VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH HYPOTHYROIDISM

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ABSTRACT

Background

Vitamin D has a major role in autoimmune diseases. The vitamin D receptor (VDR) is expressed in a variety of body tissues including thyrocytes. It's suggested that there is a potential role of vitamin D in the development of Hashimoto's thyroiditis and its progression to hypothyroidism. Vitamin D deficiency is a worldwide problem that has health consequences.

Objectives

To evaluate the association of vitamin D deficiency in hypothyroid patients in Sulaimani Governorate.

Methods

In this study 200 participants were included; consisted of 100 diagnosed hypothyroid patients and 100 healthy controls; age range was matched. All subjects (n = 200) were evaluated for 25(OH) vitamin D. Thyroid autoantibody [anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG)] levels with thyroid-stimulating hormone (TSH) and free thyroxine (T4) were measured in group 1.

Results

Serum 25(OH) vitamin D level was significantly lower in hypothyroid patients (13.6 ± 11.4ng/ml) than in controls (24.1 ± 20.7ng/ml), ($P < 0.001$). 83% of hypothyroid cases were vitamin D deficient, which is significantly more than control 54% ($P< 0.001$). (100) hypothyroid cases were correlated to anti-TPO and anti-Tg; (83) case had vitamin D deficiency, (66) and (46) cases of vitamin D deficient group were anti-TPO, anti-Tg positive respectively (P-value =0.42, P-value =0.13).

Conclusions

Our findings indicate that patients with hypothyroidism present with lower vitamin D levels than healthy controls; deficiency of vitamin D was linked to the presence of antithyroid antibodies.

Keywords: *Vitamin D deficiency, Hypothyroidism, Autoimmune disease.*

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INTRODUCTION

Vitamin D is a fat-soluble vitamin which is of great interest that can play a major role in decreasing the risk of many chronic conditions, including autoimmune diseases, infectious diseases, endocrine conditions and cardiovascular diseases [1]. Vitamin D deficiency is a worldwide problem that has health consequences, it is pandemic [2]. It is a global health problem caused mainly by insufficient exposure to sunlight [3]. The main sources of vitamin D is from sun exposure, food, and supplements, which is considered to be biologically inactive, and must undergo activation through 2 consecutive enzymatic hydroxylation reactions occurring in the liver and kidney [4].

The vitamin D receptor (VDR) is expressed in a wide variety of body tissues, including the brain, heart, skin, GIT(gastrointestinal tract), gonads, prostate, breast, and immune cells, as well as bone, kidney and thyroid gland [5].

Vitamin D has a great effect on the immune system; this effect includes an enhancement of innate immunity associated with regulation of acquired immunity. There is a relationship between vitamin D deficiency and the prevalence of some autoimmune diseases like diabetes mellitus [6], rheumatoid arthritis [7], inflammatory bowel disease [8], and multiple sclerosis [9]. It has been suggested that vitamin D supplementations prevent the development of autoimmune diseases, also it could be used in their treatment [10, 11].

Improving patients' vitamin D status is an essential aspect of primary care. As adequate vitamin D status is necessary for good health, it is beneficial for reducing the risk for bone disease and plays a great role in the reduction of pain, autoimmune diseases, cancer, heart disease, and cognitive function [12].

Hypothyroidism is a common endocrine disorder**.** Hashimoto's thyroiditis (HT chronic lymphocytic thyroiditis) is the most common cause of hypothyroidism [13–15].

Many studies may suggest a potential role of vitamin D in the development of Hashimoto's thyroiditis and its progression to hypothyroidism[16,17].

The aim of the study is to evaluate the association of vitamin D deficiency in hypothyroid patients in Slemani Governorate.

PATIENTS AND METHODS

The study was a case-control study, involved 200 cases, and the study population consist of adult hypothyroid patients and controls. According to the history taken, they are classified into two different groups: Group 1 are Hypothyroid patients (previously diagnosed by physician and were using Levothyroxine as treatment); [18Male and 82 Female], and group 2 were controls whom were healthy individuals [19 Male and 81 Female], they were not complaining from any chronic medical diseases, with no history of thyroid diseases that may interfere with our results, in addition, they weren't receiving vitamin D supplementation.

These cases were collected in Central Medical Laboratory -1 in Slemani. All of the recruit's cases gave their informed consent to be engaged in the study.

