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Original Research Article

Hypovitaminosis D in patients with Hashimoto's Thyroiditis in the region of Constantine

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Abstract

Hashimoto's thyroiditis (HT) is the most prevalent autoimmune disease. Recently, several works demonstrated the effective role of vitamin D on immunity and the incidence of autoimmune diseases. We conducted a cross-sectional observational study. Its main objective was analyzing the relationship between hypovitaminosis D and autoimmune HT. Our study was carried out at the biochemistry and immunology laboratories of the regional university hospital of Constantine, for a period of 2 months. The study group consisted of 45 HT patients. After data was collected, serum concentrations of vitamin D (25(OH) D), TSH, anti-TPO and anti-Tg autoantibodies were assessed. Our results indicated that the majority of HT patients were woman (64 %). The mean age of the patients was 43.22 ± 11.24 years. In the group 53% of patients had hypothyroidism and 16% of them had type 2 diabetes. Hypovitaminosis D with levels below 30 ng/ml was recorded in 80% of the patients. It was more marked in females than in males with 13.98 ± 14.07 ng/ml and 23.20 ± 9.96 ng/ml respectively. Vitamin D levels varied between the different stages of the pathology. In the group, 31.11% had a severe deficiency (< 10 ng/ml), 24.44% had a deficiency (10-20 ng/ml), and likewise, 24.44% of patients had an insufficiency (20-30 ng/ml). A possible association between hypovitaminosis D and HT was highlighted in this study as a large number of patients had vitamin D levels below normal range. However, these findings do not confirm the existence of a causal relationship. Further investigations and prospective trials are desirable to characterize this relationship.

Keywords:
Hashimoto's thyroiditis, hypovitaminosis D, autoimmunity, 25(OH) D

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1. Introduction

Autoimmunity is a pathological disorder that appears secondary to an immune dysfunction and a breakdown of tolerance towards self antigens. Hashimoto's thyroiditis is the most prevalent of the autoimmune diseases, affecting approximately 2-20% of the general population [1]. The increase in serum auto-antibodies anti-thyroperoxidase (anti-TPO-Ab), anti-thyroglobulin (anti-Tg-Ab) and lymphocyte infiltration leads to tissue destruction and abnormal thyroid function. Several endogenous factors like genetic susceptibility, gender and other environmental factors have been identified as risk factors for the development of HT. Some other factors are still not well characterized and their interactions are still not understood [2] [3] [4][5] .

Vitamin D is a secostreoid hormone with widespread effects in the organism. It has experienced renewed interest following the discovery of its pleiotropic actions on different tissues and systems, including the immune system [6] [7]. Its modulating action on the innate and adaptive immunity and the expression of its receptor VDR in several immune cells suggests that a lack of this hormone could affect immune functions and thereby contribute to autoimmunity. The prevalence of vitamin D deficiency has increased these last decades. It varies by population (24% in the USA, 37% in Canada, and 40% in Europe) and has become a global health issue [8]. Several studies have focused on the deficiency and its consequences on human health. It has been associated with a greater risk of cardiovascular diseases, diabetes, cancer as well as inflammatory and autoimmune diseases [9] [10][11].

The impact of hypovitaminosis D on the incidence of HT has been examined in various works. Some have reported a link between vitamin D deficiency and the development of HT, whilst others found limited to no association [12] [13] [14] [15]. Given these conflicted results, our study has focused on the assessment of vitamin D status of patients with HT, the study of the relationship between serum vitamin D levels, thyroid function and disease severity as well as the examination of the link between serum concentrations of vitamin D and thyroid auto-antibodies.

2. Methods

Our study was carried out at the biochemistry and immunology laboratory units of the regional university hospital of Constantine, Algeria. It was conducted in summer time. The study population included 45 Hashimoto's thyroiditis patients diagnosed between the years 2017and 2021. The diagnosis was based on elevated antithyroperoxidase antibodies (Anti-TPO-Ab $\geq 50 IU/ml$) and/or antithyroglobulin antibodies ($Anti - Tg - Ab \geq 100 IU/ml$) levels.

The patients included were adults (>18 y.o.). Patients developing pathological disorders (renal or hepatic failure, celiac disease, irritable bowel disease, . . .) and/or using a medication that affects vitamin D levels were excluded, only if the so mentioned occurred after the development

of HT. Patients treated with vitamin D supplements for less than two months prior to the study were also excluded.

