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Vitamin D and Selenium in Hashimoto's Thyroiditis: bystanders or players?

Vitamin D e Selênio na Tireoidite de Hashimoto: espectadores ou jogadores?

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Abstract

Objective: To investigate the scientific evidence of how vitamin D and selenium are related to serum levels of thyroid hormones,anti-TPOAb antibodies and enzymatic activity, as well as the effect of supplementation. *Methodology:* The study was carried out by using *PubMed*, *Scopus* and *Web of Science* databases, limited according to type of study (original articles and meta-analyses), language (English, Spanish and Portuguese) and publication time (last ten years). *Results:* Individuals with Hashimoto's thyroiditis have a higher prevalence of vitamin D deficiency (n= 11), which may contribute to the proliferation of antibodies, but it is unrelated to the hormones thyroxine and triiodothyronine. As for selenium, supplementation contributed to the reduction of antibodies (n=5) and improvement of the hormonal profile (n=6). *Conclusion:* Individuals with Hashimoto's thyroiditis have low serum levels of vitamin D and the supplementation of both calcitriol and selenium seem to be effective for the reduction of antibodies and improvement of the hormonal profile, but so far there is no convincing scientific evidence to support such practice.

Keywords: Hashimoto Disease. Vitamin D. Selenium.

Resumo

Objetivo: investigar as evidências científicas da relação da vitamin D e do selênio sobre os níveis séricos de hormônios tireoidianos, anticorpo TPOAb e da atividade enzimática, bem como o efeito da supplementation. *Metodologia:* a pesquisa foi realizada utilizando-se as bases de dados *PubMed*, *Scopus* e *Web of Science*, e os limites, tipo de estudo (artigos originais e metanálises), idioma (inglês, espanhol e português) e o tempo de publicação (últimos dez anos). *Resultados:* indivíduos com tireoidite de Hashimoto possuem maior prevalência de Deficiency de vitamin D (n= 11), a qual pode contribuir para a proliferação de anticorpos, porém sem relação com os hormônios tiroxina e triiodotironina. Quanto ao selênio, a supplementation contribuiu para redução de anticorpos (n= 5) e melhora do perfil hormonal (n= 6). *Conclusão:* indivíduos com tireoidite de Hashimoto cursam com baixos níveis séricos de vitamin D, e a supplementation tanto de calcitriol quanto de selênio parece ser eficaz para a redução de anticorpos e melhora do perfil hormonal, porém ainda não há evidências científicas convincentes que sustentem essa conduta.

Palavras-chave: Doença de Hashimoto. Vitamin D. Selênio.

Introduction

the thyroid is a gland of the endocrine system that arises from the pharyngeal epithelium. It is located in the anterior and caudal region of the laryngeal cartilage. This gland is responsible for secretion of hormones thyroxine (T4) and triiodothyronine (T3), and its function is regulated by suprathyroid and intrathyroid mechanisms.[1]

Suprathyroid regulation is performed by the thyroid-stimulating hormone (TSH), secreted by the basophils of the anterior pituitary. TSH stimulates hypertrophy and hyperplasia of the thyroid and the synthesis of thyroid hormones, also, it regulates metabolism and participates in the synthesis of nucleic acids and proteins. Intrathyroidregulation is performed by the organic iodine fraction of the gland, which is essential for the synthesis of T3 and T4.[1]

Vitamin D also stands out for its immunomodulatory properties on macrophages, T and B lymphocytes and dendritic cells, because of the existence of the vitamin D receptor (VDR) in the cell nucleus, and the enzyme 1-alpha-hydroxylase on the surface of those cells. This vitamin is able to inhibit the activation of T cells, production of T ***helper***cells 1 (Th1), dendritic cells, interferon gamma (INF-y) and interleukin 2 (IL-2). It also inhibits proliferation and induces apoptosis of B cells, which may lead to a protective effect on autoimmune diseases.[2,3]

In the event of calcitriol deficiency, there is increased expression of human leukocyte antigen (HLA-DR) class II on thyrocytes, proliferation of lymphocytes, increased secretion of inflammatory cytokines, maturation of dendritic cells and increased expression of major histocompatibility complex class II (MHC-II). Consequently, there is greater proliferation of B cells and antibody production, thus leading to cell damage.[4,5]

In addition to iodine, selenium is another important mineral for metabolism and for synthesis of thyroid hormones. It is a constituent of the main selenoproteins expressed by the gland, such as glutathione peroxidase (GPX), thioredoxin reductase (TR) and iodothyronine desiodinases (DIO), responsible for the processes of elimination of hydrogen peroxide (H_2O_2) and deiodination.[6]

In selenium deficiency, there is a reduction of the activity of GPX and TR, which are responsible for catalyzing the reduction of peroxides and hydroperoxides, produced during the synthesis of hormones T3 and T4, in addition to a reduction of the activity of DIO, which are responsible for deiodination processes. Thus, when this mineral is deficient, there may be an increase of reactive oxygen species, leading to oxidative damage in the follicular structure of the gland, which activates the immune system and the process of fibrosis, and there is inefficient conversion of thyroid hormones.[6]

Thyroid autoimmune diseases represent the most prevalent endocrine pathology in the population.[7] Hashimoto's thyroiditis characterized by high rates of the antibodies antithyroglobulin (TG) and thyroperoxidase (TPOAb), and by infiltration of T and B cells, which contribute to gland deterioration and exacerbation of symptoms. An autoimmune reaction is triggered when thyrocytes express HLA-DR class II, a process induced by the production of Th1 cells and inflammatory cytokines, especially IFN-gamma, which can be inhibited by calcitriol.[3,8]

In this perspective, and in view of the immunomodulatory action of vitamin D and the role of selenium in thyroid metabolism, the objective of this research was to investigate the scientific evidence of the relationship of these nutrients with hormone levels, TPOAb antibody and enzyme activity, as well as the effect of supplementation on Hashimoto's thyroiditis.

