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RESEARCH ARTICLE

Correlation between Vitamin D Status and Antithyroid Antibody Levels in Patients with Newly Diagnosed Hashimoto Thyroiditis: Case-Control Study in Tlemcen (Algeria)

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ABSTRACT

Introduction: Hashimoto thyroiditis (HT) is characterized by the presence of antithyroid antibodies with lymphocyte infiltration of the thyroid gland. Its etiology results from the interaction between environmental factors and genetic susceptibility traits. One of the factors most recently involved in autoimmunity is vitamin D. The principal aim of our study was to investigate a possible relationship between vitamin D status and antithyroid antibody levels in patients with newly diagnosed Hashimoto diseases, from Tlemcen.

Materials and methods: Cross-sectional case-control study, including 310 subjects, divided into two groups: a group of cases (n = 155) with newly diagnosed HT and a group of apparently healthy controls (n = 155). The 02 groups were matched by sex, age ± 02 years, body mass index (BMI) and the same season (blood collection period). All subjects benefited from hormonal assays, anti-thyroid antibodies and biochemical parameters (Thyroid Stimulating Hormone (TSH), Free Thyroxine (FT4), anti-peroxydase antibody (anti-TPO), anti-thyroglobulin antibody (anti-Tg), 25 hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH), calcemia, phosphoremia, albuminemia and alkaline phosphatases).

Results: High prevalence of hypovitaminosis D in our study population: 98% at the threshold of 25(OH)D < 30 ng/mL, 89% at the threshold < 20 ng/mL. The most significant risk factors associated with low levels of 25(OH)D are lack of sun exposure, season, skin color and lack of physical activity. The 25(OH)D deficit is more pronounced in the HT group than in the control group with a significant difference (11.45 ± 5.16 vs 13.02 ± 7.45; p = 0.03). In the HT group, the correlation between the status of 25(OH)D and the anti-TPO is inverse and significant (r = - 0.185; p = 0.02), relationship confirmed by multivariate analysis by linear regression where the 02 variables statistically related to anti-TPO are Vit D and TSH. Moreover, no correlation between 25(OH)D and anti-Tg and not between 25(OH)D and the degree of depth of biological hypothyroidism.

Conclusion: There is an inverse and significant statistical relationship between serum levels of 25(OH)D and anti-TPO in the case group, however the exact involvement of vitamin D in the immunopathogenesis of Hashimoto's diseases remains to be substantiated.

Keywords: anti-peroxidase anticoprs (anti-TPO), anti-thyroglobulin antibodies (anti-Tg), vitamin D, Hashimoto thyroiditis (HT).

Introduction

Autoimmune diseases (AID) are the third leading cause of morbidity and mortality in industrialized countries, behind cancer and cardiovascular disease[1].

The occurrence of AID would result from the interaction between environmental factors and susceptibility genetic traits, which in isolation are neither necessary nor sufficient to induce AID. One of the most recent factors involved in autoimmunity is vitamin D (Vit D). In addition to its role in phosphocalcic homeostasis, Vit D deficiency is associated with other non skeletal effects, including predisposition to autoimmune disorders[1,2]. The 25-hydroxy-vitamin D3 (25(OH)D) is the main circulating form and its serum level reflects Vit D reserves[2,3]. Values of 25(OH)D between 30 and 80 ng/mL are considered by most specialists to be sufficient and < 30 ng/mL as an indicator of Vit D deficiency[4,5,6]. It is estimated that more than one billion people worldwide have a deficiency of Vit D (< 20 ng/mL) or insufficient (between 21-29 ng/mL). Low levels of Vit D are attributed to lack of solar exposure, low physical activity and obesity.

Vitamin D supplementation was considered beneficial for the primary prevention of some AID in humans[4,7]. Most effects of Vit D are mediated by the vitamin D3 receptor (VDR)[8]. The immune modulation properties of Vit D are attributed to its effect on T and B lymphocytes, all of which contain VDR[9]. Together, these Immune- modulatory effects can lead to the protection of target tissues, such as thyroid cells in autoimmune diseases.

