Letter to the Editor

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High prevalence of anti-thyroid antibodies associated with a low vitamin D status in a pediatric cohort

Keywords: anti-thyroid antibodies; pediatric cohort; thyroid function; vitamin D status.

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To the Editor,

Vitamin D (Vit D) is well recognized as an immunomodulator. It is now recognized that 1,25 (OH)2D3 receptor (Vit D receptor) and the key enzyme 25-hydroxyvitamin D3-1α-hydroxylase (CYP27b1) are expressed in cells of the immune system [1]. Indeed, evidence shows that Vit D modulates both innate and adaptive immunity [2]. Vit D insufficiency has been associated with autoimmune thyroid disease [3, 4]. The effects of Vit D status on immune function depend on the nature of the immune challenge [5]. Chailurkit et al. [6] have described that a high Vit D status in younger individuals is associated with low circulating thyrotropin (TSH), however, it is unclear how Vit D status is related to thyroid function and TSH levels in the pediatric population.

The purpose of the present study is to investigate the association between Vit D status and anti-thyroid antibodies: thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb), serum thyroid hormones, and serum TSH in a pediatric cohort with balanced bone metabolism.

Our study is a human non-interventional retrospective chart review and written consent is not required for human non-interventional studies. One hundred and fifty-three patients, 57 boys (37%), and 96 girls (63%) with ages ranging from 1 to 18 years, with calcium (Ca), phosphorus (P), parathyroid hormone (PTH), and alkaline phosphatase (ALP) levels within the normal range according to age and sex. Thyroid function was assessed with thyroid hormones: triiodothyronine (T3), tiroxine (T4) and free tiroxine (fT4), TSH, and anti-thyroid antibodies: TPOAb and TgAb.

We divided the cohort into three groups according to The Endocrine Society 2011 clinical practice guidelines on the evaluation, treatment, and prevention of Vit D deficiency, which defined Vit D deficiency as having levels below 20 ng/mL, insufficiency as having levels between 21 and 29 ng/mL, and normal as having levels above 30 ng/mL.

Ca by O-cresoftalein complexone (CV% 1.8), P using Molibdate, UV method (CV% 2.8) and ALP with p-nitrofenilfosfate, with the procedure recommended using IFCC (CV% 2.9) were assessed by Cobas 501, Roche Laboratories. PTH (CV% 8.55), ultrasensitive TgAb (CV% 8.36) and TPOAb (CV% 6.73) were performed with the Chemiluminescence method, by Immulite 2000, Siemens. Anti-thyroid antibodies were considered positive when the result was over the analytical sensitive limit for each assay. Vit D (CV% 11.76), thyroid hormones T3 (CV% 6.12), T4 (CV% 3.62) and fT4 (CV% 3.86) and TSH (CV% 2.57), were done using the CMIA method, by Architect i2000, Abbott.

The results were analyzed using χ^2-test for differences of anti-thyroid antibodies between groups of status of Vit D, deficient, insufficient and normal, we considered statistical significance a $p<0.05$.

Pearson's correlation test was used for analyzing the degree of lineal covariations between different variables, we considered statistical significance a $p<0.05$. The regression line analysis was used for assessing the linear correlation between levels of Vit D and T3, T4, fT4 and TSH. The statistical analysis was performed by SPSS IBM software.

The presence of thyroid antibodies was statistically significantly higher in the deficient group (Vit D between 10 and 20 ng/mL) (53.3%) than in the normal group (Vit D above 30 ng/mL) (25.0%) ($p<0.015$). Between the deficient group and the insufficient group (Vit D 21–29 ng/mL) (35.9%) and between the insufficient and normal group there were no significant differences (Figure 1).

Pearson's correlation for Vit D is statistically significant for Ca, P, ALP, PTH, as expected for feedback mechanisms, also correlated statistically significant for TSH and thyroid hormones; whereas TSH only presented statistical significance with Vit D and PTH.

We have found a statistically significant positive correlation between levels of Vit D (ng/mL) and T3 (ng/mL); T4 (μg/dL), and fT4 (ng/dL) and a statistically significant negative correlation between Vit D and TSH (μIU/mL) levels was observed (Figure 2).

Is well known that thyroid function is critical in the pediatric population for several processes such as development of the central nervous system, growth, metabolic processes and bone health.