Method

Selection of research databases and search strategies

This review was carried out in the databases *PubMed, Scopus* and *Web of Science,* over the last ten years (2007 to 2017), using the search strategies shown in Figure 1.

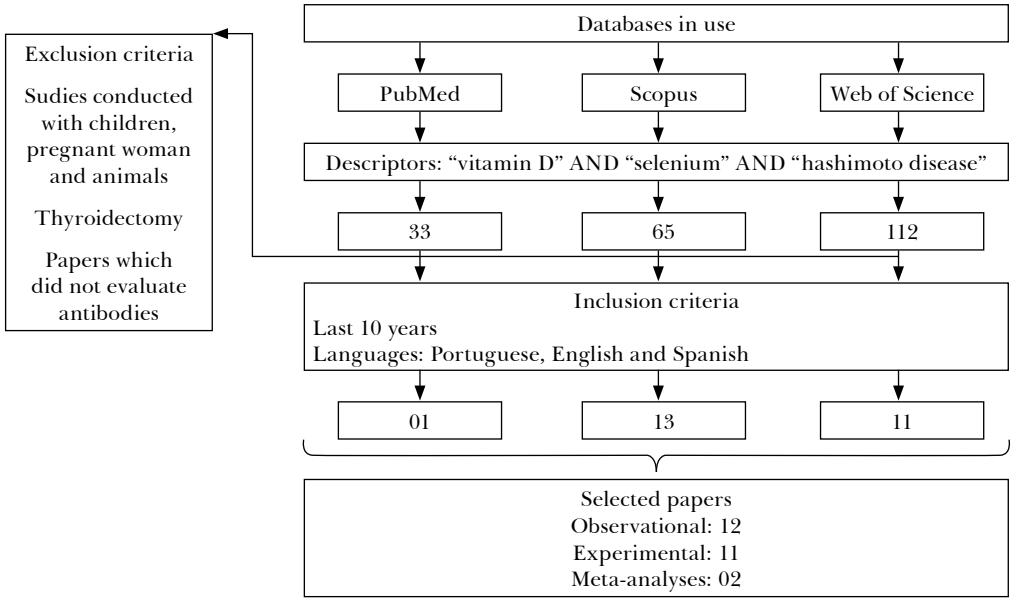

Figure 1. Schematic representation of bibliographic research strategies.

In addition to the articles found in databases, the references of previously selected papers, as well as technical-scientific publications, were included in this review, in order to expand research on the topic.

Inclusion and exclusion criteria

Articles were included when they had an observational, experimental design and meta-analysis, with clearly defined methodology and intervention protocols. In addition, articles were only included if they assessed the TPOAb antibody as a diagnostic criterion of Hashimoto's thyroiditis. Studies were excluded when they had been conducted with children, pregnant women and individuals who had undergone thyroidectomy, as well as in animal models.

Critical analysis

After the papers were selected, they were read in full, and the main information was tabulated in Tables 1 and 2. Critical analysis was performed by two authors, who evaluated the objectives of the papers, type of study, methodological consistency, intervention protocol, results and conclusion. The ***checklist*** of the PRISM method was used as a parameter for critical analysis.[9]

Results

Twenty-five papers were selected, as shown in Figure 1. The studies were conducted in various regions: Greece, southern Italy, Thessaloniki, Rome, Amsterdam, Turkey, South Korea, Iran, Istanbul, China and Poland.

Serum levels of vitamin D

Eleven studies analyzed the prevalence of deficiency of vitamin D in individuals with Hashimoto's thyroiditis. All of them found significantly lower levels in these individuals, when compared to the control group.[2,4,5,10-17]

Vitamin D and TPOAb antibodies

Ma et al.[11] and Mansournia et al.[12] found a negative relation between serum levels of vitamin D and antibodies. However, Giovinazzo et al.,[5] Shin et al.,[13] Unal et al.[14] and Bozkurt et al.[4] found a positive relationship (r=0.17 and r=0.669), and were in agreement with Mazokopakis et al.[18] and Chaudhary et al.,[19] who after oral supplementation with cholecalciferol, found a reduction of serum levels of TPOAb antibodies (r=0.43), with a concomitant increase in the levels of vitamin D. It is noteworthy that the doses of supplementation ranged from 1.200 to 60.000 IU.

Vitamin D and thyroid hormones

Chaudhary et al.[19] found that individuals with TSH<10 mIU/L had a significant reduction of TPOAb antibodies after supplementation with cholecalciferol, which was not found in the group with TSH>10mIU/L. Giovinazzo et al.,[5] Mazokopakis et al.,[18] Kim[16] and Guleryuz et al.[15] found a negative relationship between the variables, contradicting the findings of Unal et al.[14] and Mansournia et al.,[12] who found a positive relationship between vitamin D and TSH (r=0.21; r= 0.34; respectively).

