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Review

World J Oncol. 2024;15(1):14-27

Autoimmune Thyroid Disease and Differentiated Thyroid Carcinoma: A Review of the Mechanisms That Explain an Intriguing and Exciting Relationship

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Abstract

Autoimmune thyroid disease is a complex and highly frequent disease, where a wide variety of genetic, epigenetic and environmental factors (among others) come together and interact, and is characterized by the presence of two clinical outcomes: hypothyroidism (in Hashimoto's thyroiditis) and hyperthyroidism (in Graves-Basedow disease). For its part, differentiated thyroid carcinoma (mainly papillary carcinoma) is the most common type of cancer affecting the thyroid (and one of the most prevalent worldwide). An important co-occurrence between autoimmune thyroid disease and differentiated thyroid carcinoma has been documented. In this article, studies that have evaluated possible associations and relationships between autoimmune thyroid disease and differentiated thyroid cancer are systematically described and summarized. To date, the underlying mechanism that explains this association is inflammation; however, the characteristics and designs of the studies evaluated do not yet allow a causal relationship between the two entities to be established. These aspects have made it difficult to establish "causality" in the continuum of the pathogenesis between both conditions.

Keywords: Thyroid cancer; Thyroiditis; Autoimmune; Hypothyroidism; Hyperthyroidism

Introduction

Autoimmune thyroid disease (AITD) is the most frequent organ-specific autoimmune disease; generally, an extended immune response - both humoral (mediated by antibodies against multiple thyroid autoantigens) and cellular (mediated by autoreactive T lymphocytes (TL)) - is considered responsible for targeting self-peptides [1, 2].

Consequently, two great extremes of phenotypic presentation can occur: hypothyroidism (in Hashimoto's thyroiditis (HT), also known as autoimmune thyroiditis (AIT) or chronic lymphocytic thyroiditis (CLT)) and hyperthyroidism (in Graves-Basedow disease (GBD)). In iodine-sufficient geographic areas, HT is the main cause of hypothyroidism, with a significant predominance in women [1-3].

The HT prevalence varies according to the geographical region studied and socioeconomic income, being 11.4% (low-middle-income group), 5.6% (upper-middle-income group), and 8.4% (high-income group). By geographic region, the prevalence in Africa was 14.2%, Oceania 11.0%, South America and Europe 8.0%, North America 7.8%, and Asia 5.8% [4].

For its part, GBD represents between 70-80% and around 50% of hyperthyroidism cases worldwide in areas with iodine sufficiency or deficiency, respectively; and is estimated to affect 2-3% of the general population. Similarly (and as with HT) GBD affects women more, by a ratio of 5 - 10 to 1 and is more common in Caucasians as compared to Asians and least common among Africans [5].

Otherwise, the incidence of thyroid cancer (TC) varies according to the geographical area studied, documenting a higher incidence in higher-income countries (Canada, Italy, Korea, Israel, France, Croatia, Austria, and USA), as well as in middle- to upper-middle-income countries (Turkey, Brazil, Costa Rica and China). However, despite these differences, TC mortality rates are very low, and have low variability according to geographic area [6, 7].

In descending order and from the histological point of view, the most frequent TCs are papillary carcinoma (PTC, 90%), follicular carcinoma (FTC, 4%), Hurthle cell carcinoma (2%), medullary carcinoma (MTC, 2%), and anaplastic carcinoma (ATC, 1%) [7-9].

Some studies have evaluated a possible association between AITD and the risk of different types of cancer; for example, HT patients have been found to have an increased risk of myeloproliferative and lymphoproliferative neoplasms, as well as an increased risk of breast, digestive system, lung, and urogenital cancer, and malignant thyroid lymphoma. The above adds to the fact that a co-occurrence (8-37%) between HT and PTC has also been found [10, 11].

Otherwise, in individuals with GBD, a 23% co-occurrence of thyroid nodules has been documented, with a malignancy rate of 2-46% in palpable nodules [12]. Therefore, AITD has been proposed as a risk factor for TC. However, despite the biological plausibility that may explain the association between

Manuscript submitted September 12, 2023, accepted November 24, 2023
Published online December 9, 2023

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doi: https://doi.org/10.14740/wjon1728

