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HASHIMOTO THYROIDITIS: STUDY OF THE GENETIC AND ENVIRONMENTAL ASPECTS THAT MAY INFLUENCE ITS EPIDEMIOLOGY, WITH HIGHLIGHT FOR EXCESSIVE IODIUM CONSUMPTION

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Abstract: Hashimoto's thyroiditis, an autoimmune thyroid disease, has a wide range of factors that can contribute to its development. Thus, this work aimed to study the genetic and environmental factors, highlighting the excessive consumption of iodine, which can influence the development and epidemiology of this pathology. MATERIALS AND METHODS: The research method used was the narrative review, considering the last ten years, with exceptions for when the material presented information relevant to the topic. Various materials were collected, including textbooks, websites and scientific publications, in addition to consulting the Pubmed database. The first phase of the evaluation of the works obtained in this database included the reading of titles and abstracts, with subsequent analysis in full of the selected works, considering only the most suitable for the development of the final text. RESULTS: We considered 26 studies obtained from the Pubmed database, nine related to genetic aspects, 16 to environmental aspects and three to different aspects. CONCLUSIONS: Hashimoto's thyroiditis has been better understood over the last few years, but there is still a need to obtain more robust epidemiological data, especially when considering developing countries. The environmental and genetic factors that contribute to the development of Hashimoto's Thyroiditis are varied and can be influenced by the specific characteristics of a given region. In this sense, it is also worth remembering that such factors can serve as a basis for the creation of government public policies to prevent the development of Hashimoto's Thyroiditis.
Keywords: Hashimoto's Disease; autoimmune thyroiditis; hypothyroidism.

INTRODUCTION

The term thyroiditis correlates with the existence of inflammation in the thyroid gland, and can be classified according to the onset of symptoms, underlying etiology and clinical features. It is a condition that can occur due to autoimmune disease, infection, medications or fibrosis (FARIDUDDIN; SINGH, 2020).

Autoimmune thyroid diseases (AIAD) are organ-specific, with Hashimoto's Thyroiditis (HT; chronic lymphocytic thyroiditis) and Graves' Disease being the most important. HT was described in 1912 by Hikaru Hashimoto, but only after 1950 was its autoimmune aspect demonstrated. Recent findings have indicated that the development of Hashimoto's Thyroiditis depends on immune imbalances in an individual with genetic susceptibility under the influence of environmental factors. However, the pathogenesis of HT is still under study (PYZIK et al., 2015).

Considering these aspects, the objective of this study was to evaluate genetic and environmental factors, with emphasis on excessive consumption of iodine, which may influence the development of Hashimoto's Thyroiditis and, consequently, contribute to the understanding of its global epidemiological variation.

METHODOLOGY

The research method used was the narrative review, through the survey of technical-scientific publications, textbooks, national and international documentation, websites of national and international governmental organizations, or other materials holding relevant information.

In addition, the PubMed database (U.S. National Library of Medicine National Institutes of Health) was consulted, using the descriptors Hashimoto Disease (entry terms: Disease, Hashimoto; Hashimoto Thyroiditis; Chronic Lymphocytic

Thyroiditis; Hashimoto's Disease); Thyroiditis, Autoimmune (entry term: Thyroiditis, Lymphocytic) and Hypothyroidism (entry term: Primary Hypothyroidism).

In the first phase of analysis, after applying a filter for the last ten years to the total results obtained in the Pubmed database with the descriptors mentioned above, titles and abstracts were read, and the works were selected in accordance with the proposal. to be studied. In the second phase of analysis, the full reading of the previously selected titles was carried out, and, again, only the works aligned with the proposal of this study were considered for the elaboration of the final text.

The collection of relevant information in textbooks, websites, or other means was also carried out concomitantly with the process of preparing this study, whenever deemed necessary.

RESULTS

In the first phase of analysis, after applying a filter for the last ten years to the total results obtained in the Pubmed database with the descriptors mentioned above (item 2.), titles and abstracts were read, and the works were selected in accordance with the proposal to be studied. In the second phase of analysis, the full reading of the previously selected titles was carried out, and, again, only the works aligned with the proposal of this study were considered for the elaboration of the final text. As a result, nine works were obtained related to genetic aspects, three to different aspects, and 16 to environmental aspects (figure 1).

DISCUSSION

GENETIC FACTORS INFLUENCING HASHIMOTO'S THYROIDITIS

Ataxin Two (ATXN2), Thyroid Peroxidase (TPO), RAS Guanyl Releasing Protein One (RASGRP1)

Brčić et al. (2016) identified a possible nominal association of the following genetic variants with TH: rs11675434 in the TPO gene, rs10774625 in the ATXN2 gene, G allele of rs7171171 near the RASGRP1 gene.

Cytotoxic T lymphocyte-associated antigen four (CTLA4)

CTLA4 polymorphisms have been associated with TH. CTLA4 is a negative regulator of the T cell response, and therefore polymorphisms related to this gene result in a reduced level of the protein or its function, leading to a predisposition to autoimmune disease (KUMAR et al., 2010).

Zaletel and Gaberšček (2011) indicated that the microsatellite polymorphism (AT)n in the three' untranslated region (considering a Caucasian and Japanese population), the SNP 49A/G related to exon 1, and the SNP 6230A/G (or CT60) could be related to TH. However, the authors state that additional research is needed to study these and other CTLA4 gene polymorphisms that could be related to this clinical condition.