Table 1. Vitamin D in Hashimoto's Thyroiditis

Author	Type of study	Sample	LT4	Vitamin D		T3	T4	TSH	TPOAb	Results
				Reference	Sample					
Maciejewski et al., 2015	Case-control	**Location:** Poland **Case group** 62 n (females) =56 n (males) =6 **Control group** 32 n (females) =28 n (males) =4	S	**Sufficiency** > 75 nmol/L **InSufficiency** 50 - 75 nmol/L **Deficiency** < 50 nmol/L	**Case group** 20.09±12.66 nmol/L **Control group** 30.31±19.5 nmol/L	---	---	---	889 IU/mL (mean)	**Case group** ↓ vitamin D (p=0.029) **Prevalence of deficiency** 98.4% (case) vs. 84.4% (control)
Giovinazzo et al., 2016	Case-control	**Location:** Italy **Case group** 100 n (females) =87 n (males)=13 **Control group** 100 n (females)=88 n (males)=12	N	**InSufficiency** <30 ng/mL **Deficiency** <20 ng/mL	**Case group** 21.2±12.9 ng/mL (16.2ng/mL) **Control group** 35.7±16.71ng/ml (37.4ng/mL)	**Case group** 2.1-4.2 pg/ml **Control group** 2.2-4.3 pg/mL **Ref. 2.0-4.4 pg/ml**	**Case group** 10.6–20.5 pmol/l **Control group** 10.3–20.8 pmol/l **Ref. 10.3–22.0 pmol/l**	**Group Caso** 0.45–4.2mIU/L **Control group** 0.8–3.8 mIU/L **Ref. 0.27–4.2 mIU/l**	133.5 IU/ml	**Case group** ↓ vitamin D (p<0.0001) **Prevalence of deficiency** 70% (case) vs. 18% (control) **↓vitamin D ↑TPOAb (r = 0.669)**
Ma et al., 2015	Case-control	**Location:** China **Case group** 140 (HT:70; GD:70) n (females HT) = 51 n (males HT) = 19 **Control group** 70 n (females)= 49 n (males)= 21	---	**Sufficiency** > 75 nmol/L **InSufficiency** 50 - 75 nmol/L **Deficiency** < 50 nmol/L	**Case group** HT: 31 nmol/L GD: 31.71nmol/L **Control group** 41.33 nmol/L	**Case group** 2.97-4.29 pmol/L **Control group** 4.73–5.25 pmol/L **Ref.: 2.63–5.70 pmol/L**	**Case group** 5.92-9.97 pmol/L **Control group** 15.89-7.54 pmol/L **Ref.: 9.01-19.05 pmol/L**	**Case group** 18.6-87.76 mIU/L **Control group** 1.33–2.75 mIU/L **Ref.: 0.35–4.94 mIU/L**	572.40 -1000IU/mL	**Case group** ↓ vitamin D (p=0.002) **Prevalence of deficiency** 94.29% (case) vs. 77.14% (control) **Unrelated to antibodies**
Mansournia et al., 2014	Case-control	**Location:** Iran **Case group** 41 n (females)= 34 n (males)= 7 **Control group** 45 n (females)= 33 n (males)= 12	---	**InSufficiency** <30 ng/Ml **Deficiency** <20 ng/mL	**Case group** 15.9±12.1 ng/mL **Control group** 24.4±17.3 ng/Ml	---	---	**Case group** 18.1±20.1 mIU/L **Control group** 2.3±1.5 mIU/L	---	**Case group** ↓ vitamin D (p=0.018) **↓ vitamin D ↑ TSH** (r= 0.34) **No relation between vitamin D and TPOAb** (r = 0.06)

continue

Table 1. Vitamin D in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	LT4	Vitamin D		T3	T4	TSH	TPOAb	Results
				Reference	Sample					
Tamer et al., 2011	Case-control	**Location:** Istambul **Case group** 161 n (females)= 155 n (males)= 6 **Control group** 162 n (females)= 151 n (males)= 11	---	**Insufficiency** <30 ng/mL	**Case group** 16.3±10.4 ng/mL **Control group** 29.6±25.5 ng/mL	---	---	---	---	**Case group** ↓ vitamin D (p<0.0001) **Unrelated to disease progression**
Shin et al., 2014	Case-control	**Location:** South Korea **Case group** 111 **Control group** 193	N	---	**Case group** 12.6±5.5 ng/mL **Control group** 14.5±7.3 ng/mL	**Case group** 1.55±1.02 ng/dL **Control group** 1.20±0.62 ng/dL	**Case group** 1.41±0.75 ng/dL **Control group** 1.24±0.67 ng/dL	**Case group** 0.39-3.37 uIU/mL **Control group** 0.82-2.61 uIU/mL	298.5±336.7 IU/mL	**Case group** ↓ vitamin D (p<0.001) ↓vitamin D ↑ TPOAb (r=0.252)
Unal et al., 2014	Case-control	**Location:** Istambul **Case group** 54 **Control group** 124	---	**Deficiency** <20 ng/mL	**Case group** 17.05 ng/mL (mean) **Control group** 19.9 ng/mL (mean)	---	---	**Case group** 2.47mIU/L (mean) **Control group** 1.75mIU/m (mean)	**Case group** 117.68 IU/mL (mean)	**Case group** ↓ vitamin D (p<0.001) ↓vitamin D ↑ TPOAb (r=0,17) ↑ TPOAb ↑ TSH (r=0,21)
Bozkurt et al.,2013	Case-control	**Location:** Turkey **Group 1 (euthyroid)** 180 **Group 2 (Hashimoto)** 180 **Control group** 180 n (females)= 369 n (males)= 171	S	**Mild deficiency** 21-30 ng/dL **Moderate deficiency** 11-20 ng/dL **Severe deficiency** <10 ng/dL	**Group 1** 11.4±5.2 ng/dL **Group 2** 13.1±5.9 ng/dL **Control group** 15.4±6.8 ng/dL	---	**Group 1** 1.13±0.2 ng/dL **Group 2** 1.13±0.2 ng/dL **Control group** 1.12±0.3 ng/dL **Ref.: 0.74-1.52 ng/dL**	**Group 1:** 2.7±1.5 mIU/Ml **Group 2** 2.6±1.4 mIU/Ml **Control group** 2.1±0.1 mIU/mL **Ref.: 0.55-4.78 mIU/mL**	**Group 1** 630.4-1,755 IU/mL **Group 2** 411-1,647 IU/mL	**Case group** ↓ vitamin D ↓vitamin D ↑ TPOAb (r=0,361) ↓vitamin D