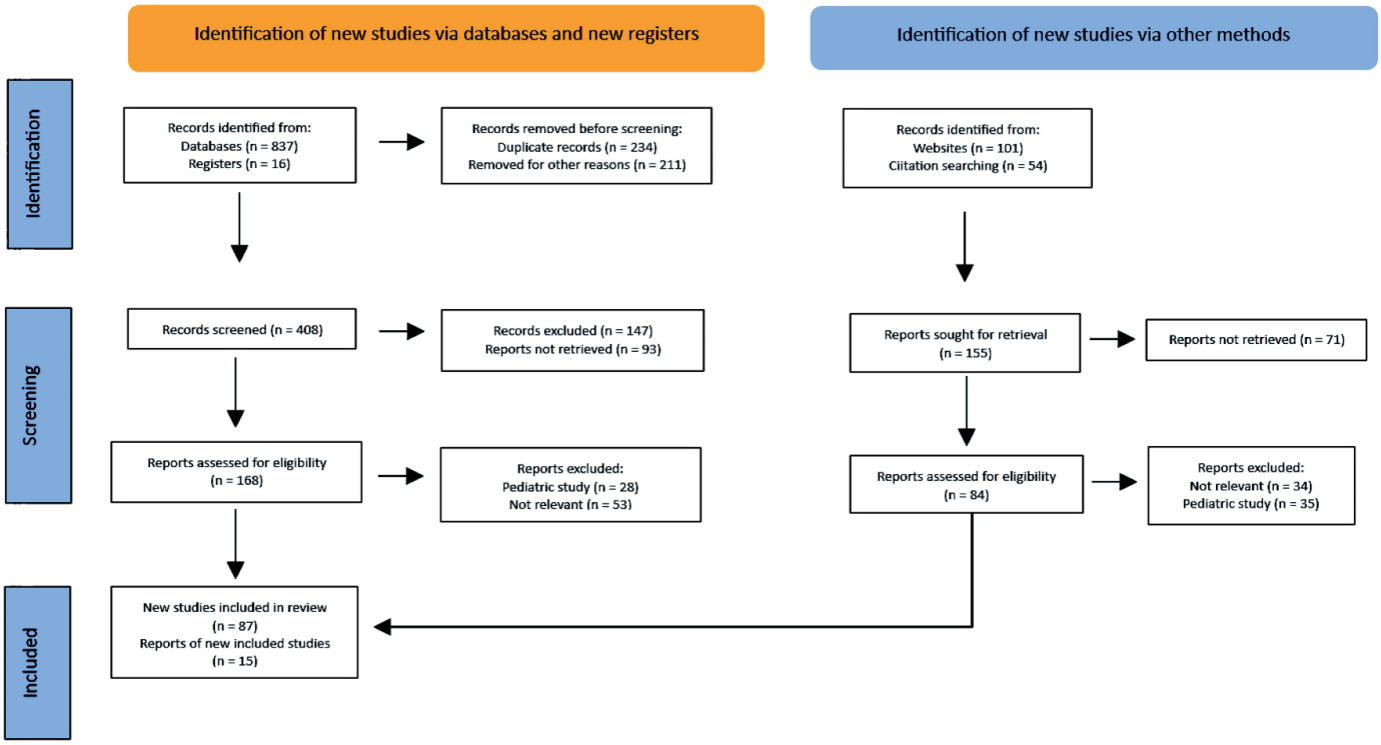

Figure 1. PRISMA flow diagram. Method for the selection of articles. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

AITD and TC, the data from observational studies (in many cases) are discordant.

Materials and Methods (Search Strategy)

This review describes and summarizes the results of the different observational studies evaluating the association between AITD (HT and GBD, as an independent variable) and differentiated thyroid carcinoma (DTC, dependent variable), as well as the possible mechanisms that may explain, at least in part, this association.

The literature in the following databases was rigorously and systematically searched: Scopus, PubMed, PubMed Central, BIOSIS, EMBASE, Web of Science and UpToDate. Articles were selected according to the following keywords: chronic lymphocytic thyroiditis, HT, Graves-Basedow disease, AITD and DTC. Only English-written articles were included (Fig. 1).

Studies Evaluating the Association Between Hyperthyroidism and DTC

Some studies have evaluated the possible association between hyperthyroidism (in different definitions) and DTC. These studies have focused on patients with GBD, toxic multinodular goiter (TMG), toxic nodules, toxic uninodular goiter (TUG), and unspecified toxic nodular goiter (UTNG) (Table 1) [12-20].

In general terms, the results have described the following: 1) The risk of DTC in young men (20 - 39 years) with GBD is particularly high (and the most frequently found DTC in individuals with GBD is papillary microcarcinoma); 2) The evidence of increased risk of DTC is "modest" in individuals with GBD vs. TMG (without differences in risk between GBD and other causes of hyperthyroidism); 3) The risk of TC in GBD (with thyroid nodular component vs. without nodular component) demonstrated "strong" evidence of increased risk of TC in subjects with a thyroid nodular component. Similarly, a higher risk of TC was also found in subjects with a solitary thyroid nodule vs. in those with multiple nodules.