Hashimoto thyroiditis (HT), a typical form of chronic lymphocytic thyroiditis (TLC)[10,11], is accompanied by goiter, antithyroid antibody production, lymphocyte infiltration, and varying degrees of thyroid dysfunction[4,12]. Although the exact mechanism of progressive destruction of thyroid tissue is not clear, HT is considered an immune disorder of T cells caused by the interaction of susceptibility genes, cytotoxic-associated T lymphocytes 4 (CTLA-4), HLA (Human Leukocyte Antigen), TSH receptor (TSHR) and environmental factors, which are not yet fully elucidated[4,13]. Several studies have shown low levels of 25(OH)D in patients with HT indicating an association between Vit D deficiency and thyroid autoimmune disease (AITD)[4,5,14,15], however, it is not known whether low levels of 25(OH)D are at the origin of the AID process or part of its cause.

However, if a definitive association between these two conditions exists, it is still controversial. The reason why we conducted a cross-sectional study, type control cases whose main objective was to investigate the existence of a statistical relationship between serum concentrations of 25(OH)D and antithyroid antibody levels in subjects with newly diagnosed HT from our town.

Materials and Methods

This is a cross-sectional study, type control cases carried out between January 2015 and December 2017 at the University Hospital of Tlemcen (UHT) having included 310 subjects aged over 18 years.

Recruitment was done via the endocrinology consultation and at the nuclear medicine laboratory (subjects oriented for TSH, anti-TPO and/ anti-Tg assays). Subjects were divided into two groups: a case group (n=155) and a control group (n=155). Case and control selection was based on biological results. Since the diagnosis of HT is based on the positivity of anti-TPO and/or anti-hTg[16], patients in euthyroidism or biological hypothyroidism with antibody (Ab) levels above the normal thresholds included the case group. Subjects in biological euthyroidism with normal Ab values were included in the control list. These were matched to the cases according to the inclusion criteria.

The choice of match (01 control for 01 cases) by sex, age 02 ± years, body mass index (BMI) and the same season (sampled subjects during the same seasonal period) was made by random draw.Excluded from this study were all subjects resident outside Tlemcen, those who refused to participate in the study, subjects with Basedow disease, subjects with hypothyroidism with antithyroid Ab, pregnant or lactating women, people with a history of AID, insulin-dependent diabetes, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, people with malabsorption syndrome (celiac disease, Crohn), kidney failure, people with liver disease, people with a history of metabolic radiotherapy Iodine 131, external radiotherapy of the cervical region, thyroid or parathyroid surgery, drug intake such as Levothyroxine (LT4), corticosteroids, antiepileptics, interferon, lithium drugs, anti-osteoporotic treatment, Calcium and/or Vit D. Cases and controls were biologically assessed for thyroid function: TSH, FT4, anti-TPO and anti-Tg, determination of PTH, 25(OH)D and biochemical assay (calcemia,

phosphoremia, albuminemia, alkaline phosphatases, blood sugar, uremia, creatinine and transaminases).

At the nuclear medicine laboratory of UHT, hormonal assays, anti-TPO, PTH and 25(OH)D were measured on the Abbott Labs Architect i1000 SR automate (USA), using the technique of immunological microparticular dosage with chemi-luminescence (CMIA). The anti-Tg was dosed by radio-immunometric technique (IRMA) with the Beckman-Coulter kit.

The biochemical assays were performed at the hemodialysis laboratory of the nephrology department of UHT with Thermo scientific Indigo automate using the colorimetric technique. The methods used and the normal intervals of the measured parameters are represented in Table 1.

Table 1: Assayed parameters and methods used

Parameters	Method	Intervals
TSH (µUI/mL)	CMIA	[0,35 – 4,94]
FT4 (pmol/L)	CMIA	[09 – 19,04]
Anti-TPO (IU/mL)	CMIA	< 5,61
Anti-hTg (IU/mL)	IRMA	< 30
25(OH)D (ng/mL)	CMIA	[30 – 80]
PTH (pg/mL)	CMIA	[15 – 68,30]
Calcemia (mmol/L)	Colorimetry	[2,02 – 2,50]
Phosphoremia (mmol/L)	Colorimetry	[0,60 – 1,80]
Albumin (g/L)	Colorimetry	[35 – 50]
Protidemia (mmol/L)	Colorimetry	[65 – 80]
PAL (U/L)	Colorimetry	[33 – 90]

*CMIA: Chemiluminescence Microparticle Immunoassay
*IRMA: Immunoradiometric assay

Vitamin D was classified into 04 thresholds according to the recommendations of the American Society of Endocrinology (ASE)[6]: deficiency < 10 ng/mL; moderate deficit between 10-20 ng/mL; Insufficiency between 20-30ng/mL; optimal > 30 ng/mL.