continue

Table 1. Vitamin D in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	LT4	Vitamin D		T3	T4	TSH	TPOAb	Results
				Reference	Sample					
Kim, 2016	Case-control	Location: Korea Group 1 369 Group 1a (GD) 148 Group 1b (HT) 221 Control group 407 n (females)= 641 n (males)= 135	S	Insufficiency <30 ng/mL	Case group 94.6±56.7 ng/mL Control group 99.6±53.9 ng/mL	---	Case group 23.2±16.7 pmol/L Control group 15.5±3.9 pmol/L Ref.: 0.78-1.94 ng/dL	Case group 5.4±11.9 mIU/L Control group 2.8±6.6 mIU/L	443.1±735.6 mIU/l	Case group ↓ vitamin D associated with disease progression (p= 0.011) There was no relation between vitamin D and TSH
Guleryuz et al., 2016	Case-control	Location: Turkey Group 1 (euthyroid) 49 Group 2 (subclinical) 49 Group 3 (hypothyroidism) 38 Control group 50 n (females) = 124 n (males)= 12	---	Insufficiency <30 ng/dL Deficiency < 20 ng/dL	Case group 14.88±8.23 μg/L Control group 15.52±1.34 μg/L	---	---	---	---	Case group ↓ vitamin D Prevalence of deficiency 93,4% (case) vs. 82% (control) No relationshp between vitamin D and TSH (r=0,02) Positivity association between genotype TT of TaqIpolymorphism and HT
Feng et al., 2012	Meta-analysis	---	---	---	---	---	---	---	---	Homozygous genotype bb of BsmI polymorphism and TT of TaqI polymorphism, associated with a higher risk of AITD (p<0,001)
Wang et al., 2015	Meta-analysis	Case group 1782 Control group 1821	---	---	---	---	---	---	---	Serum levels of vitamin D <50 nmol/L were associated with a higher risk of antibody proliferation

continue

Table 1. Vitamin D in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	LT4	Intervention	Vitamin D		T3	T4	TSH	TPOAb	Results
					Reference	Sample					
Mazokopakis et al., 2015	Experimental	**Location:** Crete, Greece **Total N** 218 n (females)=180 n (males)=38	S	**Colecalciferol Dose** 1200-4000UI **Time** 4 months	**Insufficiency** <30 ng/mL **Deficiency** <20 ng/mL	***Baseline*** 14.6±7.2 ng/mL **Intervention** 45.7±4.3 ng/mL	***Baseline*** 2.5±1.7 μIU/mL **Intervention** 2.4±1.5 μIU/mL Ref.: 0.35-4.94 μIU/mL	---	***Baseline*** 1.1±0.3 μIU/mL **Intervention** --- Ref.: 0.7-1.48 ng/dL	***Baseline*** 364±181 IU/mL **Intervention** 290±116 IU/mL (p<0.0001)	↑ vitamin D ↓ TPOAb (r= 0,43) **No relation between T4 and TSH (p= 0.54)**
Chaudhary et al., 2016	Experimental	**Location: India Group 1** 50 N (females)= 39 N (males)= 11 **Group 2** 50 N (females)= 37 N (males)= 13	S	**Colecalciferol (UI) + Carbonato de cálcio (mg) Group 1** 60000UI + 1200mg **Group 2** 1200mg Time 2 months	**Insufficiency** ≤ 75 nmol/L **Deficiency** < 50 nmol/L	**Group 1** ***Baseline*** 33.25 nmol/L **Intervention:** 98.52 nmol/L **Group 2** ***Baseline*** 39.61 nmol/L **Intervention** 41.61 nmol/L	**Group 1** ***Baseline*** 6.88 (138.98) **Intervention** 3.16±2.07 **Group 2** ***Baseline*** 6.8 (149.36) **Intervention** 3.39±2.19	---	**Group 1** ***Baseline*** 13.90±3.86 pmol/L **Intervention** 116.47±2.06 pmol/L Group 2 ***Baseline*** 14.03±3.99 pmol/L **Intervention** 16.86±1.93 pmol/L	**Group 1** ***Baseline*** 739.1±343.2 **Intervention** 387(46,7%) **Group 2** ***Baseline*** 687.8±255.1 **Intervention** 553.5 (16,6%)	↑ vitamin D ↓ TPOAb (r=0,43) **Group 1** ↑vitamin D ↓TPOAb (-46,73%) **No relation between T4 and TSH**
		Group A (TSH ≤10mUL/L) 68 **Group A1 (supplementation)** 34 **Group A2** (control) 34	S	**Cholecalciferol (UI) + Calcium carbonate (mg) Group 1** 60000UI + 1200mg **Group 2** 1200mg **Time** 2 months	**Insufficiency** ≤ 75 nmol/L **Deficiency** < 50 nmol/L	**GroupA1** ***Baseline*** 36.62 nmol/L (93.77) Intervention 97.54nmol/L (119.11) **Group A2** ***Baseline*** 36.72nmol/L (116.31) **Intervention** 40.24nmol/L (100.06)	**Group A1** ***Baseline*** 4.79 (9.98) mIU/L Intervention 2.98±1.63 mIU/L **Group A2** ***Baseline*** 4.88 (9,16) mIU/L **Intervention** 3.49±1.84 mIU/L	---	**Group A1** ***Baseline*** 15.70±2.96 pmol/L Intervention 16.43±2.19 pmol/L **Group A2** ***Baseline*** 15.83±2.96 pmol/L **Intervention** 16.73±1.67 pmol/L	**Group A1** ***Baseline*** 722.8±336.6 Intervention 421 (1127) **Group A2** ***Baseline*** 704.32±251.3 **Intervention** 579.5 (1002)	**Group A1** ↑ vitamin D ↓TPOAb (-29,06%) **Group A2** There were no significant changes in TPOAb

>↑ higher; <↓ lower; Ref.: reference; Vs.: versus; LT4: levothyroxine; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone; TPOAb: anti-thyroid peroxidase antibodies; Y: yes; N: no; --: data not shown

