relationship between the concentration of VitD3 and autoantibodies was inversely proportional and strong. Additionally, anti-TPO and anti-TG concentrations showed a moderate negative correlation with VitD3 levels (r=-0.66, r=-0.75).

Table 2. Correlation between TSH, 1,25 VitD3 and autoantibodies (ENA, gp120 and IgG4-RD)

Autoantibodies	Correlation coefficient r	p-value
	Patients	
TSH and ENA	+0.76	0.002
TSH and gp120	+0.78	0.004
TSH and IgG4-RD	+0.99	0.003
1,25 VitD3and ENA	-0.80	0.002
1,25 VitD3and gp120	-0.79	0.001
1,25 VitD3and IgG4-RD	-0.99	0.001

TSH: Thyroid-stimulating hormone 1,25 VitD3: 1,25 vitamin D3 ENA: Extractable nuclear antigen, gp120: Glycoprotein 120, Ig: Immunoglobulin, IgG4-RD: IgG4-related disease

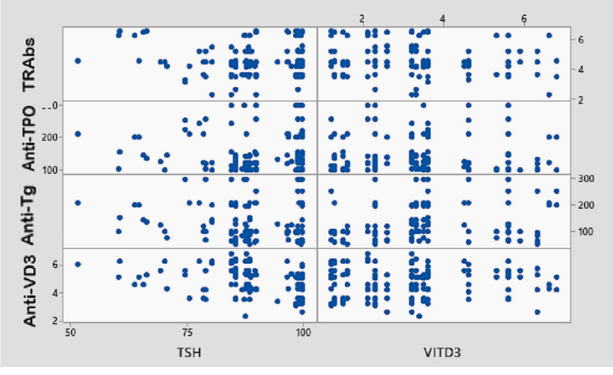

Figure 4. Correlation between TSH, 1,25 VitD3 and their autoantibodies according to the matrix plot.
TSH: Thyroid-stimulating hormone, 1,25 VitD3: 1,25 vitamin D3, Anti-TPO: Anti-thyroid peroxidase, Anti-TG: Anti-thyroglobulin antibody, Anti-VD3: Anti-vitamin D3

Discussion

Several studies have shown that among HT patients, 47% belonged to the O-blood group, 30% to the A blood group, 15.2% to B, and the rest to the AB blood group (25). In a study conducted by Jasim et al. (26), the findings showed that 52% of patients with HT had blood type O, 26% had blood type A, while blood type B and AB were observed in 14%and 8% of patients, respectively.

Our study suggests that middle-aged individuals are at a heightened risk of developing HT compared to other individuals. Our findings were in line with those of Gambineri et al. (27), who found that the incidence of HT was the highest among individuals who were aged 30-50 years, with a peak in those aged 40-50 years. Furthermore, another study revealed a notable increase in the prevalence of HT with advanced age, with the highest incidence being among individuals who were aged 40-60 years (28).

As shown in Figure 3, patients exhibited a decrease in the levels of FT3 and FT4 compared to the control group. This decrease indicates hypothyroidism, in which the thyroid gland does not produce enough hormones, resulting in an inverse relationship with TSH since the body tries to compensate for the deficiency by increasing TSH production. Compared to the control group, we also noticed a significant decrease in 1,25 VitD3 levels. This study suggests a positive correlation between the deregulation of thyroid hormones and uncontrolled metabolism of 1,25 VitD3.

Immune system mistakenly attacks to thyroid gland in patients (29). Furthermore, Fantini et al (30). demonstrated that deregulation in thyroid hormones may contribute to a 1,25 VitD3 deficiency, weakening the regulation of the immune system and leading to an increased risk of immune reactions (30). Also, genetic factors or lifestyle patterns in patients with HT could lead to reduced 1,25 VitD3 levels (31-33). Additionally, some metabolic changes that because hypothyroidism may lead to alterations in the metabolism that might affect how the body processes and absorbs vitamin D3 (34).

Table 1 summarizes the comparative concentration of autoantibodies in serum patients versus the control cohort. We have shown increases in serum levels of anti-thyroid, anti-1,25 VitD3, anti-ENA, anti-gp120, TRAbs, and IgG4-RD in patients compared to the controls. Those antibodies stimulate TSH receptor leading to hyperthyroidism (35). However, in HT, these antibodies may be lower, act as a stimulator or blocker, or have no effect on the receptor (36). Additionally, thyroid gland stimulation and destruction in people with HT or TRAbs can trigger the thyroid gland briefly, but usually, it is destroyed slowly by other mechanisms (37). HT is more commonly associated with anti-TG and anti-TPO antibodies, which typically serve

as biomarkers for diagnosis. The increase in anti-TPO and anti-TG levels are attributed to autoimmune reaction to TPO and TG proteins (38).

Finally, our study on an active role for IgG4-RD in HT, along with lower concentrations of active biological 1,25 VitD3 supported Han et al. (39) were suggested that IgG4-RD could be distinguished by thyroid antibodies in the blood and a high incidence of hypothyroidism (39).

Our study revealed a strong and inverse correlation between autoantibody levels and VitD3. This finding suggests that an increase in the serum level of autoantibodies may directly impact the vitamin concentration, potentially reducing a tangible amount of VitD3 in patient serum. This finding aligns with several studies indicating that VitD3 plays a crucial role in interacting with the immune system and the direct and indirect regulation and differentiation of immune cells (40). A study by Dupuis et al. (41) indicated a potential link between VitD3 deficiency and the presence of thyroid autoantibodies. These findings might suggest an association between both thyroid autoantibodies and HT (41). Finally, we have shown an association between increasing levels of TSH, 1,25 VitD3, and IgG4-RD. This is consistent with several studies that IgG-RTD may represent diagnostic criterium that would help to the aggregation of the case and using these standardized diagnostic criteria would aid in elucidating the shared underlying pathogenesis and clinical implications of IgG-RTD (42-44).

Conclusion

This study has provided insights into the substantial involvement of autoantibodies in the etiology of 1,25 VitD3 deficiency observed in male patients with HT. Significantly, elevated levels of autoantibodies, anti-1,25 and VitD3 were more noticeable in patients compared to controls. Additionally, individuals with blood type B exhibited a higher prevalence compared to other blood groups. Furthermore, the age range of 46-50 years was more sensitive to HT incidence. Further investigation of this age range (46-50 years) has proven that it can be a viable risk factor for HT incidence. Additionally, those patients had higher levels of autoantibodies (TRAbs, TPO, TG, ENA, and VitD3) and significantly elevated levels of antibody-related diseases (e.g., IG4, gp120) compared to the fixed control. Finally, we observed a positive correlation between the autoantibody profile and IgG4, a related disease with a reduced concentration of 1,25 VitD3-XP. This study suggests a potential connection between 1,25 VitD3HT patients, autoantibodies, and antibody-related diseases.

Ethics

Ethics Committee Approval: The research protocol was approved by the Health Research Ethics Committee RSUP Dr. M. Djamil Padang (decision no: LB.02.02/5.7/157/2022, date: 26.04.2022).

Informed Consent: All participants have approved on the contribution in the current study.

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Footnotes

Authorship Contributions

Concept: A.S.K., A.S.A.K., Design: A.S.A.K., Data Collection or Processing: A.S.A.K., Analysis or Interpretation: A.S.K., A.S.A.K., Literature Search: A.S.K., Writing: A.S.K., A.S.A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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