Molecular Mechanisms That May Explain the Association Between GBD and TC

Until a few years ago, the presence of GBD has been considered a protective factor for TC, however, studies have been conflicting and controversial in this regard. While some have found a significantly increased DTC risk in individuals with GBD, the molecular mechanisms explaining this association were unclear [21-23].

A possible mechanism (not fully elucidated yet) is explained by means of thyroid receptor antibody (TRAb), as this autoantibody (stimulator), through thyrotropin (TSH) receptor (TSHR), has been described as being capable of stimulating certain signaling pathways that can induce glandular growth and enhancing tumor invasiveness [22-24].

However, very few studies evaluate the role of TRAbs lev-

Table 1. Risk of DTC According to Different Definitions of Hyperthyroidism (Including Graves-Basedow Disease)

Causes of hyperthyroidism	Measure of association (SIR) and risk of DTC	95% CI
Unspecified toxic nodular goitre	0.46	0.12 - 1.82
	1.17	0.42 - 3.21
	0.09[b]	0.03 - 0.3[b]
	0.65	0.19 - 2.22
Toxic uninodular goitre	0.38	0.08 - 1.91
	2.93	0.34 - 25.15
	5.85	0.6 - 57
	0.74	0.1 - 5.66
	0.65	0.19 - 2.21
	2.71	0.15 - 49.54
	1.26	0.44 - 3.57
	0.23	0.05 - 1.16
	0.62	0.06 - 6.07
	1.3	0.52 - 3.29
Toxic multinodular goitre	0.35	0.06 - 1.91
	1.7	0.4 - 7.2
	0.96	0.12 - 7.55
	1.23	0.21 - 7.04
	0.74	0.28 - 1.95
	1.4	0.15 - 13.44
	1.67	0.62 - 4.51
	3.25	0.44 - 23.9
	0.94	0.1 - 8.56
	1.66	0.69 - 3.97
Toxic nodules	3.94 (overall)[b]	2.57 - 5.77[b]
	4.87 (men)	0.59 - 17.6
	3.88 (women)[b]	2.48 - 5.77[b]
TSH levels below the normal range	2.65 (overall)[b]	1.27 - 5.52[b]
	1.07 (men)	0.25 - 4.62
	3.74 (women)[b]	1.53 - 9.19[b]
Graves-Basedow disease[a]	1.0	0.68 - 1.46
Graves-Basedow disease[a]	0.89	0.63 - 1.26
Graves-Basedow disease[a]	5.3[b]	2.4 - 11.6[b]
Graves-Basedow disease	2.67	1.00 - 7.18
Graves-Basedow disease	3.77 (overall)[b]	2.94 - 4.75[b]
	5.84 (men)[b]	2.52 - 11.5[b]
	3.61 (women)[b]	2.77 - 4.61[b]
Graves-Basedow disease	HR: 2.98 (men)[b]	1.08 - 8.19[b]
	HR: 1.60 (women)[b]	1.11 - 2.31[b]
Hyperthyroidism (global)	HR: 6.80[b]	3.584 - 12.91[b]

[a]Meta-analysis. [b]Studies that found significant results. CI: confidence interval; DTC: differentiated thyroid carcinoma; HR: hazard ratio; SIR: standardized incidence ratio.