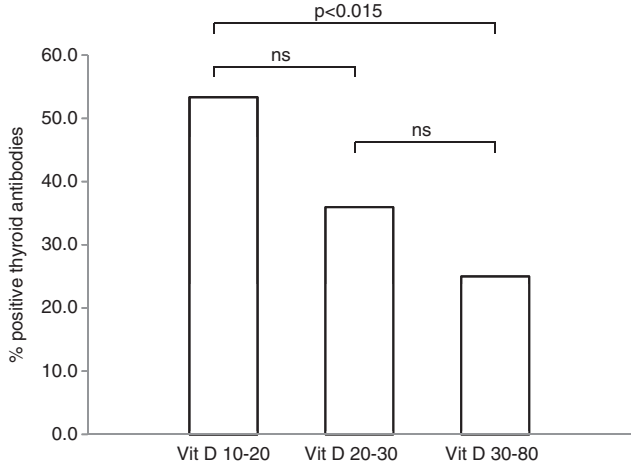

Figure 1 The presence of thyroid antibodies was statistically significantly higher in the deficient group (Vit D between 10 and 20 ng/mL) (53.3%) than in the normal group (Vit D 30–80 ng/mL) (25.0%) ($p<0.015$). Between the deficient and the insufficient group (Vit D 20–30 ng/mL) (35.9%) and between the insufficient and the normal group there were no significant differences.

Diagnosis of autoimmune thyroid disease is based upon clinical features and supported laboratory investigations. The patient may be euthyroid, hypothyroid, or hyperthyroid depending on the type of disease and the stage of the disease [7].

Change in lifestyle leading to lower sun exposure can cause inadequate Vit D status in different population groups. There is strong evidence for an association between Vit D status and the immune response as well as the expression of autoimmune diseases [8].

The alteration of the Ca^{2+} entry mechanisms in T regulatory cells affects normal immune response, both the recognition of foreign antigens as well as tolerance to self-antigens. These mechanisms are intracellular and except in extreme situations would not be associated with circulating Ca^{2+} levels. We think that with extracellular Ca^{2+} levels within normal ranges, these systems are active and actively change in the Ca^{2+} flow.

However, there is significant evidence of the direct action of Vit D on different immune cell types, including regulatory T cells, by many mechanisms described, both on innate and adaptive immunity. One of the mechanisms described is the stimulation of the expression of FoxP3 in regulatory T cells that have a direct action on the adaptive tolerance to self-antigens [9].

A modification of tolerance to self-antigens appears to be more directly related to a Vit D deficient status, via Vit D receptor, modifying the cytokine expression in regulatory immune cells. The high correlation of Vit D levels with Ca^{2+}, P, ALP, and PTH are expected because the feedback mechanisms exist even when within normal levels. Moreover, the fact that we have selected a population with balanced bone metabolism allowed us to rule out more extreme levels of circulating Ca^{2+} concentration, suggesting that the Vit D status is responsible for the inadequate autoimmune response.

In the pediatric population disorders of bone metabolism that might be associated with alterations in thyroid function have been described, this is another reason to select a population with a balanced bone metabolism [10].

Our results show that in the study group thyroid hormones were within the normal range, but were positively correlated with Vit D levels while serum TSH had a negative correlation with Vit D levels. The group of insufficient Vit D includes patients with TSH above the normal range.

In agreement with previous reports, these results suggest that Vit D might also have an immunomodulator effect on thyroid function in a pediatric cohort. We found that the positivity for thyroid antibodies (TPOAb