Data was collected, on the one hand, following access to patient's files and, on the other hand, by a questionnaire covering the various criteria of selection. This allowed us to record all the information needed for our investigation: age, sex, BMI (Body Mass Index), clinical dataof HT and associated diseases if present. Serum levels of TSH (Thyroid Stimulating Hormone),fT3 (Triiodothyronine), fT4 (Thyroxine), anti TPO-Ab, anti Tg-Ab and vitamin D were takenif already available. Serum 25-hydroxy-vitamin D (25(OH) D) levels were measured in the hospital laboratory as well as other private laboratories. It was preformed with the cobas e-411 automated analyzer using the Electrochemiluminescence (ECL) technology. Values superior to 30 ng/ml were considered sufficient, 20-30 ng/ml were considered insufficient, 10-20 ng/ml deficient and below 10 ng/ml severely deficient, in accordance with manufacturer's definition. Thyroid hormone fT4 and TSH tests were also evaluated by the cobas e-411 analyzer. Normal TSH levels: 0.27 – 4.2 UI/ml and normal fT4 levels: 12 - 22 pmol/l. Auto-antibodies were detected and quantified with a commercial ELISA kit (BioSystems S.A., Barcelona), for both anti TPO-Ab and anti Tg-Ab.

Statistical analyses were preformed with Microsoft Excel. Spearmen's rank test was used for evaluating correlations. Statistical significance was calculated with Student t test.

3. Results

3.1. General characteristics of the population

In the studied group 64% of patients were woman (29 cases). The mean age of all subjects is 43.22 ±11.24 years. The cases had other diseases associated with HT like type 2 diabetes(7 cases), arterial hypertension (3 cases), heart disease (2 cases) as well as other diseases like anemia, allergy osteoarthritis and adrenal insufficiency. Subjects presented variable BMI values. Among woman 34% were overweight and 24% obese. Man had more normal BMI (75%) compared to woman (34%). The variability in BMI ranges between males and females are seen in (Figure 1). TSH, fT4 and thyroid autoantibodies variations are seen in (Figure 2).

3.2. Vitamin D

Patients with 25(OH) D levels below 30 ng/ml were considered below normal values and were divided into three ranges: insufficient, deficient and severely deficient. The percentage of each range and mean levels of each group were summarized in (Table 1). Low serum concentrations of 25(OH) D were noted in 80% of the group. Females had lower vitamin D levels compared to males. The mean serum values were 13.98 ± 14.07 ng/mL and 23.20 ± 9.96 ng/mL respectively.

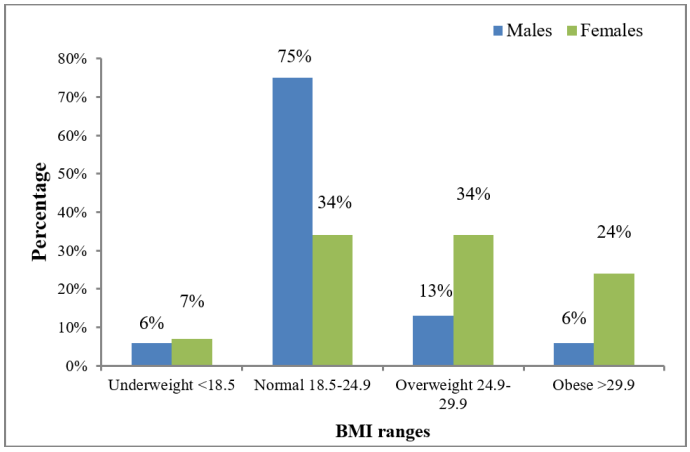

Figure 1: BMI ranges expressed in percentage in both female and male groups of HT