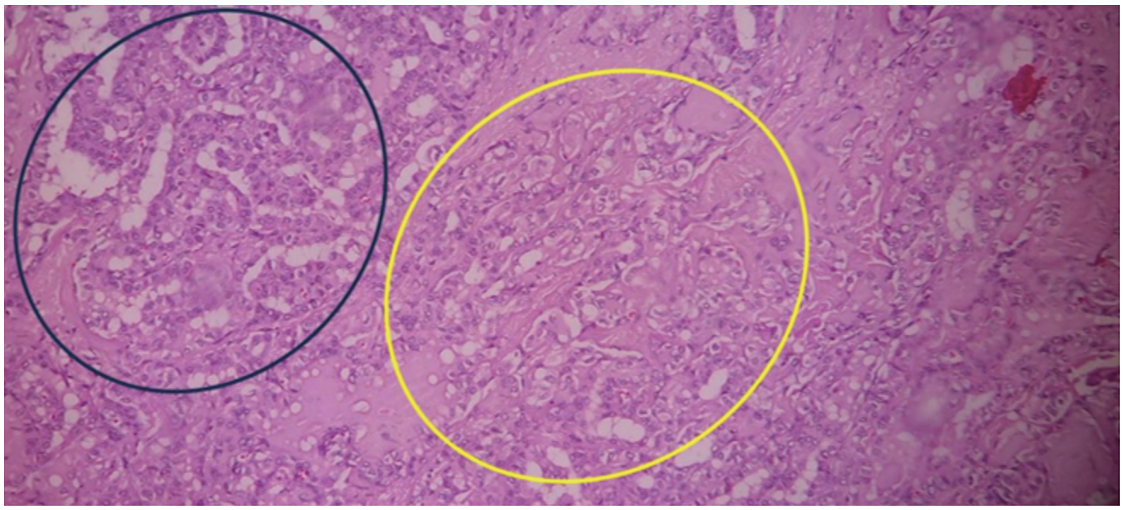

Figure 2. Histopathological findings in a total thyroidectomy specimen from an individual with GBD and PTC. On the upper left side (blue circle), thyroid follicles of different sizes are observed, lined by predominantly cuboidal follicular cells, with little colloid inside, pale pink in color and slightly scalloped (characteristic of GBD). In the central part (yellow circle), lighter thyroid cells are observed, with ground glass nuclei, which form microfollicles or are loose, invading the stroma, with mild fibrosis partially delimiting the lesion (corresponding to PTC); there is little interstitial lymphocytic infiltrate which predominates on the right side of the image (× 40, stained with hematoxylin and eosin). GBD: Graves-Basedow disease; PTC: papillary thyroid carcinoma.

els as a predictor of DTC. In fact, no direct relationship between TRAbs positivity and the presence of DTC has been found in observational studies; while others had documented that low titers of TRAbs are associated with a higher probability of DTC; furthermore, high titers of TRAbs have also been reported to be associated with a low risk of malignancy [22, 23-27].

Additionally, a possible role of T4 and T3 (as tumor promoters) has also been proposed, as they may be involved in stimulating angiogenesis (through αvβ3) mediated by phosphatidylinositol-3-kinase and MAPK [28, 29].

In this sense, some studies in rodents and humans have found an increased risk of prostate, breast, colon, and lung cancer in the presence of elevated T4 and T3, and although the role of this elevation on the risk of TC is not well established, angiogenesis clearly plays a major role in its development and progression [30].

In fact, tumor neovascularization originates after the imbalance between numerous proangiogenic and antiangiogenic factors; however, tumors can change their phenotype to a predominantly angiogenic one [31, 32].

Among the multiple signaling factors and receptors related to the regulation of angiogenesis, the family of vascular endothelial growth factor (VEGF) and their receptors stand out, which seem to be the main proangiogenic determinants in different types of cancer (including DTC); additionally, VEGF upregulation in human thyroid carcinoma is linked to malignancy and a poor prognosis [33].

Taking into account a highly vascularized thyroid gland, a predominance of the angiogenic phenotype could potentially favor the formation of numerous new blood vessels that can promote the initiation and progression (metastasis) of DTC. Moreover, the relationship between inflammation and cancer is widely accepted, some described mechanisms that can mediate this association are the greater induction of genomic instability, added to some alterations in epigenetic mechanisms with inappropriate gene expression, which would stimulate cell proliferation, greater resistance to apoptosis, and increased tumor neovascularization, among others [34].

Thus, an infiltrate with inflammatory characteristics with macrophages and dendritic cells has also been documented in PTC, with abundant mast cell infiltration, and even a tumor phenotype with greater invasive capacity has been associated to the extent that the mast cell infiltration is of greater magnitude [35, 36].

Similarly, in GBD, the histopathological characteristics demonstrate a mixed inflammatory lymphocytic infiltrate within the stroma surrounding the follicles, with increased number of dendritic cells and mast cell degranulation [37, 38].

In its florid form, in the GBD, the gland develops a diffusely increased cellularity with epithelial hyperplasia, forming papillary invaginations into the follicular lumen. These findings sometimes make histopathologic differentiation between GBD and PTC difficult; however, the papillae of GBD have fibrovascular cores of variable thickness but are often delicate, displaying a branching pattern. These papillary structures must be distinguished from the papillae of PTC [38-42] (Fig. 2).

In summary, these findings could suggest that the inflammatory phenomenon present in GBD may induce a greater risk of PTC, as chronic inflammation sustained over time is a factor contributing to cell proliferation and transformation, with a potential effect on the induction of tumorigenesis and tumor progression (Fig. 3).