Major Histocompatibility Complex (MHC) - Human Leukocyte Antigen (HLA)

The MHC complex, modulator of antigen binding and presentation, encodes human histocompatibility antigens (HLA, human leukocyte antigen), located on chromosome 6p21. Possible associations with TH are described for the alleles HLA-DR3 and DQB1*0301 in Caucasians, HLA-DRw53 in Japanese, HLA-DR9 in Chinese. Goiter HT was associated with HLA-DR5, and atrophic HT with HLA-DR3 (SGARBI; MACIEL, 2009).

Vita, Cernaro and Benvenga (2019) also associated TH with the HLA DR4 allele (DRB1*04, DQB1*03 and DQA1*03).

Phosphodiesterase 8B (PDE8B)

Barić et al. (2017) developed a study in which they observed that the A minor allele of rs4704397 in the PDE8B gene would be associated with an increased risk of developing

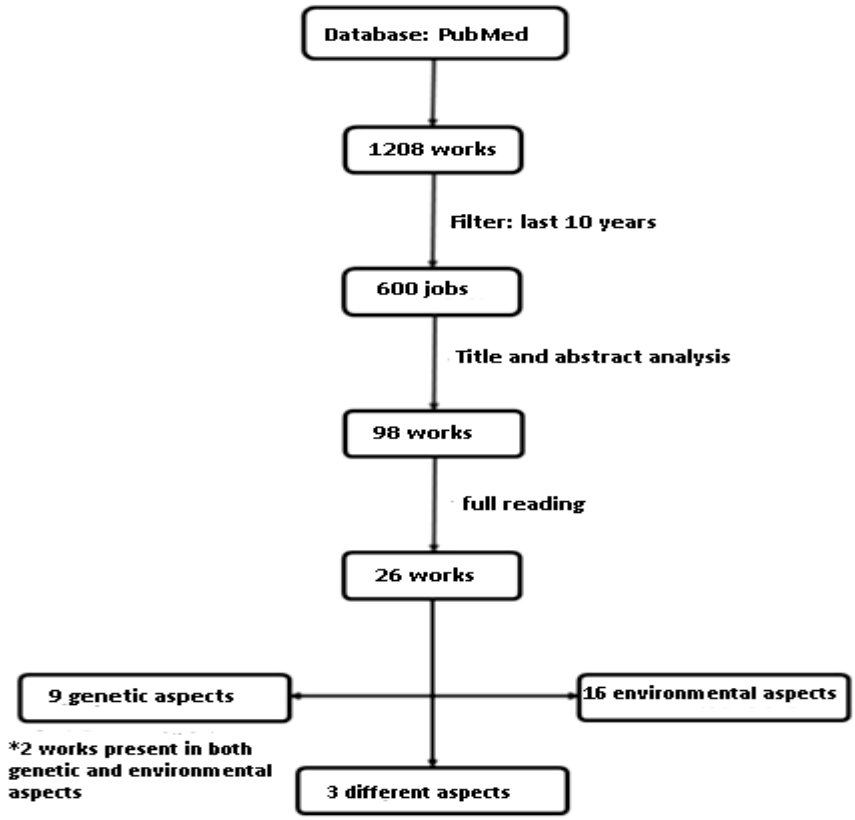

Figure 1: Flowchart with results obtained for the method of searching scientific papers in the PubMed database.

HT. According to the authors, this gene encodes a cyclic nucleotide phosphodiesterase that catalyzes the hydrolysis of the second messenger cAMP.

Inositol hexaphosphate kinase three (IP6K3)

Brčić et al. (2019) performed a genetic association analysis study in 405 patients with HT and 433 controls. A possible genetic influencer of susceptibility to Hashimoto's Thyroiditis found was the SNP (single nucleotide polymorphism) rs791903 related to the IP6K3 gene, located close to the MHC region. This SNP has already been associated with another autoimmune disease, rheumatoid arthritis.

Interleukins (IL)

Gerenova e Stanilova (2016), demonstrated in their study that there is an association of the -1082GG IL-10 genotype with susceptibility to thyroid autoimmune disease. Another point highlighted by the authors was that the concomitant presence of IL-12B +1188CC and IL-10-1082 GG genotypes would contribute to the development and progression of HT. Song et al. (2017) found evidence that some IL-22 loci would be associated with susceptibility to AITD in the Han Chinese population. The GG genotype at rs1179251 would be related to AITD in women, and the A allele at rs2046068 and the T allele at rs2227478 would decrease the risk for HT by 44.3% and 43.6%, respectively. The C allele at rs1179251 would increase the predisposition to HT by 73.9% in male patients. The AA genotype at rs2046068 and the TT genotype at rs2227478 would be related to the risk of adolescents developing AITD, and the C allele at rs1179251 would increase the risk of AITD in adolescents by 39.7%. Furthermore, the authors suggested that the IL-22 rs11611206 polymorphism, including the G allele and GG genotype, could be a genetic risk factor for HT autoimmune hypothyroidism.

Sidekick cell adhesion molecule two (SDK2)

Brčić et al. (2019) found a possible genetic influencer of susceptibility to Hashimoto's Thyroiditis, the SNP rs12944194, located 206 kb from the SDK2 gene, which encodes a protein that is part of the immunoglobulin superfamily.

Tumor necrosis factor alpha-induced protein three (TNFAIP3 or A20)

A study by Hori et al. (2019) analyzed patients from a family with A20 haploinsufficiency who developed HT by an autosomal dominant inheritance. A20 is a negative regulator of multiple intracellular immune signaling pathways, including the tumor necrosis factor alpha signaling pathway. In the family analyzed in this study, a heterozygous mutation c.2209delC of TNFAIP3 was identified in all tested members, which, according to the authors, could contribute to the onset of AITD.

