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Association among Vitamin D Deficiency with some Inflammatory Marker in Iraqi Patients with Autoimmune Thyroiditis

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Abstract

Background: Hashimoto thyroiditis (HT) is a common chronic autoimmune disease of the thyroid gland, characterized by painless goiter and elevated thyroid antibodies. Hypovitaminosis D (vitamin D insufficiency and deficiency) is common among patients with HT.

Method: : the study include (60) subjects compared with 30 apparently healthy control group were visiting nursing home hospital in Baghdad medical city, Levels of serum thyroid-stimulating hormone (TSH), free-triiodothyronine (FT3), free thyroxine (FT4), TgAbs, and TPOAbs were determined with automated immuno chemiluminescent assay (ICMA) kits (Abbott Laboratories, IL, USA). Levels of serum 25-hydroxyvitamin D 25(OH) D) were determined using a competitive protein-binding assay (Roche Diagnostics, Mannheim, Germany). The inter-assay variation coefficient for 25(OH)D measurement was 8.5%.

Results: the level of the study parameters in autoimmune thyroiditis which show significant correlation in age ,BMI, vitamin D, anti TPO antibody,IL-17, TNF-α and thyroid function ($p<0.05$) ($p<0.01$) test but calcium shoe non significant correlation between patients and control group.

Conclusion: The present work shows a significant association between circulating 25(OH)D and HT, also IL-17.

Keywords: *Vitamin D; autoimmune thyroiditis; Iraqi patients*

Introduction

Autoimmune thyroid disease (ATD) is the most prevalent endocrinopathy [(1)].The prevalence of ATD was as high as 60% of patients, 40% of whom additionally suffered from thyroid disorders including overt hypothyroidism (24%), subclinical hypothyroidism (8%), and hyperthyroidism (8%) [(2)]. According to Krzewska et al. the ATDs Hashimoto's thyroiditis and Graves' disease, are the most prevalent autoimmune diseases in children and adolescents. The autoimmune pathology in clinical practice seems a difficult task for endocrinologists, with many unknowns. Modern laboratory diagnosis with high sensitivity allows the detection of autoantibodies in autoimmune thyroiditis (AIT) and the monitoring of a wide spectrum of markers of the immune status of patients for diagnostic research and treatment [(3)].

Hashimoto thyroiditis (HT) is the most common chronic autoimmune thyroid disease characterized by painless goiter and elevated serum thyroid antibodies. HT may emerge with stimulation of environmental factors in genetically susceptible individuals. Predisposing genes are human leukocyte antigen (HLA), cytotoxic T lymphocyte antigen-4 (CTLA-4), protein thyrosin phosphatase non-receptor type 22 (PTPN22) and thyroglobulin (Tg) genes [(4)]. In recent years, vitamin D deficiency is reported to cause autoimmune diseases. Vitamin D receptors (VDR) were shown to be present in intestinal epithelium cells, osteoblasts, renal cells and most importantly immune system cells (T lymphocytes, monocytes, dendritic cells and also B lymphocytes). Vitamin D inhibits T lymphocyte proliferation, particularly T helper 1 (Th1) lymphocytes. It may increase T helper 2 (Th2) lymphocyte formations. Role of vitamin D in pathogenesis of HT is reduction

of anti-inflammatory Th lymphocytes and elevation of inflammatory Th1 cells. T helper 17 (Th17) cells were also found to be associated with HT pathogenesis [5].

25-hydroxyvitamin D [25(OH)D] is involved in the regulation of many physiological processes in the body and beneficial effects related to treatment with cholecalciferol were noted in immunodeficiency, cardiovascular disorders, anemia, diabetes, various pathologies of the liver, and gastrointestinal tract disorders, as well as for tuberculosis and malignant tumors of the breast and intestine [6,7]. Both genetic predisposition and environmental factors may contribute to the development of autoimmune diseases. Increased levels of immune inflammation markers may affect the course of immuno-endocrine pathology. A gradual development of the autoimmune inflammatory process, when combined with hypothyroidism and DM, may significantly contribute to the development of endothelial dysfunction and the consequent development of vascular complications [8].