Studies Evaluating the Association Between HT and DTC

The possible association between HT and DTC has also been

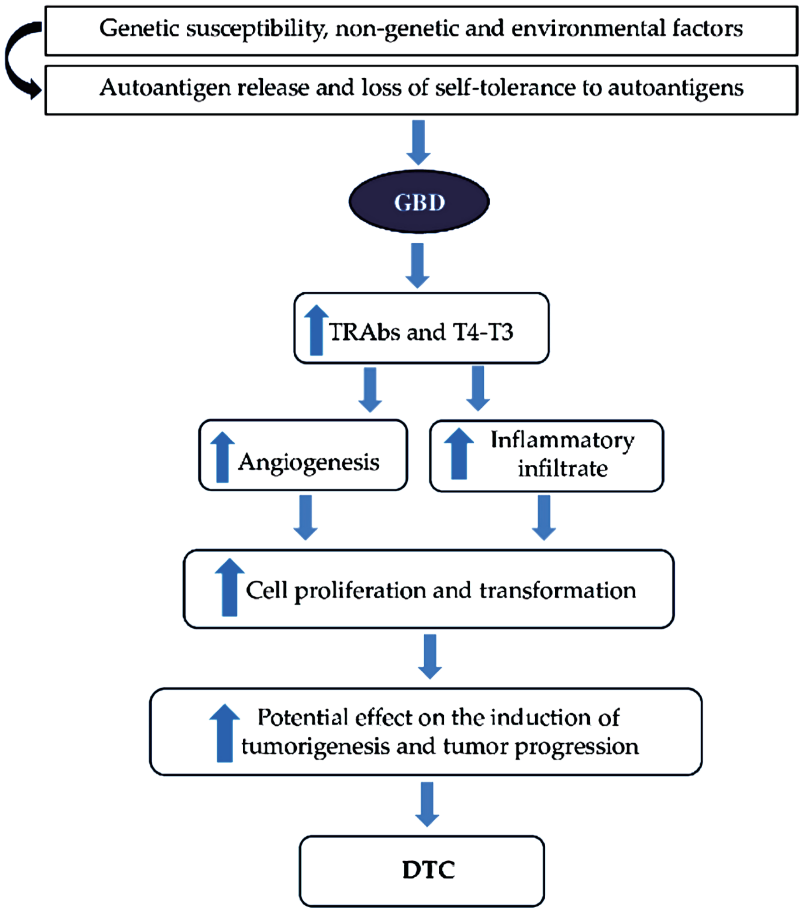

Figure 3. Molecular mechanisms most frequently associated between GBD and DTC. GBD: Graves-Basedow disease; DTC: differentiated thyroid carcinoma; TRAb: thyroid receptor antibody.

evaluated in multiple studies. Most of them have found that HT significantly increases the risk of DTC (especially PTC); however, other studies have not found this association (Table 2) [10, 43-63].

In general, these studies have described the following: 1) The findings based on thyroid cytology samples show a prevalence of PTC of 1.2%, reaching 27.5% in thyroidectomy samples; 2) The risk of documenting a PTC increases in surgical specimens in which changes consistent with HT are observed; 3) Most cases of DTC (in patients with HT) correspond to PTC (microcarcinoma); 4) PTC in individuals with HT is more frequent in women than in men; 5) The possible association between HT and FTC is weak and less established; 6) A histological subtype of oncocytic PTC (Warthin-type variant) is associated with HT; 7) A higher DTC frequency has been proven in individuals with HT and thyroid nodules (together with an elevated TSH value).

Probable Molecular Mechanisms Associated Between HT and DTC

Several mechanisms have been linked between HT and DTC, the first being (also proposed for GBD) the presence of inflammation. Thus, the inflammatory response is capable of inducing a favorable environment for malignant transformation, as cytokines and some growth factors directed towards stromal cells can malignantly transform epithelial cells [64]. In an inflammatory setting, DNA methyltransferase 1 is affected by ROS and other proinflammatory factors, consequently increasing the DNA methylation of tumor suppressor genes and microRNAs (increasing the risk of cancer) [64-66].

The direct effect of TSH as a thyroid growth factor explains the second mechanism; thus, TSH plays an important role in regulating thyroid function, in addition to increasing the number, size, and secretory activity of the gland, as well as increasing thyroid blood flow [67-69].

Classical TSH actions are mainly mediated through the Gαs-adenylyl cyclase-protein kinase A-cyclic adenosine monophosphate pathway, which is associated with T4 and T3 production and thyrocyte proliferation. In this sense, several meta-analyses had associated higher serum TSH concentration with higher odds of TC [69-71].