Selenium, antibodies and thyroid hormones

Nine articles evaluated the relationship between selenium supplementation, antibodies and hormones TSH, T3 and T4. Six studies found a significant reduction of antibodies after supplementation of sodium selenite or selenomethionine.[20-25] However, the quantities supplemented (80μg to 200μg/day), as well as the duration of the studies (3, 6 or 12 months), varied greatly. On the other hand, three studies found no benefits after supplementation.[26-28] Furthermore, out of all studies, four of them found significant changes in thyroid hormones.[21-23, 26]

Table 2. Selenium in Hashimoto's Thyroiditis

Author	Type of study	Sample	Intervention	Selenium		TSH	T3	T4	TPOAb	Results
				Reference	Sample (serum levels)					
Mazokopakis et al., 2007	Experimental	**Location:** Chania, Greece **Group A** 40 **Group B** 40 n (females)=80	**Selenomethionine Dose** 200μg **Time** **Group A** 12 meses **Group B** 6 months	---	**---**	**---**	**---**	**---**	**Group A** ***Baseline*** 955 (530–2010) **Intervention** 775 (410-1780) **Group B** ***Baseline*** 770 (340-1300) **Intervention** 694 (210–1180) **Ref.: 0 – 50 IU/mL**	**Group A** ↓ TPOAb (-23,5%) (p<0,0001) **Group B** 3 months without supplementation led to ↑TPOAb by 4.8% Unrelated to T4 and TSH
Esposito et al., 2016	Experimental	**Location:** Southern Italy **Group A**38 **Group B**38 n (females)=76	**Selenomethionine** **Group A** 166μg **Group B** Sem supplementation **Time** 6 months	---	**---**	**---**	**---**	**---**	**Group A** *Baseline* 2070 ± 575 IU/ml Intervention **Group B** *Baseline* 3049 ± 757 IU/m Intervention	There was no reduction of TPOAb Significant change in T3 (p<0.04) and T4 (p<0.03)
Anastasilakis et al., 2012	Experimental	**Location:** Thessaloniki **Group Se3**15 **Group Se6** 46 **Control group** 25 N(females)=53 N(males)=33	**Selenomethionine** **Groups Se3, Se6** 200μg **Control group** Sem supplementation **Time** 6 months	**---**	**Groups Se3, Se6** 83.29 ± 2.4 μg/L **Control group** 83.22 ± 4.1 μg/L	**Groups Se3, Se6** ***Baseline*** 3.084±0.67 **Control group** ***Baseline*** 5.03±2.42	**Groups Se3, Se6** ***Baseline*** 2.59 ± 0.08 pg/ml **Control group** ***Baseline*** 2.65 ± 0.05 pg/ml	**Groups Se3, Se6** *Baseline* 1.08±0.02 ng/dl **Control group** *Baseline* 1.03±0.04 ng/dl	**Groups Se3, Se6** ***Baseline*** 611.36±102.7 **Control group** ***Baseline*** 621.31±171.07	No significant changes in thyroid antibodies and hormones

continue

Table 2. Selenium in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	Intervention	Selenium		TSH	T3	T4	TPOAb	Results
				Reference	Sample (serum levels)					
Nordio; Basciani, 2017	Experimental	**Location:** Rome N (total)= 87 N (females)= 79 N (males)= 8	**Myo-inositol + selenomethionine** 600mg + 83μg **Time** 6 months	---	---	***Baseline*** 4.32 ± 0.06 mIU/L **Intervention** 3.12 ± 0.09 mIU/L **Ref.: 1,0 - 2,5 mIU/L**	***Baseline***2.67± 0.04 pg/ml **Intervention** 2.79± 0.03 pg/ml	***Baseline*** 0.94± 0.02 ng/ml **Intervention** 1.07± 0.02 ng/ml ---	***Baseline*** 720.67± 52.39 IU/ml **Intervention** 620.38± 50.90 IU/ml **Ref.: >50 IU/mL**	Significant change in antibodies (p<0.001), T3 (p<0.01), T4 (p<0.001) and TSH (p<0.001)
Nordio; Palajich, 2013	Experimental	**Location:** Rome **Group A** 24 **Group B** 24 n (females)= 48	**Group A** 83μg selenomethionine **Group B** 600mg myo-inositol + 83μg selenomethionine **Time:** 6 months	---	**Group A** ***Baseline*** 127.4±15.3 μg/L **Intervention** 223.5 ± 15.3 μg/L **Group B** ***Baseline*** 129.2±15.1 μg/L **Intervention** 225.4±12.5 μg/L	**Group A** ***Baseline*** 4.33 ± 0.91 mIU/mL **Intervention** --- **Group B** ***Baseline*** 4.4±0.9 mIU/mL **Intervention** 3.1 ± 0.6 mIU/mL	---	---	**Group A** *Baseline* 905.6±401.6 mIU/mL Intervention 522.6 ± 236.8 mIU/mL **Group B** *Baseline* 913.9±543.9 mIU/mL Intervention 516.1±315.4 mIU/mL **Ref.: >350 IU/ml (Critério de inclusão)**	Significant change in antibodies in both groups (p <0.01) Significant change in TSH only in group B (p<0.01)