Adapter protein three SH2B (SH2B3)

According to Baric et al. (2017), the major T allele of rs3184504 in the SH2B3 gene, which has been associated with a wide variety of autoimmunities, is associated with an increased risk of developing HT.

Guanine nucleotide binding protein alpha-14 (GNA14)

Brčić et al. (2019) evaluated the SNP rs75201096, related to the GNA14 gene, as a possible genetic influencer of susceptibility to Hashimoto's Thyroiditis. Genetic variations of this region are relevant for TH, as they have been associated with cytokines (compounds that play an important role in autoimmune diseases), and with IgG glycosylation (may be associated with TH-specific autoantibodies).

Protein tyrosine phosphatase-22 (PTNP22)

PTNP22 encodes a lymphoid tyrosine phosphatase that has T cell inhibitory function. Functional polymorphisms in the PTNP22 gene have also been associated with

TH (KUMAR et al., 2010).

39A transmembrane protein (TMEM39A)

A study by Yao et al. (2019) analyzed whether four SNPs of the TMEM39A gene, rs1132200, rs12492609, rs2282175, and rs7629750, would be associated with DAIT. This gene has been associated with some autoimmune diseases and its biological function is still under investigation, being located on chromosome 3q13.33. The study included 906 patients with AITD, of which 293 had HT. The results found showed that the T allele of rs12492609 could decrease the genetic susceptibility to DAIT and TH. Another finding suggested that the CTA haplotype related to this gene would have a protective role regarding susceptibility to DAIT and TH. Furthermore, the rs12492609 and rs7629750 polymorphisms could be associated with hypothyroidism in Hashimoto's Thyroiditis.

Thyroglobulin (TG)

There is evidence that polymorphisms in the TG gene, more specifically in chromosome 8q24, would be related to AITD. The TG gene encodes thyroglobulin and is therefore a specific gene for the thyroid gland. Its variants could initiate the thyroid autoimmune response by altering the presentation of the TG peptide by the antigen-presenting cell (APC) to T cells (SGARBI; MACIEL, 2009).

ENVIRONMENTAL FACTORS INFLUENCING HASHIMOTO'S THYROIDITIS

Alcohol

Patients with overt autoimmune hypothyroidism generally consume less alcohol compared to euthyroid individuals, so moderate alcohol consumption has a protective effect. This association is independent of the type of alcoholic beverage consumed, gender, iodine consumption, or the fact of being a smoker or not. The mechanism of action of this protective effect, however, remains not completely elucidated (WIERSINGA, 2016).

Laurberg et al. (2013) also state that moderate alcohol consumption may be associated with dose-dependent protection against the development of autoimmune hypothyroidism. A direct effect of alcohol on the immune system may be a possible mechanism involved, as such a protective action has also been described for other autoimmune diseases.

Stress and other psychiatric conditions

To date, the relationship between exposure to stress and the development of Hashimoto's Thyroiditis has been poorly studied, and no clear association has been found between this factor and overt autoimmune hypothyroidism (WIERSINGA, 2016). Vita, Cernaro and Benvenga (2019) reported a case of a patient with HT whose euthyroid status was affected by a psychological stressful event, with subsequent development of thyrotoxicosis (hashitoxicosis) and transient hypothyroidism. However, according to the authors, the long time interval between the onset of the autoimmune response and the onset of HT makes it difficult to assess stress as a trigger for this disease. A review and meta-analysis study by Siegmann et al. (2018) indicated that autoimmune thyroiditis is associated with depression and anxiety disorders. Therefore, it is important that patients with such psychiatric conditions are tested for the presence of autoimmune thyroiditis, so that the best treatment can be recommended taking into account the possibility of using antidepressants.

Intrauterine factors

According to Sgarbi and Maciel (2009), intrauterine factors associated with low fetal weight could be the first environmental risk factors associated with the development of AITD. The prevalence of anti-TPO antibodies was found to be higher in women with low fetal birth weight, and among homozygous twins

who were born with a lower birth weight. This could be explained by the association of fetal malnutrition with lower splenic and thymic weight, a factor that could result in an early maturation of the thymus and a decline in suppressor T cells.

Iron

According to Rayman (2019), TPO, an essential component for the synthesis of thyroid hormones, is a heme-dependent enzyme that has an iron atom in its active center, becoming active in the apical membrane of thyrocytes only after its binding with such a prosthetic group. Adequate iron intake is therefore essential for the synthesis of thyroid hormones. According to the author, patients with subclinical hypothyroidism or HT often have lower serum iron concentrations and a higher prevalence of iron deficiency when compared to healthy individuals.

Female gender

It is suspected that sex hormones and biased inactivation of the X chromosome may be triggers for hypothyroidism (TAYLOR et al., 2018).

Zaletel and Gaberšček (2011) state that a possible explanation for the high female predominance in thyroid autoimmunity could be associated with the fact that the X chromosome contains a certain amount of genes related to immunity and gender that are of paramount importance in the preservation of tolerance. immune. Another potential mechanism of impaired immunotolerance in women would be related to the biased inactivation of the X chromosome, which would lead to the escape of X-related autoantigens from presentation in the thymus, with subsequent loss of T cell tolerance.

For Sgarbi and Maciel (2009), the most likely influencer would be the possible effect of sex hormones on the immune system, where estrogens would have an exacerbating role and testosterone a protective effect.

