Lack of Vitamin D and Autoimmune Diseases of the Thyroid – Evidences Based on Meta–Analysis

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Abstract: To verify whether there is a difference between serum vitamin D averages in patients with Graves’ disease and Hashimoto’s thyroiditis, when compared with a group of healthy individuals. This is a systematic review and meta-analysis according to the PRISMA protocol. The test of difference of means with random effect and chi-square of heterogeneity was performed, considering an alpha <0.05 for acceptance of the hypotheses. The tests were performed using the STATA® 16.0 software. There were differences between serum vitamin D averages: group with Graves’ disease compared to healthy individuals (Mean = 10.06; 95% CI =0.99–19.14); Group with Hashimoto’s disease compared to healthy individuals (Mean = 12.49; 95% CI = 5.9 – 19.79); group of children with Hashimoto compared to healthy children, (Mean = 19.46; 95% CI = 10.25–28.68). The mean serum vitamin D levels were significantly higher in healthy individuals, demonstrating that the depletion of this nutrient may be related to the pathophysiological process of these diseases, taking into account the immunomodulatory function that this vitamin has.

Keywords: Hashimoto disease, Graves Disease, Vitamin D Deficiency, Thyroiditis.

Histórico do Artigo: O autor detém os direitos autorais deste artigo.

Resumo: Verificar se há diferença entre médias séricas de vitamina D em portadores de doença de Graves e tireoidite de Hashimoto, quando comparados com um grupo de indivíduos sadios. Trata-se de uma revisão sistemática e metanálise de acordo com o protocolo PRISMA. Foi realizado o teste de diferença de médias com efeito aleatório e qui-quadrado de heterogeneidade, considerando um alfa <0.05 para aceitação das hipóteses. Os testes foram realizados com auxílio do software STATA® 16.0. Houve diferenças entre as médias séricas de vitamina D: grupo com doença de Graves comparado a indivíduos saudáveis (Média =10.06; IC95%=0.99–19.14); Grupo com doença de Hashimoto comparado a indivíduos saudáveis (Média = 12.49; IC95%= 5.19–19.79); grupo de crianças com Hashimoto em comparação com crianças saudáveis, (Média = 19.46 (IC95%=10.25–28.68). Os níveis médios de vitamina D sérica foram significativamente maiores em indivíduos saudios, demonstrando que a depleção desse nutriente pode estar relacionada ao processo fisiopatológico dessas doenças, levando–se em consideração a função imunomoduladora que essa vitamina exerce.

Palavras-chave: Doença de Hashimoto, Doença de Graves, Deficiência de Vitamina D, Tireoidite.
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**INTRODUCTION**

Autoimmune diseases are characterized by the absence of immunological tolerance, caused by the combination of environmental and genetic factors, however, the knowledge about the function of each of these susceptibility factors is not yet precise (MERRILL; MINUCCI, 2018; WEETMAN, 2003). They also involve phenotype factors, of which the main diseases they represent are Hashimoto's thyroiditis (HT) and Graves' disease (GD) (RAGUSA et al., 2019; LAZARUS; PARKES, 2002).

Autoimmune thyroid diseases are polygenic diseases, which result in the combination of genetic predisposition (specific thyroid genes and immunomodulators) and environmental stimuli (selenium, iodine, infections, stress, smoking, etc.) (KÖHLING et al., 2017; KLECHA et al. 2008). TH is a common autoimmune chronic disease of the thyroid gland, characterized by inflammation of the gland, development of diffuse goiter with elevated thyroid antibodies, which occurs through the infiltration of immune cells in the thyroid (DJUROVIC et al., 2018).

After invasion of the thyroid gland by lymphocytic cells, there is follicular atrophy and associated hyperemia of oncocytic metaplasia of the cell follicles, the atrophy of the thyroid tissue, occurs gradually, this leads to the development of hypothyroidism, even with normal thyroid activity (RYDZEWSKA et al., 2018; PEARCE et al., 2003). In GD there is a slight infiltration of lymphocytes, with the involvement of TCD4 + helper cells, known as T helper 2 (Th2), which stimulates the production of antibodies binding to thyroid stimulating hormone (TSH) receptors. Where, after binding to receptors, they induce cell growth, increasing their...
metabolism, causing hyperthyroidism, indicating a humoral immune response (SAWICKA et al., 2020; KLECHA et al., 2008).