continue

Table 2. Selenium in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	Intervention	Selenium		TSH	T3	T4	TPOAb	Results
				Reference	Sample (serum levels)					
Pirola et al., 2016	Experimental	**Location:** Itália **Group A** 96 n(females)=60 n(males)=36 **Group B** 96 n(females)=63 n(males)=33	**Group A** 83μg selenomethionine **Group B** No supplementation **Time:** 4 months	---	---	**Group A** ***Baseline*** Respondents (30) 5.88±1.25 No Respondents (66) 6.11±1.51 **Intervention** Respondents (30) 3.21±0.61 No Respondents (66) 5.97±0.94 **Group B** ***Baseline*** Respondents (3) 5.92±1.15 No Respondents (93) 6.39±1.48 **Intervention** Respondents (3) 3.47±0.91 No Respondents (93) 6.10±0.99 **Ref.: 0.4–4.5 mIU/L**	---	**Group A** ***Baseline*** Respondents (30) 10.4±1.3 Não Respondents (66) 10.2±1.5 **Intervention** Respondents (30) 10.7±1.4 Não Respondents (66) 10.5±1.5 **Group B** ***Baseline*** Respondents (3) 10.4±1.2 Não Respondents (93) 10.3±1.4 **Intervention** Respondents (3) 10.6 ± 1.4 Não Respondents (93) 10.4±1.5 **Ref.: 8.0–19.0 pg/mL**	**Group A** ***Baseline*** Respondents (30) 453±110 Não Respondents (66) 444±102 **Intervention** Respondents (30) 422 ± 88 Não Respondents (66) 399±78 **Group B** ***Baseline*** Respondents (3) 467±120 Não Respondents (93) 520±130 **Intervention** Respondents (3) 401±110 Não Respondents (93) 498±140 **Ref.: < 60 U/mL**	Significant reduction of antibodies ($p < 0.0001$) and TSH ($p<0.0001$) Supplementation was able to restore the euthyroid state in 17.2% of the participants

continue

Table 2. Selenium in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	Intervention	Selenium		TSH	T3	T4	TPOAb	Results
				Reference	Sample (serum levels)					
Farias et al., 2015	Experimental	**Location:** Italy **Group SeMe 28** N (females)= 26 N (males)= 2 **Control group 27** N (females)= 24 N (males)= 3	**Group SeMe** 200 μg selenomethionine **Control group** No supplementation **Time:** 3 months	53–109 μg/L	**Group SeMe** ***Baseline*** 37 **Intervention** 3 months 63.4±12.8 μg/L 6 months 41.11±9.0 μg/L **Control group** ***Baseline*** 37 **Intervention** 3 months 36.8±9.6 6 months 41.4±10.8 μg/L	**Group SeMe** ***Baseline*** 1.7 ± 0.5 μU/mL **Intervention** 3 months 3.0 ± 1.5 μU/mL 6 months 3.2 ± 1.6 μU/mL **Control group** ***Baseline*** 1.7 ± 0.4 μU/mL **Intervention** 3 months 2.2 ± 1.5 μU/mL 6 months 2.5 ± 1.5 μU/mL Ref.: 0.5–4.5 μU/mL	---	---	Group SeMe ***Baseline*** 1009 ± 1015 U/mL **Intervention** 3 months 958 ± 913 U/mL 6 months 768 ± 845 U/mL **Control group** ***Baseline*** 1206 ± 969 U/mL **Intervention** 3 months 1405 ± 1070 U/mL 6 months 1430 ± 1132 U/mL **Ref.: <35 U/mL**	↓antibodies TPO after 6 months (5% during the 1st quarter; 20% during the 2nd quarter) (p<0.001) ↑ increased thyroid vascularization without increased inflammatory markers
Uysal; Ayhan, 2016	Transversal	**Location: Turkey** 84	---	---	---	1.89 μU/mL (0.96e3.22)	---	1.10 ng/dL (0.99-1.19)	287.19 IU/mL (22.72-762.20)	↑ antibody levels were associated with lower quality of life (p<0.001)
Wu et al., 2015	Transversal	**Location:** Ziyang and Ningshan **Ziyang Group** 3.038 **Ningshan Group** 3.114 **Thyroid disease** 1499	---	---	---	---	---	---	---	Ningshan (low levels of selenium in soil): higher prevalence of thyroid disorders. Ziyang (levels of adequate selenium in soil): higher serum levels of selenium when compared to participants of Ningshan

continue

Table 2. Selenium in Hashimoto's Thyroiditis (continued).

Author	Type of study	Sample	Intervention	Selenium		TSH	T3	T4	TPOAb	Results
				Reference	Sample (serum levels)					
Eskes et al., 2014	Experimental	**Location:** Amsterdam **Group 1** 30 **Group 2** 31 N (females)=61 N (males)=0	**Group 1** 200 μg sodium selenite **Group 2** No supplementation **Time** 6 months	50–150 μg/L	**Group 1** ***Baseline*** 74 ±14 μg/L **Intervention** 95 μg/L	**Group 1** ***Baseline*** 2.1 (0.5–4.3) **Intervention** 3 months: 1 .9 (0.3–6.9) 6 months 1.7 (0.0–5.3) 9 months 1 .6 (0.1–7.4) **Group 2** ***Baseline*** 2.4 (0.7–4.4) **Intervention** 3 months 2 .2 (0.8–12.6) 6 months 2. 2 (0.2–4.3) 9 months 2. 6 (1.0–5.5) **Ref.: 0.5–5.0 mU/l**	---	**Group 1** ***Baseline*** 14.3 (10–18) **Intervention** 3 months 13.7 (10–17) 6 months 13.8 (9–23) 9 months 14.0 (10–21) **Group 2** ***Baseline*** 13.3 (10–22) **Intervention** 3 months 12.9 (9–18) 6 months 12.8 (10–20) 9 months 13. 5 (9–21) **Ref.: 10–23 pM**	**Group 1** ***Baseline*** 895 (130–6800) **Intervention** 3 months 1040 (130–6600) 6 months 1360 (60–7050) 9 months 1080 (50–7000) **Group 2** ***Baseline*** 1090 (120–9200) **Intervention** 3 months 950 (80–8350) 6 months 1130 (80–9900) 9 months 1100 (70–7600) **Ref.: 0 -100 kU/L**	No significant changes in thyroid antibodies and hormones Supplementation did not contribute to a better quality of life
Nacamulli et al., 2010	Experimental	**Location:** Italy **Group 1:** 30 **Group 2:** 46	**Group 1** No supplementation **Group 2** 80 μg sodium selenite **Time** 12 months	---	**---**	**Group 1** ***Baseline*** 3.2 ± 2.1 6 months 2.7 ± 1.8 12 months 1.8 ± 0.9 **Group 2** ***Baseline*** 3.4 ± 1.86 6 months 2.93 ± 1.47 12 months 2.92 ± 1.5 **Ref.: 0.27 – 4.2 mIU/l**	---	**Group 1** ***Baseline*** 14.5 ± 10 6 months 14 ± 1.9 12 months 17.5 ± 6.7 **Group 2** ***Baseline*** 14.5 ± 2.1 **Intervention** 6 months 14.5 ± 2.2 12 months 15.6 ± 8.4 **Ref.: 12 – 22 pmol/L**	**Group 1** ***Baseline*** 87–232 IU/mL **Intervention** 6 months 77–208 IU/mL 12 months 91–243 IU/mL **Group 2** ***Baseline*** 100–295 IU/mL **Intervention** 6 months 85–259 IU/mL 12 months 72–210 IU/mL **Ref.: <16 IU/ml**	Significant reduction of TPOAb after 12 months of supplementation ($p<0.0001$) There were no significant changes in TSH and T4 hormones