Age

According to Sgarbi and Maciel (2009), age seems to play a role in the pathogenesis of AITD, given the existence of evidence demonstrating an increase in the prevalence of thyroid autoantibodies with aging. This could occur, as age would increase the time of exposure to environmental factors, producing changes in immunoregulation, which could contribute to the triggering of autoimmune thyroiditis.

Infections and the Hygiene Hypothesis

According to Ragusa et al. (2019) there is evidence of an association between the hepatitis C virus and AITD. Furthermore, it has been shown that such a virus is able to enter thyrocytes, stimulating the production of inflammatory cytokines.

Zaletel and Gaberšček (2011) propose a possible relationship with parvovirus, rubella, herpes simplex virus, Epstein-Barr virus, and human T-lymphotropic virus type one. However, the authors state that the evidence is scarce, and further studies are needed to confirm the causal role of infections.

As a counterpoint, in the hygiene hypothesis, the immune system would be educated through multiple and different infections, which would result in better control of the immune response. However, urban development and the improvement of population hygiene conditions would lead to less exposure to microbial agents, resulting in an increased risk of developing autoimmune disease (SGARBI; MACIEL, 2009).

Magnesium

A study by Wang et al. (2018) aimed to investigate the relationship between serum magnesium levels and autoimmune thyroiditis. Magnesium has functions related to the immune system, cellular oxidative stress, and inflammatory reactions. It was found that serum magnesium levels ≤0.55 mmol/L would be related to the risk of positivity for

TG-Ab and prevalence of TH, while extremely low serum levels of this nutrient would not be associated with increased positivity for TPO-Ab. According to the study, such divergent effects in relation to thyroid autoantibodies would indicate that extremely low serum magnesium levels would not be the initiating factor of autoimmune thyroiditis, but could be an aggravating factor through inflammatory action.

Medicines

Amiodarone, an antiarrhythmic agent, lithium, widely used in the treatment of bipolar mood disorders, and interferon-gamma, an immunoregulator, may be related to hypothyroidism (TAYLOR et al., 2018). Interleukin-two and granulocyte and macrophage colony-stimulating factor were related to thyroid autoimmunity (SGARBI; MACIEL, 2009).

Regarding HT, oral contraceptives, by preventing pregnancy, reduce the risk of AITD, as postpartum thyroiditis is considered a precursor of permanent autoimmune hypothyroidism. There is also evidence that interferon-alpha, alemtuzumab and highly active antiretroviral therapies are able to induce AITD, including HT (WIERSINGA, 2016).

Other immune conditions

There are associations between AITD and organ-specific/systemic autoimmune diseases, as it is not uncommon to find patients with more than one immune-mediated endocrinopathy. As a result, there is the occurrence of a polyglandular autoimmune syndrome, characterized by the failure of different endocrine glands. This explanation for the association of AITD with other autoimmune diseases considers genetic and environmental influences (RAGUSA et al., 2019). Liontiris and Mazokopakis (2017) cited the relationship between AITD and celiac disease, which could be explained in part due to the increased immunosensitivity of celiac patients, as part of an autoimmune polyglandular syndrome, by the deficiency of essential elements such as selenium and iodine caused by malabsorption or due to antibodies, and it is recommended that patients with AITD be tested for this clinical condition.

Selenium

There are hypotheses that selenium deficiency could be associated with thyroid autoimmunity, in addition to the possibility that selenium supplementation may be beneficial (VALEA; GEORGESCU, 2018; WIERSINGA, 2016).

Rayman (2019) also related selenium to DAITs, including TH. According to the author, there is evidence that high serum levels of this nutrient would be associated with significantly lower probabilities of autoimmune thyroiditis. Also, although the clinical benefit of selenium supplementation has not been confirmed for thyroid autoimmunity, the author argues that adequate consumption of this nutrient must be ensured, given its importance for human health, and particularly for the thyroid.

Smoking

According to TAYLOR et al. (2018), smokers have an approximately 30 to 45% reduction in the probability of becoming positive for TPO-Ab, in addition to a 50% lower prevalence for subclinical hypothyroidism, and a 40% lower prevalence for overt hypothyroidism, compared to non-smokers.

Sawicka-Gutaj et al. (2014) stated in their study that there is a possibility that exposure to cigarette smoke may inhibit the production of Th1 cytokines and lead to an increase in the Th2 response. As HT is considered a predominantly Th1 disease, the suppressive effect of smoking on the Th1 response could explain the reduced risk of this disease among smokers. However, the authors also highlight the need for further studies on this aspect.

For Laurberg et al. (2013), smoking

cessation is associated with a marked, albeit transient, increase in the risk of developing autoimmune hypothyroidism in the first two years. The mechanisms that could explain this fact, according to the authors, would be related to an excess of iodide transported to the thyroid, tissue damage mediated by reactive oxygen species, or even the action of mechanisms not yet known that decrease thyroid autoimmune activity.

Vitamin: D

According to Tamer et al. (2011), vitamin D is an important regulator of the immune system. In the study conducted by the authors, patients with HT had lower levels of 25-hydroxyvitamin D compared to healthy participants, and the prevalence of vitamin D insufficiency was higher in patients with HT, suggesting a possible role of this nutrient in autoimmune processes. However, the authors recommend the need for further studies to determine whether vitamin D insufficiency is a causal factor in the pathogenesis of HT or a consequence of the disease.

Sönmezgöz et al. (2016) concluded in their study that the rate of vitamin D deficiency is high among children with HT, and that deficiency of this nutrient is common in children affected with this AIT.

Kim (2016) found evidence that vitamin D insufficiency would be associated with AITD and HT, as well as with the progression of thyrocyte damage in HT.