Statistical Analysis

The statistical analysis of the data was carried out with the software SPSS version 21 (Statistical Package for the Social Sciences-USA). The descriptive analysis of quantitative variables was done by means of the average as an indicator of central trend ± standard deviations. For qualitative variables, the descriptive analysis is expressed as a percentage. The student test for two independent samples and the ANOVA variance analysis were used for the comparison of continuous variables; the degree of association between two quantitative variables was assessed by the Pearson correlation test; a p-value < 0.05 was considered statistically significant. We also used the multiple linear regression test to explain the association between the quantitative dependent variable and quantitative independent variables. The threshold of significance for introduction into the model is $p \leq 0.20$.

Results

The cases and controls (n = 310), are all from Tlemcen town with more than half coming from the center of the town with respectively: 60% of cases vs 56% of control. The average age is 40.76 ± 12.32 with 40.47 ± 12.46 in women vs 44.64 ± 9.67 in men. There is a female predominance (93%) with a sex ratio of 0.07. Vit D deficiency is predominant in our study population with 98% of subjects having levels < 30ng/mL, 89% are deficient (< 20 ng/mL) and 42.5% are deficient (< 10ng/mL). Univariate analysis showed that sun

exposure factor, season, skin color and lack of physical activity were significantly associated with low Vit D levels ($p < 0.01$). The mean of 25(OH)D in the case group was 11.45 ± 5.16 ng/mL vs 13.02 ± 7.54 ng/mL in the control group with a significant difference ($p = 0.03$). In the case group, all subjects have anti-TPO and/or anti-hTg positive. A value above the normal limits is considered positive. The prevalence according to the presence or absence of antithyroid Ab in the case group is represented in Table 2.

Table 2: Prevalence by presence or absence of antithyroid antibodies in the case group

	TH Group (n=155)			
	anti-TPO		anti-hTg	
	Present	Absent	Present	Absent
n	131	24	107	48
%	84,52	15,48	69,03	30,97

n= number of patients

The family history of thyroid pathology, whether autoimmune or not, is found in 34.52% of the population (107/310) of which 42% in the case group (65/155) vs 27% in the control group (42/155) with a significant difference ($p = 0.006$).

In the case group, there is an inverse and significant statistical correlation between serum concentrations of 25(OH)D and anti-TPO Ab ($r = - 0.185$; $p = 0.02$), figure 1. In order to confirm this correlation, a multiple linear regression with the bottom-up method was used taking anti-TPO as a dependent variable and 25(OH)D, age, TSH and anti-Tg as independent variables. The results show that the two variables with

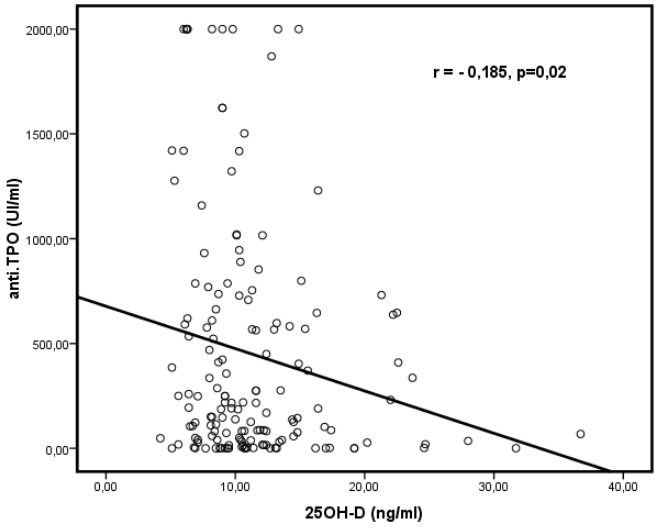

Figure1: Correlation between anti-TPO and 25(OH)D

The mean TSH (µUI/mL) in the case group was 9.07 ± 17.71 vs 1.75 ± 0.95 in the control group with a significant difference

($p < 0.001$). However, there is no correlation between plasma TSH levels and 25(OH)D according to the level of depth of biological hypothyroidism.