Blood samples were collected randomly started in December 2018, completed in March 2019, serum samples stored in the laboratory until sample analysis is performed.

Exclusion criteria for the study includes, pregnant women, hypothyroidism from thyroidectomy, cases on vitamin D supplementations, fractures or bone diseases, chronic kidney disease ,drugs that may affect metabolism of vitamin D {Statins, Antiepileptic drugs, and Corticosteroids [18] }.25 hydroxyvitamin D level 25 (OH) D was evaluated in both groups using electrochemiluminescence (ECL) with Cobas E411 analyzer. The Hypothyroid group were analyzed for Free Thyroxine (FT4),thyroid-stimulating hormone (TSH), anti-thyrotropin antibody (anti-TPO) and anti-thyroglobulin antibody(anti-Tg) using ECL with Cobas E411 analyzer.

Depending on the lab reference; patients whose serum 25 (OH) D levels were below (20 ng/ml) were considered as vitamin D deficient, anti-TPO above 34IU/ml and anti-Tg above 115 IU/ml considered as autoantibody positivity.

Data entry performed via using an excel spreadsheet then the statistical analysis was performed by the SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences).

Some variables as Anti-TPO, anti-Tg, TSH and Vitamin D concentration were shown to be not normally distributed. The data presented in tabular forms showing the frequency and relative frequency distribution of different variables among both groups of patients. The

statistical significance of the difference in mean (for normally distributed quantitative variables) between two groups was assessed using an independent sample t-test.

For non-normally distributed quantitative variable which can be described by Median. In such conditions the mean rank is useful for comparing the central tendency (group center) of compared groups. The difference in the mean rank between 2 groups was assessed by non-parametric test (Mann- Whitney).

Chi-square tests were used to compare the categorical data between these two groups of patients for different variables. P-values of 0.05 were used as a cut off point for the significance of statistical tests.

RESULTS

A total of 200 participants were included in the study, and there was no age difference between the groups. The hypothyroid cases consisted of 18 males and 82 females, controls included 19 males and 81 females. The mean age of the hypothyroid group was (46.2 ± 13.2 years) and for controls was (45.9 ± 12.4 years) Table (1).

Serum 25 (OH) D levels was significantly lower in hypothyroid patients than in controls (P < 0.001) as illustrated in Table (2). The prevalence of low 25(OH) D level in cases of hypothyroid (83%)was more than that of healthy control (54%) as shown in Table (3), (P< 0.001).

For hypothyroid patients (n=100), we measured levels of vitamin D and both autoantibodies (anti-TPO, anti-Tg), then classified them into two groups according to vitamin D level {vitamin D deficient group and vitamin D sufficient group} consisted of 83 and 17 patients respectively.

As a result, 66 and 46 cases of vitamin D deficient group were anti-TPO, anti-Tg positive respectively, thus when investigating the association of thyroid autoantibodies, we found that there was a correlation between these autoantibodies and vitamin D level and thyroid-stimulating hormone (TSH) levels although it wasn't significant Table (4).

Table 1. Number of participants according to gender and age.

Participants	Cases	Control	P value
Gender			
Male	18	19	0.86
Female	82	81	
Age			
20 - 35 years	26	24	0.9
36 - 50 Years	37	40	
51 - 70 years	37	36	
Mean age ± SD	46.2 ± 13.2	45.9 ± 12.4	0.9

Table 2. Mean± SD and median of serum 25(OH) D levels in hypothyroid cases and control.

Vitamin D	Cases	Control	P value
Mean ± SD	13.6 ± 11.4	24.1 ± 20.7	< 0.001 *
Median (Mean rank)	8.9 (79.8)	18.2 (121.2)	< 0.001**

Table 3. Prevalence of serum 25(OH) vitamin D levels in hypothyroid cases and control.

Vitamin D / cases		Cases	Control	P value
Vitamin D	Normal	17	46	< 0.001
	Deficiency	83	54	
Total		100	100	

Table 4. Thyroid autoantibody and TSH levels according to the vitamin D status.