>↑ higher; <↓ lower; Ref.: reference; Vs. versus; Se: selenium; T3: triiodothyronine; T4: thyroxine; FSH: follicle-stimulating hormone; TPOAb: anti-thyroid peroxidase antibodies; data not shown.

Discussion

Vitamin D and Hashimoto's thyroiditis

The prevalence of vitamin D deficiency has been increasing all over the world, hence it is a health problem that affects more than a billion people. Calcitriol has anti-inflammatory and immunomodulating functions, and it is related to the development of autoimmune diseases.[29] For analysis of vitamin D deficiency, studies use the values adopted by the *Endocrine Society Clinical Practice Guidelines* as a reference.[30] In this case, deficiency, insufficiency and sufficiency of vitamin D values are defined as being less than or equal to 20 ng/mL (50 nmol/L); between 21 ng/mL to 29 ng/mL (52,5 -72,5 nmol/L) and equal to or greater than 30 ng/mL (75 nmol/L), respectively.[30]

Maciejewski et al.[10] reported that the serum levels of vitamin D were significantly lower and more prevalent in patients with thyroiditis in comparison with the control group (98.4% vs. 84.4%), thus corroborating the findings of Bozkurt et al.[4] and Kim.[16] These studies were conducted in individuals under hormone replacement therapy, which can contribute to increased metabolic clearance of calcitriol. However, the studies conducted in individuals who were not receiving hormone replacement therapy had similar results, as shown in Table 1.

Tamer et al.[2]also found lower serum levels of vitamin D in the Hashimoto group, however they were unrelated to the progression of the disease. Ma et al.[11] and Mansournia et al.[12] also reported that the increase of 5 nmol/L in serum levels of vitamin D was associated with a reduction of 1.62 and 0.81 (respectively) of the risk of developing the disease.

In vitamin D deficiency, there is increased expression of Th1 cells, increased production of inflammatory cytokines and increased expression of MHC II on the surface of dendritic cells, contributing to greater proliferation of B cells and, consequently, increased production of antibodies.[4,5]Giovinazzo et al.,[5] Shin et al.,[13] Unal et al.[14] and Bozkurt et al.[4] found an inverse relationship between serum levels of vitamin D and antibodies (r= 0,17 to r=0,669), even after the confounding factors (age, BMI and sex) had been adjusted. Only two studies found a positive relationship between vitamin D and serum levels of thyroid hormones.[12,14] In a meta-analysis, Wang et al.[17] concluded that serum levels of vitamin D <50 nmol/L are associated with a greater risk of proliferation of TPOAb antibodies.

It can be argued that there is still scarce literature about the effect of supplementation of vitamin D on Hashimoto's thyroiditis. Mazokopakis et al.,[18] when analyzing the effect of cholecalciferol supplementation (1.200 to 4.000IU) on antibody levels for four months, found a significant reduction of such levels (r=0.43). Chaudhary et al.[19] also found similar results, the supplemented group had a reduction of 46.73% in antibody levels, but the dose in use was much higher (60.000IU of cholecalciferol) in less time (2 months). The benefits found for supplementation were not dose-dependent.

The relationship between Hashimoto's hypothyroidism and VDR polymorphisms may also be associated with lower levels of vitamin D and greater susceptibility to developing the disease, whereas autoreactive T cells can develop in the absence of functional VDR, as seen in the following studies. Guleryuz et al.[15] associated with the homozygous genotype TT of TaqI polymorphism in the VDR gene with a higher risk of developing the disease, while Djurovic et al.[31] found a higher association related to the VDR-FokI polymorphism. In a recent meta-analysis, Feng et al.[32] found a significant association between the homozygous genotype bb of BsmI polymorphism and the genotype TT of Taql polymorphism ($p<0.001$) at a higher risk of developing autoimmune diseases of the thyroid which are not related to Apal and Fokl polymorphism. However, Giovinazzo et al.[5] found no association between Hashimoto's thyroiditis and genotypic variation. The data are conflicting because many studies do not analyze the direct influence of allelic variation on the expression of VDR, but on the physiological parameters of interest.[31]

Thus, there is not sufficient scientific evidence about vitamin D supplementation in Hashimoto's thyroiditis. In addition, the studies have very distinct methodological designs, which highlights the discrepancies in the dose and the duration of such studies.