Therefore, a constant tissue stimulation by TSH is capable of producing follicular epithelial hyperplasia; consequently, its elevation could be considered a TC promoter.

Table 2. Risk of DTC in Patients With HT

Causes of hypothyroidism	Measures of association (SIR) and risk of DTC	95% CI
Studies in patients with Hashimoto's thyroiditis	1.93[b]	1.6 - 2.34[b]
	2.24[b]	1.22 - 4.11[b]
	4.16[b]	2.87 - 6.04[b]
	3.02[b]	1.94 - 4.69[b]
	1.64[b]	1.38 - 1.95[b]
	1.34	0.96 - 1.85
	1.56	0.68 - 3.58
	1.80[b]	1.53 - 2.11[b]
	0.99	0.65 - 1.50
	1.57[b]	1.38 - 1.78[b]
	2.33	0.92 - 5.92
	1.39[b]	1.26 - 1.52[b]
	2.52	0.36 - 17.81
	1.58[b]	1.45 - 1.71[b]
	0.40	0.09 - 1.70
	1.44	0.97 - 2.13
	1.16	0.74 - 1.82
	11.8[b]	4.24 - 33.1[b]
	2.76[a, b]	1.95 - 3.92[b]
	1.49[a, b]	1.42 - 1.57[b]
	1.65 (for PTC)[b] and 0.73 (for FTC)[a]	1.04 - 2.61[b] and 0.41 - 1.27 (respectively)
	1.83[a, b] (for CLT (+) vs. CLT (-))	1.51 - 2.21[b]

[a]Meta-analysis. [b]Studies that found significant results. CI: confidence interval; CLT: chronic lymphocytic thyroiditis; DTC: differentiated thyroid carcinoma; FTC: follicular thyroid carcinoma; PTC: papillary thyroid carcinoma; SIR: standardized incidence ratio; HT: Hashimoto's thyroiditis.

The third mechanism refers to the increased expression of certain oncogenes, for example, *RET*/PTC gene rearrangement. In this aspect, the inflammatory process present in HT may favor the appearance of rearrangement; additionally, the greater predisposition of thyrocytes to *RET* recombination could be explained by the arrangement of chromatin in the interphase nuclei [72].

Hence, an inflammatory phenomenon in which a scenario with an increased synthesis of free radicals, greater secretion of cytokines, and increased cell proliferation (among others) can promote the appearance of rearrangement in the cell thyroid follicle predisposed to it by alterations in chromatin conformation. An induced state in which the thyrocytes are in a modified environment (loop-mediated with autocrine and paracrine patterns) in the presence of chemokines and cytokines could promote autonomous thyrocyte proliferation [73-75].

On the other hand, the members of the p53 family include p53, p63, and p73, and mutations in *p63* have been proposed to have a role in the interface between HT and PTC; in fact, a high expression of p63 has been found in both. These results have increased the debate regarding the possibility of p63 having a pathobiological link; however, these findings need to be clarified and reproduced [76, 77].

Otherwise, *BRAF* mutation (BRAFV600E) is the most frequently observed genetic abnormality in PTC, which is capable of inducing excessive proliferation and differentiation of tumor cells in its initial stages (and is also involved in tumorigenesis and in the conversion to a more aggressive undifferentiated phenotype) [78-80].

Thus, individuals in whom PTC coexists with HT have been observed to be at lower risk of extrathyroidal extension of the PTC and additionally, it has been suggested that HT antagonizes PTC progression in the presence of *BRAF*V600E. Therefore, the *BRAF*V600E mutation is less frequent in individuals in whom HT coexists with PTC, probably because HT and the *BRAF*V600E mutation operate independently in the formation and progression of PTC [81-76].

Finally, some altered cell-signaling pathways with loss of cell cycle control mechanisms have been implicated in neoplastic transformation. For instance, phosphatidylinositol 3-kinase (PI3K), which plays a key role in the balance between cell survival and apoptosis, is also important in the inflammatory response, as it can activate chemokine receptors and leukocyte migration [83, 84].