Recently, Th17 cells and their hallmark cytokine (interleukin, IL)-17 have been recognized as crucial contributors to the pathogenesis of thyroid autoimmunity [9]. Production of IL-17A and IL-17F is characteristically attributed to Th17 cells. These ILs can act on a broad range of cells, including epithelial cells, fibroblasts, and macrophages inducing the release of proinflammatory tissue mediators such as interleukins IL-1β, IL-6, and IL-8, growth and hematopoiesis stimulating factors – tumor necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor, and granulocyte colony-stimulating factor (G-CSF), and tissue components degrading enzymes metalloproteinases [10]. Early studies demonstrated that IL-17 stimulates production of other cytokines such as IL-6, IL-8, and G-CSF in nonimmune cells such as connective tissue fibroblasts and epithelial cells via activation of the nuclear factor-κB (NF-κB) transcription factor [10].

In addition, IL-17 demonstrates strong synergic action being combined with other cytokines, such as IL-1β and TNFα. Previous studies have shown that patients suffering from AITD have enhanced levels of IL-17A and Th17 lymphocytes revealed in blood and colonizing thyroid tissue as well as a marked in vitro differentiation of Th17 cells [10].

Methods and material:

The study include (60) subjects compared with 30 apparently healthy control group were visiting nursing home hospital in Baghdad medical city between October to April 2019. The diagnosis of Hashimoto thyroiditis was made on the basis on clinical examination, and Anti TPO antibody in all of patients.

The Demographic and clinical variables were obtained from participant report and electronic medical records. Demographic include age, sex,and body mass index (BMI). BMI was calculated as weight (kg)/squared height (m^2). A fasting morning venous blood sample was obtained from each participant. Levels of serum thyroid-stimulating hormone (TSH), free-triiodothyronine (FT3), free thyroxine (FT4), TgAbs, and TPOAbs were determined with automated immuno chemiluminescent assay (ICMA) kits (Abbott Laboratories, IL, USA). Levels of serum 25-hydroxyvitamin D (25(OH)D) were determined using a competitive protein-binding assay (Roche Diagnostics, Mannheim, Germany). The inter-assay variation coefficient for 25(OH)D measurement was 8.5%.

Inclusion Criteria

The age range samples were taken between 18–45years for two groups and without any chronic condition other than thyroid are included in this study.

Exclusion Criteria

The criteria were excluded from this study including: bone and muscle cardiac disease, pancreatic, hepatobiliary, diabetes, hypertension, malignancy, oral contraceptive pills (OCP), and pregnancy.

Statistical analysis

The Statistical Analysis System- SAS (2012) program was used to effect of difference factors in study parameters. The standard deviation was used to significant compare between means. The correlation coefficient between difference parameters in this study was estimated.

Results

Table(1) show the level of the study parameters in autoimmune thyroiditis which show significant correlation in age ,BMI, vitamin D, anti TPO antibody,IL-17, TNF-α and thyroid function ($p<0.05$) ($p<0.01$) test but calcium shoe non-significant correlation between patients and control group.

Table(1) show the level of the study parameters in autoimmune thyroiditis

Parameters	Mean ± SD		P-value
	panties	control	
Age(year)	31.5±8.2	39.4± 10.2	0.00096*
BMI(kg/m^2)	29.9±2.2	27.03±2.7	000023*
Vitamin D (ng/ml)	11.15±4.35	35.16±4.2	0.00001**
Anti TPO antibody (IU/ml)	173.58±19.43	13.69±1.5	0.00001**
IL-17 (pg/ml)	2.23±0.7	1.48±0.44	0.00001**
TNF-α(pg/ml)	10.81±1.69	6.5±1.6	0.00001**
TSHmIU/mL	3.5±1.17	1.42±0.12	0.00001**
FT3 ng/L	0.9±0.3	7.0±1.5	0.00001**
FT4 ng/L	4.75±2.3	9.8±1.5	0. 00001**
PTH(pg/ml)	45.17±5.7	40.89±2.1	0.000195*
Calcium mg/dl	8.7±1.5	9.07±0.46	0.168664NS
* (P<0.05), ** (P<0.01), NS: Non-significant.			