The correlation between rates of 25(OH)D and BMI is negative and significant ($r = - 0.167$ and $p < 0.01$) and it is positive between age and BMI ($r = 0.24$; $p < 0.001$). PTH is inversely correlated with serum levels of 25(OH)D ($r = - 0.20$, $p < 0.01$). There is a positive and significant correlation between serum levels of 25(OH)D and corrected calcium ($r = 0.20$; $p < 0.01$) and a positive and significant correlation between corrected calcium

and phosphoremia (r = 0.26; p < 0.01). On the hand, most significant association with anti-TPO are TSH (p = 0.009) and 25(OH)D (p = 0.02). Moreover, there is no correlation between anti-Tg and 25(OH)D (r = - 0.09; p = 0.28).

On the other hand, no correlation of 25(OH)D with phosphoremia (r = 0.05; p = 0.29) and not with alkaline phosphatases (PAL). The main results are shown in Table 3.

Table 3: Summary table of results obtained in both groups.

Quantitative variables	Case group (n = 155)	Control group (n = 155)	*p*
Âge (years)	40,78 ± 12,40	40,75 ± 12,27	0,98
Sexe (Man/Woman)	11/155	11/155	/
BMI (kg/m²)	27,71 ± 5,29	27,46 ± 5,14	0,68
25(OH)D (ng/mL)	11,45 ± 5,16	13,02 ± 7,54	***0,03***
FT4 (pmol/L)	12,97 ± 2,82	13,48 ± 1,48	***0,000***
TSH (µUI/mL)	9,07 ± 17,71	1,75 ± 0,95	***0,000***
Anti-TPO (UI/mL)	446,44 ± 562,53	0,67 ± 0,56	***0,000***
Anti-Tg (UI/mL)	151,14 ± 376,40	15,30 ± 3,73	***0,000***
Corrected serum calcium (mmol/L)	2,18 ± 0,15	2,13 ± 0,17	***0,02***
Phosphoremia (mmol/L)	1,05± 0,19	1,04 ± 0,18	0,58
PTH (pg/mL)	81,54 ± 32,67	75,80 ± 29,39	0,10
Alkaline phosphatase (U/L)	72,23 ± 16,88	75,15 ± 17,69	0,13

Discussion

Vit D is classically associated with phosphocalcic and bone metabolism and is most often prescribed for the treatment or prevention of osteoporosis. In recent years, an increasingly abundant literature illustrates, on the one hand, the pandemic character of Vit D deficiency, and on the other hand, its much broader involvement in human physiology, in particular its immunomodulatory effects via the nuclear Vit D receptor (VDR). By binding to its VDR, Vit D can prevent immune cells from triggering autoimmune destruction of thyroid cells. The autoimmune process is thought to be attributed to an aberration of the genetic polymorphism of VDR and other antigens on the thyreocyte surface, causing these cells to become subject to an autoimmune attack[17]. In addition to VDR, immune cells also express 1α-hydroxylase (encoded by CYP27B1), which converts 25(OH)D to 1.25(OH)2D. Thus, all these cells are able to respond not only to the active metabolite of Vit D, but also to its precursors[18]. As with other AID, low levels of Vit D have been identified as a risk factor in the development of AITD.

Many studies have assessed the association between Vit D blood levels and AITD, with conflicting results[19], however most have concluded that this association has a higher incidence of autoimmune thyroiditis[18].

In Hashimoto thyroiditis, several studies[4,5,20,21] have reported severe Vit D deficiency, often accompanied by decreased thyroid function. Also, levels of 25(OH)D appear to be an independent factor influencing the positivity of anti-TPO antibodies[22].In contrast, other studies[23], found no difference in the prevalence of anti-TPO as a function of Vit D deficiency levels.

The anti-TPO, are considered the best serological marker to diagnose Hashimoto's thyroiditis. They are found in about 95% of patients but are rare in apparently healthy controls. Unlike anti-TPO, anti-Tg Ab are less sensitive, positive in only 60-80% of patients with HT and less specific than anti-TPO, however they have their own indication[16].