IODINE

Evidence of the influence of excess iodine on the development of HT

According to Liontiris and Mazokopakis (2017), even a small increase in iodine consumption could be related to an increased prevalence of thyroid autoimmunity. As possible mechanisms of this association, the authors mentioned that the apoptosis of thyroid follicular cells present in the development of HT is probably caused by the suppression of autophagic activity, a fact induced by excess iodine. Furthermore, excess iodine would increase the intrathyroid infiltrate of Th17 cells and inhibit the development of regulatory T cells, while triggering an abnormal expression of the tumor necrosis factor-related apoptosis-inducing ligand in thyrocytes, leading to apoptosis and parenchymal destruction. Palaniappan et al. (2017) also concluded in their study that there is a possible association between increased iodine consumption and autoimmune thyroiditis, and that excessive iodine consumption can trigger thyroid autoimmunity. In that study, the authors observed that mean iodine levels were higher in children with juvenile autoimmune thyroiditis, and that this same group was also 17.94 times more likely to have urinary iodine excretion ≥300 μg/L (considered excessive), in relation to children without this condition.

Aghini Lombardi et al. (2013) evaluated the frequency and distribution of thyroid disease after starting iodine supplementation in a population living in a relatively isolated community in southern Italy, comparing data from a survey carried out in this community in 1995 and another carried out in 2010. It was found that HT was significantly more frequent in 2010, both in men and women, and that in 2010 the prevalence of HT progressively increased with age.

Duan et al. (2018) found evidence that high levels of iodine and di-n-butyl-phthalate (DBP) could exacerbate HT. On the one hand, DBP and high levels of iodine would aggravate the inflammatory response in the liver, strengthening the activation of activator protein one (AP-1), which would lead to an increase in the expression of thyroxine-binding globulin (TGB). This would influence the levels of free thyroid hormones in the blood, resulting in thyroid hormone imbalance and exacerbation of AITD. On the

other hand, DBP and high levels of iodine would also contribute to the activation of AP-1 in the thyroid gland, leading to an increase in interleukin-six (IL-6) levels, which would result in an increase in IL-17 expression, with worsening thyroid inflammation.

Probable mechanisms of action of iodine in the development of autoimmune thyroid disease

Luo et al. (2014) proposed that excess iodine could act on the development of autoimmune thyroid disease through the following mechanisms: stimulation of the lymphocytic response in the thyroid, induction of oxidative damage in the thyroid tissue, or by influencing the autoantigenicity of thyroglobulin. According to the authors, the redundant reactive oxygen species generated during the capture, oxidation and organification of excess iodine in thyrocytes (probably due to a defect in the iodine processing machinery) could generate high levels of oxidative stress, and, consequently, damage. cell. This damage could stimulate thyrocytes, similarly to a molecular pattern associated with danger, to produce and secrete cytokines and chemokines. Then, lymphocytes would be recruited to the thyroid, where they could find key thyroid autoantigens, including thyroglobulin. Modifications caused by excess iodine could alter the conformation of the thyroglobulin molecule, in order to facilitate its antigenic presentation by professional antigen-presenting cells, as well as by thyrocytes that express MHC, and its recognition by T cells. excess could eventually result in a pathological intolerance to thyroid autoantigens and the development of thyroiditis.

Brazil: history of salt and TH iodization policy

In 1953, the salt iodization policy began in Brazil, although restricted to iodine-deficient areas. It was not until 1956 that iodized salt was made available to the entire population. In 1974, the amount of iodine in salt for human consumption was established at 10 mg iodine/kg salt. In 1995, it was defined that all salt for human consumption must be iodized according to the limits established by the Ministry of Health (at that time, 40 to 60 mg iodine/kg salt). In 1998, the National Health Surveillance Agency (ANVISA) increased the concentration to 40 to 100 mg iodine/kg salt, however, in 2003, it decided to decrease it to 20 to 60 mg iodine/kg salt. This decrease was carried out because, from 1998 to 2003, it was proved that the Brazilian population was subjected to an excessive consumption of iodine, according to data on excessive urinary iodine excretion and iodine content in salt obtained at the time. This period of excessive exposure (1998 to 2003), including, can be considered a possible environmental factor influencing a high prevalence of both HT and iodine-induced hyperthyroidism (MEDEIROS-NETO, 2009). In 2013, the Collegiate Board of ANVISA approved the range of iodine in salt from 15mg/kg to 45mg/kg (ANVISA, 2013).

As an example of agreement with the facts presented above about the impact of the salt iodization policy in Brazil, a study carried out by Camargo et al. (2006) concluded that exposure to high iodine consumption in the country, especially at the time of mandatory salt iodination of 40 to 100 mg iodine/kg, may have contributed to the increased prevalence of chronic autoimmune thyroiditis in the urban population of Metropolitan region of Sao Paulo. An increase in the prevalence of chronic autoimmune thyroiditis was observed in this area from 9.4% (according to 1994 data) to 17.6%.

CONCLUSIONS

Hashimoto's thyroiditis is a disease that has been increasingly studied over the last few years. It is an important clinical

condition, given its wide global distribution and the impacts related to the development of hypothyroidism.

However, although there is increasing information that contributes to the clarification of its pathophysiological mechanism, more accurate and up-to-date epidemiological data from developing regions such as Africa, South America (including Brazil) and Southeast Asia are lacking. Still considering this aspect, worldwide, data related to the incidence and specific prevalence of HT also need further studies, as the information presented is often related to thyroid autoimmune diseases in general or to hypothyroidism.