Vitamin D is a fat-soluble molecule, has hormone-like effects and comes from the skin, in the form of cholecalciferol (vitamin D3) or acquired through diet in the form of ergocalciferol (vitamin D2) (TRIPKOVIC et al., 2012). Among its functions are the regulation of the metabolism of calcium and phosphorus and the maintenance of skeletal health, bones and parathyroid gland (DOBSON et al., 2017; DASTANI; RICHARDS, 2013).

Studies carried out in recent years report the extra skeletal effects of vitamin D, associated with the deficiency of the nutrient in question (KMIEĆ; SWORCZAK, 2015) and genetic variations, relating the impaired metabolism of this vitamin to several autoimmune diseases, including autoimmune disease thyroid (INOUE et al., 2014). With this, the present research is justified by the need to determine if there is a reduction of vitamin D in individuals with GD and HT, due to the heterogeneity between previous research results (XU et al., 2018; KE et al., 2017; MA et al., 2015). Thus, the objective was to assess the difference between the mean serum vitamin D levels, in groups of individuals diagnosed with HT and GD, comparing them with individuals without the diseases.

MATERIAL AND METHODS

This study consisted of a systematic review and meta-analysis, adopting the descriptive aspect. Meta-analysis is a method of statistical study, applied to systematic review to combine data from studies, with the objective of obtaining results in the same measure and with greater reliability (XU et al., 2015).

After consulting the Health Sciences Descriptors (DeCS), the following descriptors were identified: Hashimoto’s Disease, Graves’ Disease and Vitamin D Deficiency. With the descriptors, articles published in the databases were accessed: Latin American Literature and Caribbean Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (MEDLINE) and PubMed, considering articles published from 2002 to 2020, giving preference to articles published in the last four years.

In LILACS, 20 references were found, which were printed, all with availability of the title, year and place of publication, others also provided the summary. In SciELO 16 references were found and in PubMed 162 references. The repetitions and publications that were not related to the topic were excluded, resulting in 46 references, of which 19 contributed to the systematic
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review and meta-analysis. For the descriptive aspect, bibliographic reviews were selected that described Graves' diseases and Hashimoto's thyroiditis.

Inclusion criteria were: case-control studies, articles describing thyroid diseases and the relationship of vitamin D with individuals with Hashimoto's thyroiditis and Graves' disease, articles that compared children with the same diseases were included. Articles published in English and Portuguese were considered. The exclusion criteria were: books, course completion papers, monographs, dissertations and articles not related to the theme (Figure 1).

Figure 1. Flowchart: selection of articles used for systematic review and meta-analysis. Source: Authors, 2020.

The evaluation, extraction and tabulation of data were based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) instructions and recommendations (MOHER et al., 2009). Thus, the selected articles, for data extraction, were submitted to the evaluation of two reviewers and there were no disagreements regarding the interpretations.
After selecting the articles according to the inclusion and exclusion criteria, the data of the 19 references were tabulated, relevant to the analysis of serum vitamin D levels in individuals with Graves' disease and Hashimoto's thyroiditis. Conversions of units of measurement referring to serum vitamin D, from ng / ml to nmol / L, with the objective of obtaining results with greater reliability, were subsequently applied mean test of differences (MD) with randomized effect, the effect adopted, considered the difference between the results collected, as well as the diverse ethnicity and diverse methodologies. The chi-square test ($\chi^2$) of heterogeneity was performed, considering an alpha ≤0.05 for random or randomized effect. On the other hand, if the alpha resulted in > 0.05, the fixed effect would be adopted, that is, ignoring the existing heterogeneity, considering that the heterogeneity occurred by chance. The I$^2$ test or the Higgins and Thompson test was also carried out, in order to confirm the heterogeneity between the studies, since the number of screened samples is small and the $X^2$ test in these situations is not specific. Thus, the following interpretation was considered: 0% without heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity and 75% or more, high heterogeneity (HIGGINS et al., 2003; HIGGINS; THOMPSON, 2002). The risk of bias in the selected surveys was assessed using the Funnel Plot graph associated with the Egger and Begg tests. The verified hypothesis was: “There is a significant difference between the serum averages of vitamin D, when comparing groups with Graves and Hashimoto's disease with groups of individuals without the diseases” and if the diamond in the Forest Plot graph touched the null line, it would be considered the null hypothesis: “there is no difference between serum vitamin D averages between the groups compared”. The statistical tests were performed with the aid of the STATA® 16.0 Software.