Selenium and Hashimoto's thyroiditis

The thyroid is the tissue that has the highest concentration of selenium per unit of weight. The main functions of this mineral in the gland are related to antioxidant activity and conversion of T4 to T3,[33] and it is the main constituent of selenoprotein P (SePP) and of enzymes required for thyroid metabolism: GPX, TR and DIO.[34]

All steps of the synthesis of thyroid hormones are catalyzed by thyroperoxidase, which uses H_2O_2, which, in turn, is produced during this process. Thus, reactive oxygen species (ROS) and free radicals are formed constantly and participate in physiological and pathological processes. Cells develop defense mechanisms to limit the action of ROS and protect them from oxidative damage. In this way, selenium deficiency can result in both production of T3 and elimination of H_2O_2inefficient, moreover it contributes to initiation of oxidative damage, fibrosis and impaired thyroid tissue repair.[35]

As regards the effect of supplementation, Mazokopakis et al.,[20] when using 200μg of selenomethionine in individuals with selenium deficiency for 12 months, found a significant reduction of TPOAb antibodies (1st quarter= 5,6%; 2nd quarter= 9,9%; and in the last 6 months= 8%), while the group which did not receive supplementation, in the last six months, showed an increase of 4.8%, but without significant changes in thyroid hormones (Table 2). Farias et al.[24]found similar results when using the same supplementation, and they noted further improvements in thyroid vascularization but without an increase of inflammation markers.

Pirola et al.,[23] when supplementing individuals with Hashimoto's thyroiditis with 83μg of selenomethionine for four months, found a significant reduction of antibodies and TSH ($p<0.0001$) in 31% of the sample, supplementation could restore the euthyroid state in 17.2% ofindividuals. Nordio and Pajalich[22] and Nordio and Basciani[21] found similar results when they combined supplementation of 83μg of selenomethionine with 600mg of myo-inositol. The latter authors also noted an improvement in the quality of life of individuals, in accordance with the findings of Uysal and Ayhan.[36] These authors conducted a cross-sectional study and found an inverse relationship between serum levels of antibodies and quality of life ($p<0.001$), which was evaluated through questionnaires. Selenium supplementation is maximized when associated with myo-inositol, which is a precursor of inositol triphosphate, whose function is to regulate the activity of some hormones, including TSH.[21,22]

In two studies, supplementation was performed with sodium selenite, and divergent results were found. Nocamulli et al.,[25] when using a dose of 80μg, found a significant reduction of TPOAb ($p<0.0001$) after 12 months of intervention, but without changes in the hormonal profile. This study did not analyze amounts of serum selenium in the sample, which may have influenced the results. Conversely, Eskes et al.,[28] when supplementing individuals who presented mild selenium deficiency with 200μg for six months, did not find significant changes of TPOAb or thyroid hormones. Selenium deficiency, in the sample of this study, was lower in comparison with the studies that found positive results with supplementation.

It can be argued that the studies show no standardization of the formula to be used (selenomethionine or sodium selenite), which is a relevant factor because they follow different metabolic pathways. After saturation, selenomethionine can interfere in the serum levels of selenium, as a result of its non-regulated incorporation in methionine-containing proteins, while sodium selenite will no longer be used efficiently for biosynthesis of selenocysteine.[28] The bioavailability of sodium selenite represents two thirds of the absorption of selenomethionine, thus suggesting greater effectiveness of selenomethionine supplementation when compared with sodium selenite.[37]

It should also be noted that the amount of selenium in the soil is another factor that may be associated with the risk of developing Hashimoto's thyroiditis. Wu et al.,[38] when analyzing these variables in individuals from two regions - Ningshan (low levels of selenium in the soil) and Ziyang (adequate levels of selenium in the soil) - found a higher prevalence and greater risk (69%) of developing any thyroid disorder in individuals residing in selenium-deficient regions. In this study, the consumption of meat was a protective factor against the development of hypothyroidism and the consumption of green tea enriched with this mineral (local custom) was associated with a lower risk of developing hypothyroidism (38%) and subclinical hypothyroidism (45%).

Esposito et al.[26] supplemented individuals residing in the South of Italy, a region that has mild deficiency of selenium in the soil, with 166μg of selenomethionine for six months, but they found no significant reduction of antibodies. However, there were significant changes in thyroid hormones T3 ($p<0,04$) and T4 ($p<0,03$), suggesting higher supplementation-induced DIO activity. That paper has not examined the serum levels of selenium in the sample, which may have influenced the results. In addition, the dose in use was lower in comparison with the studies that found beneficial effects of selenomethionine supplementation, such dose may not have been sufficient for reduction of antibodies.

Finally, studies conducted with individuals who had no selenium deficiency found no benefits of supplementation of either selenomethionine or sodium selenite. This may have occurred because absorption of this mineral into the thyroid is limited and an additional dose would not bring benefits in the reduction of antibodies. [27,28]

In this way, scientific evidence about selenium supplementation in Hashimoto's hypothyroidism is controversial, although promising, in individuals who have selenium deficiency. Therefore, methodological standardization is essential in order to establish the optimum dose and time of supplementation, as well as the formula to be used. Moreover, the studies did not investigate selenium deficiency, necessarily, but only the effect of supplementation on the levels of antibodies.

Conclusion

Vitamin D deficiency was more prevalent in individuals with Hashimoto's thyroiditis and it was associated with the greatest expression of Th1 cells, increased production of B lymphocytes and, consequently, increased production of antibodies. On the other hand, in selenium deficiency, there can occur lower activity of GPX, TR and DIO, as well as, both production of T3 and elimination of H_2O_2 inefficient, thus contributing to initiation of oxidative stress, fibrosis and impaired thyroid tissue repair. However, more studies are needed to clarify whether the reduction of serum levels of vitamin D is a causal factor or a consequence of Hashimoto's hypothyroidism.

Supplementation seems to be effective for reduction of antibodies in people who have the disease. However, it should be noted the scarcity of experimental studies, lack of standard methods and that only individuals with selenium deficiency were benefited, since absorption of this mineral into the thyroid is limited and an additional dose does not bring benefits. Nevertheless, there is not sufficient scientific evidence to support the use of supplements for Hashimoto's thyroiditis.

Contributors

Vilela LRR participated in the conception of the project, bibliographical research and drafting of the article; Fernandes DC participated in the bibliographical research, writing and final revision of the article.

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