	Vitamin D level		P-value
	Vitamin D deficient group(n=83)	Vitamin D sufficient group(n=17)	
Anti-TPO			
Negative	17 (20.5%)	5 (29.4%)	0.42
Positive	66 (79.5%)	12 (70.6%)	
Anti-Tg			
Negative	37 (44.6%)	11 (64.7%)	0.13
Positive	46 (55.4%)	6 (35.3%)	
TSH			
Low	3 (3.6%)	0 (0%)	0.69
Normal	25 (30.1%)	6 (35.3%)	
High	55 (66.3%)	11 (64.7%)	
Total	83 (100%)	17 (100%)	100

DISCUSSION

Vitamin D has been shown to have potent immunomodulatory effects and play important roles in the pathogenesis of autoimmune diseases and endocrine disorders like diabetes mellitus[19], in addition to its primary role in bone and mineral homeostasis. Vitamin D supplementation prevents the onset and development of autoimmune diseases. Vitamin D receptors(VDRs) are not found in significant amounts in the B lymphocyte, but in significant concentrations in the T lymphocyte and macrophage [20, 21].

However, the highest concentration is in the immature immune cells of the thymus and mature CD8 T lymphocytes. The results of the studies show that rheumatoid arthritis, diabetes mellitus, and inflammatory bowel disease can be prevented or markedly suppressed by vitamin D administration [20]. Hypothyroidism is the most common endocrine disorder. There is a strong correlation between autoimmune hypothyroidism and vitamin D levels. Since both vitamin D and thyroid hormones act via steroid receptors; so any alteration in the level of vitamin D is likely to increase problems associated with hypothyroidism[22].

The role of vitamin D on the autoimmune processes is of great interest; in Hashimoto's thyroiditis (HT). The autoimmune process may be inhibited at different stages by 1,25dihydroxy vitamin D {1, 25(OH) 2D3}. At first 1, 25 (OH) 2D3 might inhibit dendritic cell (DC)-dependent T-cell activation [23, 24]. Then, 1, 25 (OH) 2D3 inhibits the secretion of T helper cell (Th1-cell) cytokines {interferon-gamma (IFN-g), interleukin (IL-

2), and tumor necrosis factor-alpha (TNF)}. Production of Th1 cytokines, especially IFN-gamma, which induces thyrocytes to express major histocompatibility complex class II surface HLA-DR antigens, might be inhibited by 1, 25 (OH) 2D3 [25]. Tolerogenic DCs induced by VDR agonists arrest the development of autoimmune diseases [26]. At another stage, after being activated by T cells, B cells' ongoing proliferation might be inhibited and apoptosis might be induced by 1, 25 (OH) 2D3. In this way, 1, 25 (OH) 2D3 might decrease antibodies that react with thyroid antigens [27].

Numerous studies indicate a low content of this vitamin in the serum of patients with Hashimoto's thyroiditis (HT). However, it is not entirely clear whether this level is a result of the autoimmune disease process or is one of its causes[28].

In the present study, patients with hypothyroidism had significantly lower 25 (OH) D3 levels than healthy subjects and vitamin D insufficiency was more common in patients with HT than in healthy people. Vitamin D deficiency has been a prevalent health problem and a level of vitamin D as 20 ng/ml is considered as a cutoff [29, 30].According to this value, 83% of hypothyroid cases had vitamin D deficiency.

On investigating the association of thyroid autoantibodies, we found that there was a link between vitamin D deficiency and the presence of antithyroid antibodies. In 100 hypothyroid cases, (83) cases had vitamin D deficiency and among them (66,46) cases were anti-TPO and anti-Tg positive respectively. Although not significant, we can refer this to the small sample size of the study. These results are in agreement with several clinical studies have reported a low vitamin D status in hypothyroid patients, indicating an association between vitamin D deficiency and thyroid autoimmunity This association is found in a meta-analysis published recently [31]. Also Kivity et al., reported that the prevalence of vitamin D deficiency was significantly higher in patients with HT compared with healthy individuals[32]. Likewise, vitamin D deficiency was found to be correlated with the presence of anti-thyroid antibodies (anti-TPO, anti-Tg) suggesting the involvement of vitamin D in the pathogenesis of HT [16, 33–35].

But these results are in contrary to a research done in USA, with results of the mean 25 (OH) D levels for the HT and control groups were significantly different in females but not in males thus HT is not associated with higher rates of vitamin D deficiency relative to a control group [36].

In conclusion, patients with hypothyroidism present with lower vitamin D levels than healthy controls. Deficiency of vitamin D was linked to the presence of antithyroid antibodies.

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