Regarding the genetic and environmental factors that can influence the development of TH, a considerable number and variety of candidates were obtained. In this context, it is important to consider that the unique characteristics of a country or region (sociocultural, geographic, environmental and population genetic factors) can influence the development of some of the genetic and environmental aspects presented, contributing to the triggering and progression of HT. This relationship may even help to explain the worldwide epidemiological variation of this disease.

For one of the most widely accepted environmental factors related to the development of HT, the excessive consumption of iodine, the importance of monitoring both its population serum levels (in order to avoid its deficiency or excess) and the programs of mandatory salt iodization, if any, given the example of Brazilian policy and its consequences.

Finally, the observance of the presence of some of the genetic and/or environmental factors presented in this work in a population can serve as an alert and a starting point for the development of educational and preventive government programs against Hashimoto's Thyroiditis. It is worth remembering that a careful study of planning, projection of impacts, and monitoring of results must always be carried out in any public policy, to avoid negative short, medium or long-term outcomes that could affect the population.

REFERENCES

AGHINI LOMBARDI, F.; FIORE, E.; TONACCHERA, M.; ANTONANGELI, L.; RAGO, T.; FRIGERI, M.; PROVENZALE, A. M.; MONTANELLI, L.; GRASSO, L.; PINCHERA, A.; VITTI, P. **The effect of voluntary iodine prophylaxis in a small rural community: the Pescopagano survey 15 years later.** The Journal of Clinical Endocrinology & Metabolism, [s. l.], v. 98, n. 3, p. 1031-1039, 2013. DOI: 10.1210/jc.2012-2960. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23436921/. Acesso em: 01 setembro 2020.

ANVISA - Agência Nacional de Vigilância Sanitária. **Publicada a norma sobre iodação do sal para consumo humano. 17 abril 2013.** Disponível em: http://antigo.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=2672113&_101_type=content&_101_groupId=219201&_101_urlTitle=publicada-a-norma-sobre-iodacao-do-sal-para-consumo-humano&redirect=http%3A%2F%2Fantigo.anvisa.gov.br%2Fresultado-de-busca%3Fp_p_id%3D3%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-1%26p_p_col_count%3D1%26_3_groupId%3D0%26_3_keywords%3DPublicada%2Ba%2Bnorma%2Bsobre%2Bioda%25C3%25A7%25C3%25A3o%2Bdo%2Bsal%2Bpara%2Bconsumo%2Bhumano.%26_3_cur%3D1%26_3_struts_action%3D%252Fsearch%252Fsearch%26_3_format%3D%26_3_formDate%3D1441824476958&inheritRedirect=true. Acesso em: 12 outubro 2020.

BARIĆ, A.; BRČIĆ, L.; GRAČAN, S.; LOVRIĆ, V. T.; GUNJAČA, I.; ŠIMUNAC, M.; BREKALO, M.; BOBAN, M.; POLAŠEK, O.; BARBALIĆ, M.; ZEMUNIK, T.; PUNDA, A.; PERICA, V. B**. Association of established hypothyroidism-associated genetic variants with Hashimoto's thyroiditis.** Journal of Endocrinological Investigation, [s. l.], v. 40, n. 10, p. 1061-1067, 2017. DOI: 10.1007/s40618-017-0660-8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28382505/. Acesso em: 21 julho 2020.

BRČIĆ, L.; BARIĆ, A.; GRAČAN, S.; BRDAR, D.; LOVRIĆ, V. T.; VIDAN, N.; ZEMUNIK, T.; POLAŠEK, O.; BARBALIĆ, M.; PUNDA, A.; PERICA, V. B. **Association of established thyroid peroxidase autoantibody (TPOAb) genetic variants with Hashimoto's thyroiditis.** Autoimmunity, [s. l.], v. 49, n. 7, p. 480-485, 2016. DOI: 10.1080/08916934.2016.1191475. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27268232/. Acesso em: 13 agosto 2020.

BRČIĆ, L.; BARIĆ, A.; GRAČAN, S.; BREKALO, M.; KALIČANIN, D.; GUNJAČA, I.; TORLAK LOVRIĆ, V.; TOKIĆ, S.; RADMAN, M.; ŠKRABIĆ, V.; MILJKOVIĆ, A.; KOLČIĆ, I.; ŠTEFANIĆ, M.; GLAVAŠ-OBROVAC, L.; LESSEL, D.; POLAŠEK, O.; ZEMUNIK, T.; BARBALIĆ, M.; PUNDA, A.; BORASKA PERICA, V. **Genome-wide association analysis suggests novel loci for Hashimoto's thyroiditis.** Journal of Endocrinological Investigation, [s. l.], v. 42, n. 5, p. 567-576, 2019. DOI: 10.1007/s40618-018-0955-4. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30284222/. Acesso em: 14 junho 2020.

CAMARGO, R. Y. A.; TOMIMORI, E. K.; NEVES, S. C.; KNOBEL, M.; MEDEIROS-NETO, G. **Prevalence of chronic autoimmune thyroiditis in the urban area neighboring a petrochemical complex and a control area in Sao Paulo, Brazil.** Clinics, São Paulo , v. 61, n. 4, p. 307-312, 2006. DOI: https://doi.org/10.1590/S1807-59322006000400006. Disponível em: https://www.scielo.br/scielo.php?pid=S1807-59322006000400006&script=sci_arttext. Acesso em: 21 setembro 2020.

DUAN, J.; KANG, J.; DENG, T.; YANG, X.; CHEN, M. **Exposure to DBP and high iodine aggravates autoimmune thyroid disease through increasing the levels of IL-17 and thyroid-binding globulin in wistar rats.** Toxicological Sciences, [s. l.], v. 163, n. 1. p. 196-205, 2018. DOI: 10.1093/toxsci/kfy019. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29385629/. Acesso em: 19 julho 2020.