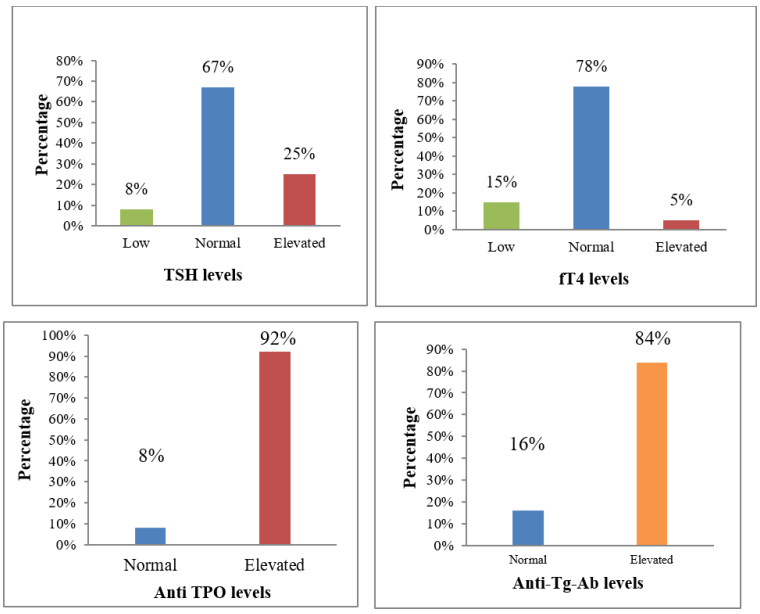

Figure 2: TSH, fT4 and thyroid auto-antibodies variations in HT subjects

No significant correlations were seen between TSH and vitamin D levels (r= 0.31; p=0.16). Serum 25(OH) D values had no significant variation with age (r=0.15; p=0.30). When studied by separate sex, a positive correlation was observed in the males group (r=0.33; p=0.20). The stages of the disease were compared to vitamin D levels and summarized in Figure 3. Patients with an euthyroid state represented 29% of the group, in the case of subclinical hypothyroidism 18% and the majority 53% were having a hypothyroidism. One patient in the group had a hyperthyroidism

Table 1: Serum 25-hydroxy-vitamin D levels and ranges.

	All Subjects	Males	Females	p value
25(OH)D mean ± SD (ng/mL)	20.17 ± 12,84	23.20 ± 9.96	13.98 ± 14.07	0.014
25(OH) D ranges :				
Sufficient	20 %	19 %	21 %	
Insufficient	24.44 %	38 %	17 %	
Deficient	31.11%	37 %	28 %	
Severely Deficient	24.44%	6 %	34 %	
Total	100 %	100 %	100 %	

that changed to hypothyroidism.

Vitamin D and auto-antibodies titers measured simultaneously were available for only 11 patients. Results showed that when vitamin D levels were low at least one of the two thyroid auto-antibodies (anti-Tg and/or anti-TPO) was elevated. When the auto-antibodies were correlated separately with vitamin D, it resulted in a positive but not significant correlation: Anti-TPO-Ab (r=0.10; p=0.74), anti-Tg-Ab (r=0.23; p=0.57).

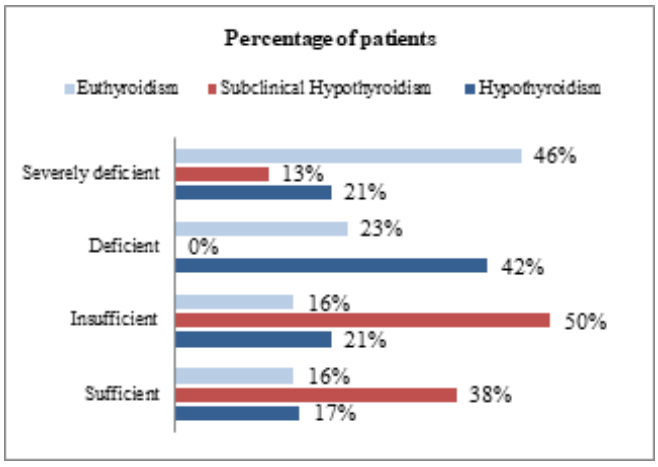

Figure 3: Vitamin D (25-OH-D) status in the different stages of HT. Euthyroidism (Normal TSH and normal fT3, fT4 levels). Subclinical hypothyroidism (Elevated TSH and normal fT4, fT3) Overt hypothyroidism (Elevated TSH and low thyroid hormones).

4. Discussion

Hashimoto's thyroiditis like other autoimmune diseases is multifactorial. Genes, hormones and environment amongst other factors contributes to the onset and the progression of the disease. Gender as seen in this study and several other studies is an important risk factor for autoimmunity [16] [17] [18]. In our group the majority were females (64%). Sex hormones like estrogens and genetic changes like those seen in the asymmetrical X chromosome inactivation contributes to this sex preponderance [19] [20].

Vitamin D in its active form (1,25 (OH)2 D) have key effects on the immune system including immunoregulatory and modulatory properties. It has been demonstrated that the hormone interacts with various immune cells like macrophages, NK cells, T and B lymphocytes and dendritic cells [21] [22]. In this study we reported an increased exposure to vitamin D deficiency in HT patients. It was more severe in females than in males (p=0.014) and various reports showed results similar to ours [23] [24] [25] [26] [27][28]. The difference of vitamin D status between the two sexes was already seen in several studies and seems to have a link with fat mass, exposure to sunlight and other genetic differences [29] [30]. It is interesting to presume that vitamin D, more marked in females, can be another cause of female sex dominance in auto-immune diseases. All females in our study were veiled, had little outdoor activity and had higher BMI levels and fat mass compared to males. The effect of the veil on 25(OH)D statues is still not well elucidated. Some authors in their studies showed no difference between veiled and unveiled women regarding serum vitamin D [31] [32] but other authors did not [33] [34] [35].