This may be the reason increased PI3K activation has been identified in various neoplasms, including TC (activation of PI3K, in turn, phosphorylates Akt, which acts on downstream

Table 3. Summary of Genetic Alterations in HT and TC

Genetic alterations	Outcomes in AITD and DTC
RET/PTC rearrangements	In experimental models in mice, designed to express RET/PTC, they more frequently develop thyroid hyperplasia, solid tumor variants of PTC and metastatic cancer and findings of chronic thyroiditis. In individuals who were exposed to radiation in the Chernobyl disaster and who had a diagnosis of HT, they more frequently developed RET/PTC-induced PTC. Between 3-60% of patients with PTC and around 90% of individuals with HT have this genetic alteration.
p63 protein	It is commonly expressed in PTC and in HT.
*BRAF*V600E	*BRAF*V600E mutation is less frequent in individuals where HT coexists with PTC.
PI3K/Akt pathway	Elevated expression of PI3K/Akt in individuals with HT and DTC.

HT: Hashimoto's thyroiditis; TC: thyroid cancer; AITD: autoimmune thyroid disease; DTC: differentiated thyroid carcinoma; PTC: papillary thyroid carcinoma.

proteins to suppress proapoptotic signals contributing to tumorigenesis) [84, 85].

An increase in the expression of PI3K/Akt in individuals with HT and DTC has been found in certain some studies, suggesting a possible role in the molecular mechanism for thyroid carcinogenesis [86, 88].

The most frequently associated genetic alterations between HT and DTC are summarized in Table 3 [73-88].

In summary, in HT (in the presence of constant and sustained stimulation of TSH), together with the inflammatory process and the expression of oncogenes have shown to be the most "consistent" mechanisms, which can potentially induce a phenomenon of tumorigenesis and tumor progression, increasing the risk of DTC (Figs. 4, 5).

Discussion

The association between AITD and DTC is controversial, and although multiple mechanisms have been described that

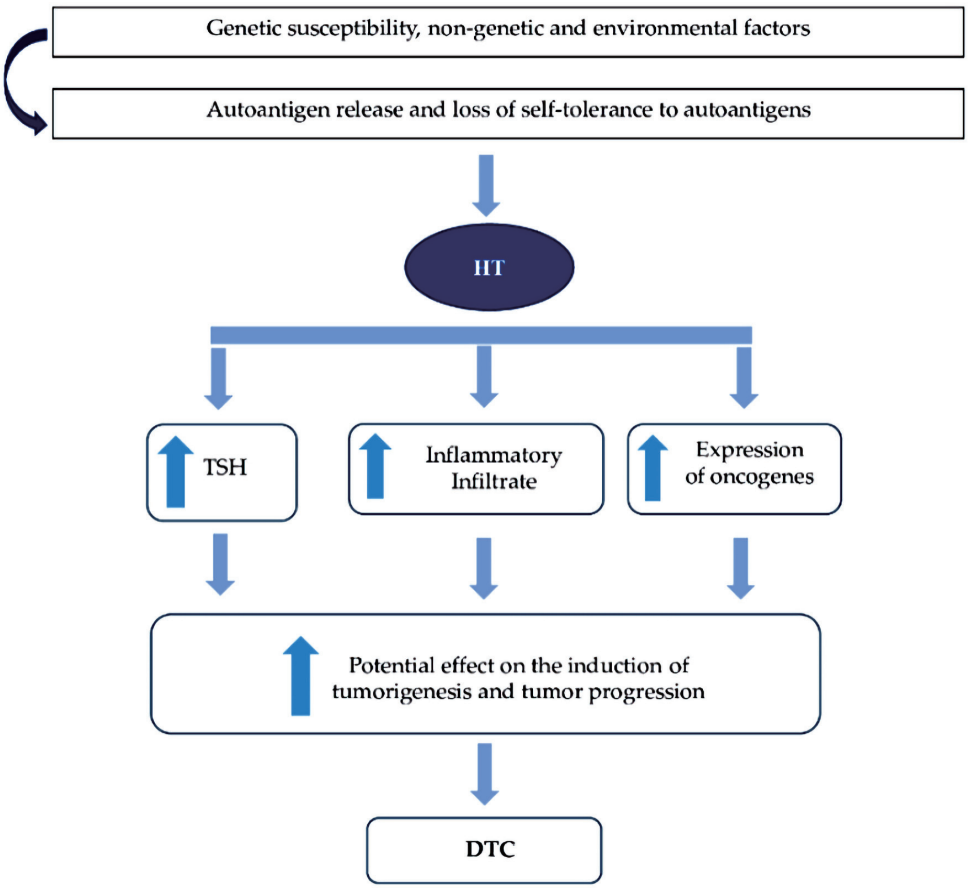

Figure 4. Molecular mechanisms most frequently associated between HT and DTC. HT: Hashimoto's thyroiditis; DTC: differentiated thyroid carcinoma; TSH: thyrotropin.