FARIDUDDIN, M. M.; SINGH, G**. Thyroiditis.** In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2020. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32310435/. Acesso em: 07 julho 2020.

GERENOVA, J.; STANILOVA, S**. IL-12B and IL-10 gene polymorphisms in the development of Hashimoto's thyroiditis.** International Journal of Immunogenetics, [s. l.], v. 43, n. 6, p. 397-403, 2016. DOI: 10.1111/iji.12293. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27774749/. Acesso em: 04 agosto 2020.

HORI, T.; OHNISHI, H.; KADOWAKI, T.; KAWAMOTO, N.; MATSUMOTO, H.; OHARA, O.; FUKAO, T. **Autosomal dominant Hashimoto's thyroiditis with a mutation in TNFAIP3.** Clinical Pediatric Endocrinology, [s. l.], v. 28, n. 3, p. 91-96, 2019. DOI: 10.1297/cpe.28.91. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31384100/. Acesso em: 10 junho 2020.

KIM, Dohee. **Low vitamin D status is associated with hypothyroid Hashimoto's thyroiditis.** Hormones, Atenas, v. 15, n. 3, p. 385-393, 2016. DOI: 10.14310/horm.2002.1681. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27394703/. Acesso em: 11 agosto 2020.

KUMAR, V.; ABBAS, A. K.; FAUSTO, N.; ASTER, J. C. **Robbins e Cotran: Patologia - bases patológicas das doenças.** 8. ed. Rio de Janeiro: Elsevier, 2010. 1458 p.

LAURBERG, P.; ANDERSEN, S.; PEDERSEN, I. B.; KNUDSEN, N.; CARLÉ, A. **Prevention of autoimmune hypothyroidism by modifying iodine intake and the use of tobacco and alcohol is manoeuvring between Scylla and Charybdis.** Hormones, Atenas, v. 12, n. 1 , p. 30-38, 2013. DOI: 10.1007/BF03401284. Disponível em: https://pubmed.ncbi.nlm.nih.gov/23624129/. Acesso em: 11 setembro 2020.

LIONTIRIS, M. I.; MAZOKOPAKIS, E. E. **A concise review of Hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients. Points that need more investigation.** Hellenic Journal of Nuclear Medicine, [s. l.], v. 20, n. 1, p. 51-56, 2017. DOI: 10.1967/s002449910507. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28315909/. Acesso em: 26 julho 2020.

LUO, Y.; KAWASHIMA, A.; ISHIDO, Y.; YOSHIHARA, A.; ODA, K.; HIROI, N.; ITO, T.; ISHII, N.; SUZUKI, K. **Iodine excess as an environmental risk factor for autoimmune thyroid disease.** International Journal of Molecular Sciences, [s. l.], v. 15, n. 7, p. 12895-12912, 2014. DOI: 10.3390/ijms150712895. Disponível em: https://pubmed.ncbi.nlm.nih.gov/25050783/. Acesso em: 28 setembro 2020.

MEDEIROS-NETO, Geraldo. **Iodine nutrition in Brazil: where do we stand?.** Arquivos Brasileiros de Endocrinologia e Metabologia, São Paulo, v. 53, n. 4, p. 470-474, 2009. DOI: http://dx.doi.org/10.1590/S0004-27302009000400014. Disponível em: https://www.scielo.br/scielo.php?pid=S0004-27302009000400014&script=sci_arttext. Acesso em: 22 setembro 2020.

PALANIAPPAN, S.; SHANMUGHAVELU, L.; PRASAD, H. K.; SUBRAMANIAM, S.; KRISHNAMOORTHY, N.; LAKKAPPA, L. **Improving iodine nutritional status and increasing prevalence of autoimmune thyroiditis in children.** Indian Journal of Endocrinology and Metabolism, [s. l.], v. 21, n. 1, p. 85-89, 2017. DOI: 10.4103/2230-8210.195996. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28217504/. Acesso em: 02 agosto 2020.

PYZIK, A.; GRYWALSKA, E.; MATYJASZEK-MATUSZEK, B.; ROLIŃSKI, J. **Immune Disorders in Hashimoto's Thyroiditis: What Do We Know So Far?.** Journal of Immunology Research, [s. l.], v. 2015, 2015. DOI: 10.1155/2015/979167. Disponível em: https://pubmed.ncbi.nlm.nih.gov/26000316/. Acesso em: 07 julho 2020.

RAGUSA, F.; FALLAHI, P.; ELIA, G.; GONNELLA, D.; PAPARO, S. R.; GIUSTI, C.; CHURILOV, L. P.; FERRARI, S. M.; ANTONELLI, **A. Hashimotos' Thyroiditis: epidemiology, pathogenesis, clinic and therapy. Best Practice & Research Clinical** Endocrinology & Metabolism, [s. l.], v. 33, n. 6, 2019. DOI: 10.1016/j.beem.2019.101367. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31812326/. Acesso em: 14 julho 2020.

RAYMAN, Margaret P. **Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease.** Proceedings of the Nutrition Society, [s. l.], v. 78, n. 1, p. 34-44, 2019. DOI: 10.1017/S0029665118001192. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30208979/. Acesso em: 17 junho 2020.