It is well known that thyroid hormones have a consistent effect on body mass by interacting with cell metabolism and energy utilization. However, an increased body mass may not always be the consequence of HT, it can rather be the cause [36]. Leptin, an adipokine and hormone produced by the adipose tissue, was found to influence the development of autoimmune thyroid diseases by interacting with the immune system as well as the thyroid and pituitary axis [37] [38] [39]. In our group, patients with high body mass were for the most newly diagnosed, patients taking no L-thyroxine treatment or those treated with L-thyroxine for a short term period. The obtained results follow the findings of Poplawska et al., (2014) [40]. To know whether this gain of weight amongst patients is secondary to Hashimoto's thyroiditis or was present before the onset of the disease further investigations are needed.

The severity of HT when compared with vitamin D status showed that patients with euthyroidism had higher rate of deficiency compared to the other stages. In the case of subclinical hypothyroidism, patients were more sufficient. Authors like Bozkurt et al., 2013, Mansournia et al., 2014 and Ke et al., 2017 [41] [42] [27] have shown results similar to ours. While those of Tamer et al., 2011 and Unal et al., 2014 [23] [27] did not agree with ours.

Variations of vitamin D concentrations with age showed no significant correlation for all subjects (r=0.15 ; p=0.30), for the males group (r=0.33 ; p=0.20) or females group ((r=0.13 ;

p=0.47). For instance, all subjects were affected with vitamin D deficiency regardless of their age. In the study of Annweiler et al., (2016) [43] an association between age and vitamin D was highlighted but in the studies of Lagunova et al., 2009 and Rabenberg et al., 2015 [29] [44] no association was seen. In the literature, vitamin D deficiency is more important in the elderly. This phenomenon is due to a decrease in skin 7-dehydrocholesterol a precursor of vitamin D. It is also believed that low concentrations in this group might be the consequence of a regression in renal function and little outdoor activity [45] [46][47].

Data regarding auto-antibodies titers and their corresponding vitamin D concentrations measured simultaneously were available only for the eleven newly diagnosed patients. We have noted, for most patients, that when 25(OH) D serum concentrations were low at least one of the thyroid auto-antibodies had elevated concentrations. When the two auto-antibodies were correlated separately with 25(OH)D, it resulted in a positive but not significant correlation: Anti-TPO-Ab (r=0.10; p=0.74), anti-Tg-Ab (r=0.23; p=0.57). The reduced number of patients may have contributed to this lack of significance. When theoretically it may be possible, the influence of vitamin D on auto-antibodies production is still not understood. While various studies like those of Tamer et al., 2011, Muscogiuri et al., 2014, Bozkurt et al., 2013 and Shin et al., 2014 [23] [30] [41] [48] have shown a negative correlation expressed by a decrease in HT auto-antibodies with increased levels of vitamin D, other studies like those of Yasmeh et al 2016 and Mansournia et al., 2014 [14] [42] did not found any correlation. Some in vivo trials with vitamin D supplementation showed promising results with a significant reduction in anti TPO-Ab titers of patients affected by HT [49] [50]. These findings encourage more investigation about the use of this hormone as therapeutic agent or to prevent the development and progression of autoimmune diseases.

5. Conclusion and Perspectives

Hashimoto's thyroiditis has a prevalence that varies with age, sex and BMI. It is more common among woman and affects a young adult population. It may appear alone or associated to other diseases like diabetes and hypertension. In our investigation regarding the role of vitamin D in the onset and development of autoimmunity and HT we have found an important expo- sure to hypovitaminosis D in the studied group. More severe in females compared to males andvaries with the stages of the disease. Auto-antibodies titers showed a positive but not significant correlation with vitamin D concentrations probably due to the small number of patients.

This study had some limitations regarding the number of patients and the control group that couldn't be completed. Because of the nature of cross sectional studies, a causal relationship between hypovitaminosis D and the development of autoimmune thyroiditis couldn't be confirmed. Prospective investigations with an important population would help clarify this relationship. Studies exploring other age categories like children and the elderly are desirable. Others

evaluating the mean vitamin D levels of the Algerian population should be considered.

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