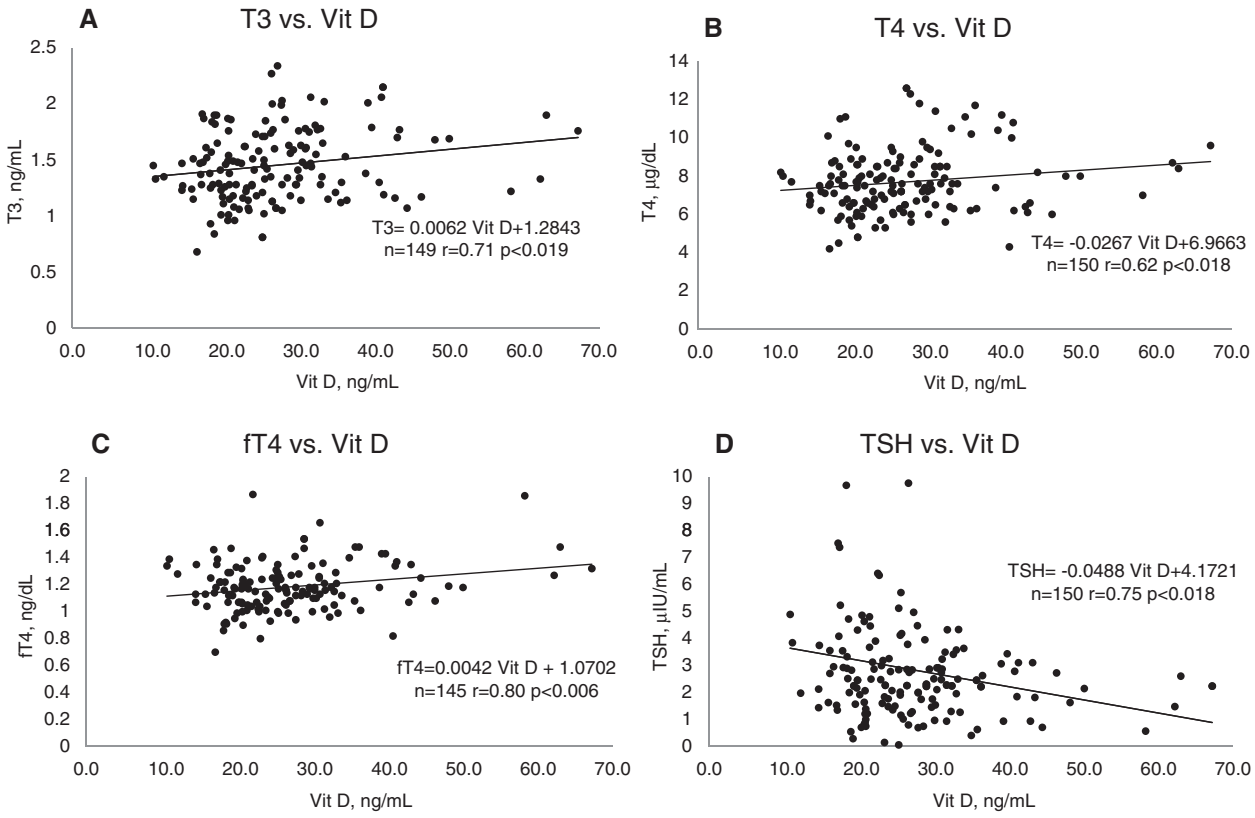

Figure 2 Statistically significant positive correlation between (A): Vit D (ng/mL) vs. T3 (ng/mL) (T3=1.2843+0.0062×Vit D, r: 0.71, p<0.019); (B): Vit D vs. T4 (µg/dL) (T4=6.9663+0.0267×Vit D, r: 0.62, p<0.049); (C): Vit D vs. fT4 (ng/dL) (fT4=1.0702+0.0042×Vit D, r: 0.80, p<0.006) and a statistically significant negative correlation (D): Vit D vs. TSH (µIU/mL) levels (TSH= 4.1721–0.0488×Vit D, r: 0.75, p<0.018), some levels of TSH are frankly pathological associated with low levels of Vit D.

and TgAb) varies according Vit D status, as well as thyroid hormones and serum TSH vary according to Vit D levels in children and adolescents with balanced bone metabolism. We concluded that Vit D deficiency is responsible for altered autoimmunity with a high prevalence of thyroid auto antibodies in these patients leading to an alteration of thyroid function with lower serum thyroid hormone levels and higher serum TSH, moreover some of these patients have pathological values of TSH.

Adequate Vit D status seems to be protective against a wide spectrum of disorders and the significant role of pharmacological doses of Vit D in autoimmune diseases has been described. So far, more than 30 positive effects of Vit D on the immune system have been reported [11].

An interesting systematic review by Antico et al. [12] concluded that basic, genetic, and epidemiological studies indicate a potential role of Vit D in the prevention of autoimmune diseases. Moreover, it was suggested that the timing of supplementation might also be important for subsequent development of autoimmune disease and this may be a result of actions of Vit D in adaptive immunity. Nevertheless, there is not enough evidence that Vit D supplementation could modify the course of autoimmune diseases, and thus, randomized and controlled trials are necessary to confirm this association.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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