RESULTS AND DISCUSSION

Data extraction resulted for Graves' disease: control group (n = 3,174) and case group (n = 779), for Hashimoto's thyroiditis: control group (n = 1,317) and case group (n = 1,304) and Hashimoto's thyroiditis in children with a mean age of 12.15 years: control group (n = 221) and case group (n = 236) (Table 1).

The assessment of bias through the asymmetry in the Funnel Plot graph, pointed out a probable bias in the surveys carried out so far. The Begg and Egger tests pointed to adults with Hashimoto: Egger with $p \geq |z| = 0.0001$ and Begg with $p \geq |z| = 0.2105$; for adults with Graves' disease: Egger with $p \geq |z| = 0.4776$ and Begg with $p \geq |z| = 0.9170$; for children with Hashimoto:
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Egger with \( p > [z] = 0.0030 \) and Begg with \( p > [z] = 1.9633 \). Despite the asymmetry of the surveys plotted on the Funnel plot graphs and the results of the Egger test point to a significant bias, the results with greater credibility were those of the Begg test, due to significant heterogeneity and the small number of surveys (Figure 2).

Table I. Data containing serum vitamin D concentrations in the case and control groups.

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<td>p-value&lt;0.00001; I²=97%</td>
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Figure 2. Funnel plot graphs for bias assessment, distribution of research results. Source: Authors, 2020.
The pertinent results to the serum comparison of vitamin D, between individuals with Graves’ disease and healthy individuals, showed a significant difference from the mean serum vitamin D (MD = 10.06; 95% CI = 0.99–19.14), indicating a mean serum nutrient equal to 10.06 nmol / L more in the control group when compared to patients with Graves’ disease. The confidence interval (CI) of the diamond, which represents the difference between means (MD), does not touch the null line, confirming the significance of the result and rejecting the null hypothesis. The results of the study by Ke et al., (2017) and Planck et al., (2017), obtained greater weight, however, of the two mentioned, only that of Planck et al., (2017), showed a significant difference. The result of the chi-square of heterogeneity with p = 0.00 and the I² = 97%, justify the application of the randomized effect (Figure 3).

Of the data collected, 90% obtained a statistically significant difference, between serum vitamin D averages, when comparing the group of individuals with Hashimoto’s thyroiditis with the group of healthy individuals. The 10% insignificance refers to the results of Kim, (2016), this can be seen in the graph, where the confidence interval of the study crosses the null line. The test showed that serum vitamin D is on average 12.49 nmol / L more in healthy individuals, with (95% CI = 5.19 to 19.79). The heterogeneity test was significant with p = 0.00, where in combination with I² = 97%, they demonstrate assertiveness in the adopted random effect (Figure 3).

In 100% of the studies plotted, referring to analyzes with data from children, with proof of Hashimoto's thyroiditis diagnosis, significance was evidenced in relation to the difference between serum vitamin D means, MD = 19.46 (95% CI = 10.25 – 28.68), the result in question points out a difference between the averages, where the group of healthy children emerged in serum mean, with 19.46 nmol / L more of the nutrient. The heterogeneity test was significant with p = 0.01 and the I² = 80%, the results together demonstrate assertiveness in choosing the randomized effect (Figure 3).
The relationship between autoimmune diseases and low serum vitamin D levels has been commonly accepted and studied by researchers. Ma et al., (2015), observed that the deficiency of 25 (OH) D or vitamin D, was significantly prevalent in patients who had some autoimmune thyroid disease, when compared to healthy individuals. Bellastella et al., (2015), concluded that the serum vitamin D level was reduced in patients with autoimmune diseases.