In our study, the prevalence of anti-TPO in the case group was 84.52% and only 69.3% of subjects had

positive anti-Tg. In addition, we excluded HT patients on Levothyroxine (LT4) replacement therapy; this is due to the fact that LT4 could potentially influence Vit D clearance[20]. Comparison of 25(OH)D (ng/mL) means between case group and control group showed a low serum rate, more pronounced in HT group compared to control group, with a significant difference (11.45 5.16 ng/mL vs 13.02 7.54 ng/mL; p< 0.03), which is consistent with most studies[4,5,20,21].

The correlation between serum rates of 25OH(D) and anti-TPO in the case group is inverse and significant (r = - 0.185; p = 0.02); however, no correlation between 25 OH (D) and anti-Tg (r = - 0.09; p = 0.28); this could be explained by the fact that, in Hashimoto thyroiditis, anti-Tg does not systematically increase with anti-TPO. This statistical association between 25(OH)D and anti-TPO and not with anti-Tg has been found in other retrospective studies[24,25]. We also used a multiple linear regression type analysis with the descending method to look for the degree of association of 25OH(D) with anti-TPO taken as dependent variable in the presence of other independent variables such as age, TSH and anti-Tg. The final model of the analysis showed that the 02 variables with the most significant association with anti-TPO are respectively TSH (p = 0.009) and Vit D (p = 0.02).

In addition, hypovitaminosis D has become a real public health problem, it is widespread throughout the world and it affects about one billion individuals[2]. It is surprisingly much more common in subjects living in sunny countries such as Italy, Spain and Greece than in people living in countries where sunshine is considered insufficient (Scandinavian countries). Increased fish consumption and Vit D fortification of foods may explain this difference[26]. Several factors can influence the synthesis of Vit D, such as age, sex, duration of sun exposure, sun protection, season, BMI, skin color and lack of physical activity[27]. In our study, cases and controls were matched by age, sex, BMI and season (Autumn -Winter, Spring-Summer.

However, Vit D deficiency was significant in our study population. Univariate analysis showed that sun exposure factor, season, skin color and lack of physical activity were significantly associated with low Vit D levels (p < 0.01). In addition, the Tlemcen town from which our sample of cases and controls came is an endemic region[28] and its latitude is 34°88'28'North[29]. As a result, it lies at a latitude slightly above 33°, a line passing through northern Morocco, northern Algeria, Iran, Iraq, Japan and the Los Angeles area (USA). Above this line the synthesis of Vit D by the skin is relatively weak or absent during most of the winter[6], this could partly explain the high prevalence of hypovitaminosis D found in our population, especially since 78% of the subjects were recruited between October and March, where the rate of sunshine is lower compared to only 22% between April and September and only 10% of the subjects reported having 30 min sun exposure, two or three times a week. Similarly, the negative and significant correlation between 25(OH)D and BMI (r = - 0.16; p = 0.003) as well as the positive and significant correlation between age and BMI (r = 0.24; p < 0.001), clearly indicates that our study population has a rather sedentary lifestyle and practices very little or no physical activity (80% of women vs 60% of men do not engage in any physical activity).

Finally, it seems important to specify that dietary intakes study, this is due to the fact that, the food industry in Algeria, does not specify the exact content of calcium and Vit D in all foods.

Conclusion

Hypovitaminosis D is important in our study population, Univariate analysis showed that the solar exposure factor, season, skin color and lack of physical activity are significantly associated with low Vit D levels. Comparison of 25(OH)D means between the newly diagnosed HT group and the control group reported a more pronounced Vit D deficit in the case group with a significant difference (11.45 ± 5.16 vs 13.02 ± 7.45 ng/mL; p = 0.03), which is consistent with most studies.

In the case group, a significant inverse statistical correlation was found between the serum concentrations of 25(OH)D and the anti-TPO rates (r = - 0.185; p = 0.02), correlation confirmed by multivariate analysis by linear regression. Moreover, no correlation between 25(OH)D and anti-Tg.

The exact involvement of Vit D in the immuno pathogenesis of Hashimoto thyroiditis remains to be substantiated, which suggests the interest of conducting an interventional study to assess the effect of Vit D supplementation on the course of autoimmune thyroid disease specially in Hashimoto thyroiditis.

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