Table (2). Correlation coefficient between vitamin D, anti-TPO,

TNF-α, IL-17 and other parameters

The group	Correlation coefficient(r)			
	Vit. D	Anti TPO	TNF-α	IL-17
Age	0.0141	-0.1416	0.1268	-0.0547
BMI	-0.0437	0.0873	-0.2315	-0.3268
TSH	-0.3024	-0.2948	-0.426	0.2143
T3	0.0712	0.1379	0.0185	-0.049
T4	-0.1353	0.079	0.1797	-0.0246
PTH	-0.0606	0.1245	0.1797	0.2484
Ca	-0.374	0.198	-0.1773	0.0659
Vit. D	------	0.1094	0.1848	-0.2689
Anti TPO	0.1094	------	-0.1321	-0.0988
TNF-α	0.1848	-0.1321	-----	0.1883
IL-17	-0.2689	-0.0988	0.1883	-----

Discussion

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune disorder characterized by the destruction of thyroid cells caused by leukocytes and antibody-mediated immune processes accompanied by hypothyroidism. In recent years, evidence has emerged pointing to various roles for vitamin D, including, proliferation and differentiation of normal and cancer cells, cardiovascular function, and immunomodulation. Vitamin D deficiency has been especially demonstrated in HT patients [(11)].

Our results show the level of the study parameters in autoimmune thyroiditis which show significant correlation in age ,BMI, vitamin D, anti TPO antibody,IL-17, TNF-α and thyroid function ($p<0.05$) ($p<0.01$) test but calcium show non-significant correlation between patients and control group.

In recent study The results of this study showed a significant reduction of anti-Tg Ab (anti-thyroglobulin antibodiesand) TSH hormone in the Vitamin D group compared to the start of the study; however, there was a no significant reduction of anti-TPO Ab in the Vitamin D group compared to the placebo group ($p=0.08$). No significant changes were observed in the serum levels of T3 and T4 hormones. Therefore, vitamin D supplementation can be helpful for alleviation of the disease activity in HT patients [(12)].

Recently, the receptors of 1,25-dihydroxyvitamin D have been found on many cells, including immune cells(13).The expression of 1α hydroxylase (cyp27B1) activity in many of these cells supports[(14-16)] the idea that the Vitamin D has immunomodulating effects. Several genetic studies have shown an association between gene polymorphism of Vitamin D receptor and of 1α hydroxylase (cyp27B1) [(17-20)] with autoimmune thyroid diseases (AITDs).

However, the relationship between Vitamin D and AITDs is still a controversial issue.[(21)] Many studies have already pointed out a relation between low concentration of Vitamin D and AITDs;[(22-25)] however, the cause and effect relationship is not known. The findings of one prospective case-control study wer54e performed in Amsterdam(26) and did not support the association between low Vitamin D level and early stages of thyroid autoimmunity.

Kivity *et al*. in a cross-sectional study compared the level of Vitamin D in patients with AITDs, non-AITDs, and healthy people. They showed that the prevalence of Vitamin D deficiency was significantly higher in patients with AITDs than healthy persons. The rate of Vitamin D deficiency was also higher in patients with non-AITDs than healthy population.[(27)]

Shin *et al*. in Korea studied the association between Vitamin D and TPO-Ab in patients with and without AITDs. They demonstrated that there was a significant negative correlation between Vitamin D level and TPO-Ab in patients with AITDs.[(23)]

In a study in Turkey, Bozkurt *et al*. studied the relation between Vitamin D deficiency and Hashimoto's thyroiditis. They compared the level of Vitamin D and severity of Vitamin D deficiency between euthyroid patients with Hashimoto's thyroiditis and a healthy control group. Their results pointed out that there was correlation between severity of Vitamin D deficiency and thyroid volume, level of thyroid autoantibodies as well as duration of Hashimoto's thyroiditis. They concluded that Vitamin D may have potential role both in development and progression of Hashimoto's thyroiditis to hypothyroidism.[(24)]

In a study in Tehran, Iran, Mansournia *et al*. reached to the similar conclusions. Furthermore, they showed that by 5 ng/mL increases in the level of Vitamin D, the risk of occurrence of Hashimoto's thyroiditis would be decreased by 19%.[(28)].

On the other hand, some studies did not support the association between Vitamin D and thyroid autoimmunity[(29-32)] Effraimidis *et al*. have conducted two case–control researches in the framework of Amsterdam AITD cohort study to determine the association between Vitamin D and early stages of thyroid autoimmunity. In one cross-sectional study, they compared the concentration of serum Vitamin D between euthyroid participants with genetic susceptibility for AITDs and negative thyroid antibodies and controls who were healthy women without family history of AITDs.

Although Th1-driven autoimmune response has long been considered as dominant for HT development, recent studies are suggesting an evident participation of Th17 cells in AITD, particularly HT pathogenesis.

Ethical Clearance: The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

Conflict of Interest: The authors declare that they have no conflict of interest.

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