In the present study, serum vitamin D levels were lower in individuals diagnosed with Hashimoto’s thyroiditis and Graves’ disease, when compared to healthy individuals. The prevalence of vitamin D deficiency is present in patients with autoimmune thyroid diseases, which suggests that vitamin D may be related to the pathophysiological process of the diseases.
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It is believed that the development of autoimmune thyroid diseases is correlated with the disproportion of T helper 1 (Th1) and T helper 2 (Th2) helper cells. Hashimoto’s thyroiditis occurs when there is an increase in the proportion of Th1 cells, which lead to the secretion of gamma interferon (IFN-γ) (KARANIKAS et al., 2005), whereas patients with Graves’ disease have an increase in the proportion of cells Th2 that secrete interleukin-4 (IL-4) (TSATSOULIS, 2006). Studies relate Th17 cytokine secretion to the development of autoimmune thyroid diseases (LI et al., 2013).

Vitamin D performs an important function in the regulation of Th1, Th2 and Th17 cells, consequently, regulation in the secretion of cytokines IFN-4, IL-4 and IL-17 (JOSHI et al., 2011). The low serum level of vitamin D is also related to the increase in anti-TSH receptor antibodies (TRAb) in the serious disease (ZHANG et al., 2015), these antibodies lead to the development of hyperthyroidism.

Vitamin D exerts its biological effects through the mediation of the vitamin D receptor (VDR, vitamin D receptor), which is found in almost all human cells and participates in direct and indirect forms of the regulation of the immune system. It plays an important role as an immunomodulatory factor, which influences the proliferation and differentiation processes of immune cells. It plays an important role in several cells, including dendritic cells, as it modifies their differentiation and maturation process, reducing the class that presents a major class II histocompatibility complex (MHC II), and also reduces co-stimulating proteins (CD40, CD80, CD86), present in the membrane of dendritic cells, in addition to making changes in the production pattern of cytokines. Due to these changes that occur in dendritic cells, vitamin D indirectly interferes with the activation of lymphocytes, and regularizes Th2 cells and directly inhibits the proliferation of T lymphocytes, especially Th1 cells. In this way, it results in a change in the proportions of Th1 and Th2 cells in anti-inflammatory processes and promotes weakening of Th2 lymphocytes, which are essential for the inflammatory process of autoimmune thyroid diseases.

The analyzed case-control studies showed a high prevalence of vitamin D deficiency in children with Hashimoto’s thyroiditis, with an average age of 12.15 years. These children, mostly are female, also verified the incidence by other authors. It is suggested that estrogen receptors act to reduce immune surveillance, which may justify the higher occurrence in women (LEE et al., 2015).
Vitamin D supplementation can reduce morbidity or alleviate the effects of manifestations in animals with autoimmunity (ETTEN-VAN et al., 2003). Results are also described, where vitamin D supplementation can benefit humans with autoimmune diseases (PIERROT-DESEILLIGNY et al., 2012) and that childhood supplementation potentiates these benefits, reducing the risk of developing thyroid disease (ZIPITIS; AKOBENG, 2008), demonstrating the need of the nutritionist associated with the endocrinologist, in the treatment and supplementation of vitamin D.

CONCLUSION

Based on the results obtained, patients with autoimmune thyroid diseases have serum vitamin D deficiency when compared to healthy individuals. The present research showed vitamin D deficiency in patients with Graves' disease and Hashimoto's thyroiditis, regardless of age. The lack of this nutrient may be related to the pathogenesis of these diseases, as an immunomodulator. However, more research is needed to confirm this hypothesis.

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Lack of Vitamin D and Autoimmune Diseases of the Thyroid – Evidences Based on Meta-Analysis

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