SAWICKA-GUTAJ, N.; GUTAJ, P.; SOWIŃSKI, J.; WENDER-OŻEGOWSKA, E.; CZARNYWOJTEK, A.; BRĄZERT, J.; RUCHAŁA, M**. Influence of cigarette smoking on thyroid gland – an update.** Endokrynologia Polska, [s. l.], v. 65, n. 1, p. 54-62, 2014. DOI: 10.5603/EP.2014.0008. Disponível em: https://pubmed.ncbi.nlm.nih.gov/24549603/. Acesso em: 23 agosto 2020.

SGARBI, J. A.; MACIEL, R. M. B. **Patogênese das doenças tiroidianas autoimunes.** Arquivos Brasileiros de Endocrinologia e Metabologia, São Paulo, v. 53, n. 1, p. 5-14, 2009. DOI: http://dx.doi.org/10.1590/S0004-27302009000100003. Disponível em: https://www.scielo.br/scielo.php?script=sci_abstract&pid=S0004-27302009000100003&lng=es&nrm=iso&tlng=pt. Acesso em: 08 junho 2020.

SIEGMANN, E. M.; MÜLLER, H. H. O.; LUECKE, C.; PHILIPSEN, A.; KORNHUBER, J.; GRÖMER, T. W. **Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis.** JAMA Psychiatry, [s. l.], v. 75, n. 6, p. 577-584, 2018. DOI: 10.1001/jamapsychiatry.2018.0190. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29800939/. Acesso em: 18 julho 2020.

SONG, R. H.; LI, Q.; WANG, W.; YAO, Q. M.; SHAO, X. Q.; ZHANG, J. A. **Variants of interleukin-22 gene confer predisposition to autoimmune thyroid disease.** International Journal of Endocrinology, [s. l.], v. 2017, 2017. DOI: 10.1155/2017/3428236. Disponível em: https://pubmed.ncbi.nlm.nih.gov/28839453/. Acesso em: 20 julho 2020.

SÖNMEZGÖZ, E.; OZER, S.; YILMAZ, R.; ÖNDER, Y.; BÜTÜN, I.; BILGE, S. **Hypovitaminosis D in children with Hashimoto's Thyroiditis.** Revista médica de Chile, Santiago, v. 144, n. 5, p. 611-616, 2016. DOI: 10.4067/S0034-98872016000500009. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27552012/. Acesso em: 10 agosto 2020.

TAMER, G.; ARIK, S.; TAMER, I.; COKSERT, D**. Relative vitamin D insufficiency in Hashimoto's thyroiditis.** Thyroid, [s. l.], v. 21, n. 8, p. 891-896, 2011. DOI: 10.1089/thy.2009.0200. Disponível em: https://pubmed.ncbi.nlm.nih.gov/21751884/. Acesso em: 16 setembro 2020.

TAYLOR, P. N.; ALBRECHT, D.; SCHOLZ, A.; GUTIERREZ-BUEY, G.; LAZARUS, J. H.; DAYAN, C. M.; OKOSIEME, O. E**. Global epidemiology of hyperthyroidism and hypothyroidism.** Nature Reviews Endocrinology, [s. l.], v. 14, n. 5, p. 301-316, 2018. DOI: 10.1038/nrendo.2018.18. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29569622/. Acesso em: 08 junho 2020.

VALEA, A.; GEORGESCU, C.E. **Selenoproteins in human body: focus on thyroid pathophysiology.** Hormones, Atenas, v. 17, n. 2, p. 183-196, 2018. DOI: 10.1007/s42000-018-0033-5. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29873029/. Acesso em: 05 julho 2020.

VITA, R.; CERNARO, V.; BENVENGA, S. **Stress-induced hashitoxicosis: case report and relative HLA serotype and genotype.** Revista da Associação Médica Brasileira, São Paulo, v. 65, n. 6, p. 830-833, 2019. DOI: http://dx.doi.org/10.1590/1806-9282.65.6.830. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31340312/. Acesso em: 11 junho 2020.

WANG, K.; WEI, H.; ZHANG, W.; LI, Z.; DING, L.; YU, T.; TAN, L.; LIU, Y.; LIU, T.; WANG, H.; FAN, Y.; ZHANG, P.; SHAN, Z.; ZHU, M**. Severely low serum magnesium is associated with increased risks of positive anti-thyroglobulin antibody and hypothyroidism: a cross-sectional study.** Scientific Reports, [s. l.], v. 8, n. 1, p. 9904, 2018. DOI: 10.1038/s41598-018-28362-5. Disponível em: https://pubmed.ncbi.nlm.nih.gov/29967483/. Acesso em: 27 junho 2020.

WIERSINGA, Wilmar M. **Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease**. Endocrinology and Metabolism, Seoul, v. 31, n. 2, p. 213-222, 2016. DOI: doi: 10.3803/EnM.2016.31.2.213. Disponível em: https://pubmed.ncbi.nlm.nih.gov/27184015/. Acesso em: 08 junho 2020.

YAO, Q.; WANG, B.; QIN, Q.; JIA, X.; LI, L.; ZHANG, JA**. Genetic Variants in TMEM39A Gene Are Associated with Autoimmune Thyroid Diseases.** DNA and Cell Biology, [s. l.], v. 38, n. 11, p. 1249-1256, 2019. DOI: 10.1089/dna.2019.4872. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31553233/. Acesso em: 07 junho 2020.

ZALETEL, K.; GABERŠČEK, S**. Hashimoto's Thyroiditis: from genes to the disease.** Current Genomics, [s. l.], v. 12, n. 8, p. 576-588, 2011. DOI: 10.2174/138920211798120763. Disponível em: https://pubmed.ncbi.nlm.nih.gov/22654557/. Acesso em: 06 setembro 2020.