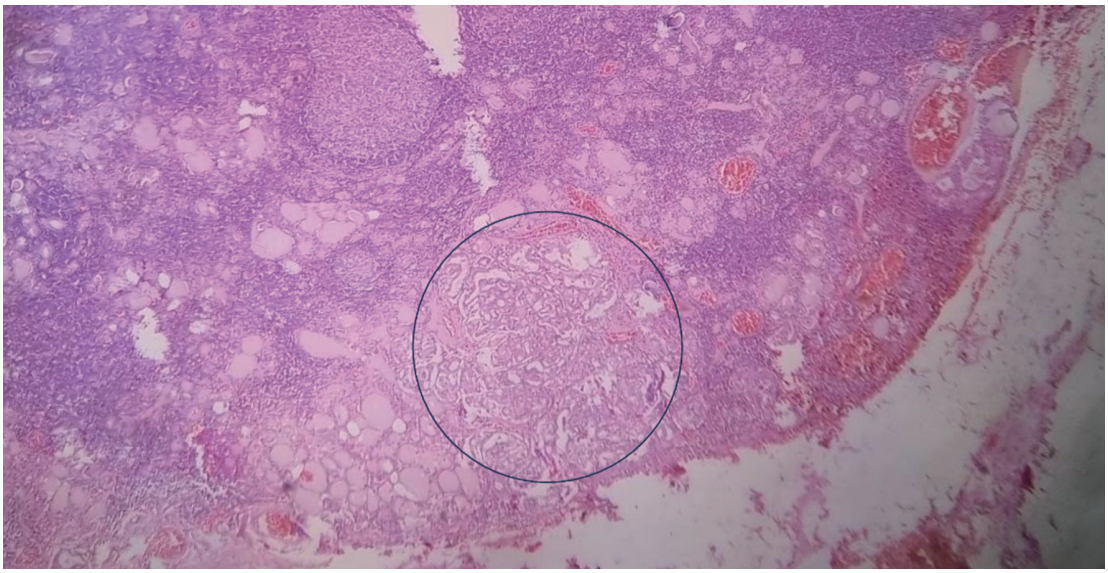

Figure 5. Histopathological findings in a total thyroidectomy specimen from an individual with HT and PTC. Histopathological section of total thyroidectomy in a patient with HT and PTC, showing an intense lymphocytic infiltrate that forms lymphoid follicles of different sizes. In the midst of this infiltrate some thyroid follicles (predominantly small) with colloid inside have been trapped. In the blue circle, neoplastic thyroid cells are observed, with a ground-glass-shaped nucleus, with scant cytoplasm, arranged in a disorganized pattern and without a capsule, corresponding to PTC (× 10, stained with hematoxylin and eosin). HT: Hashimoto's thyroiditis; PTC: papillary thyroid carcinoma.

could explain this association, uncertainty and contradictory results remain. This can be explained by multiple aspects, for instance, the results of the different studies may vary according to the way in which the disease was defined (from the clinical, biochemical, and/or imaging point of view) and if confirmed by cytological (with or without subsequent surgery) or histopathological analysis [89-91].

Additional factors could be the previous treatment received by the patients (antithyroid drugs or I-131, in GBD), use of levothyroxine (in HT), the severity of AITD (since the greater the thyroid autoimmune activity, the greater the hyperplasia, and therefore, the greater the probability of atypia and potential malignancy), the history of previous exposure to radiation and the hereditary component (especially for the development of PTC) and other environmental determinants [90-92].

Moreover, the differences in the way in which AITD is diagnosed by tissue samples (thyroid cytology or histopathology) are very remarkable (and may bias the possible association between AITD and TC); in fact, the studies that define the diagnosis of AITD based on thyroid cytology do not show correlation between them, while by histopathology, the said correlation is significantly higher [92, 93].

The above is accompanied by the fact that the frequency of PTC in individuals evaluated by means of thyroid cytology is 1.2%, while it is 27.5% by means of histopathology. In accordance with it, a selection bias is clearly denoted in the choice of cases that undergo thyroidectomy in the different studies. It should also be considered (and as previously noted) that the histopathological characteristics of GBD may overlap with that of PTC, therefore, the risk of misclassification at the time of pathological diagnosis cannot be ruled out [93].

Otherwise, the pool of results of the published studies is difficult to interpret, given the high heterogeneity, retrospective temporality, observational design (predominantly), small sample size, and single-center experiences, among others [94]. Additionally, many of them denote the absence of disease definition criteria, sample size calculation, and surgical indication of patients.

All of the above is compounded by the fact that a significant number of studies did not adjust for some confounding factors that may affect the magnitude of the association (body mass index (BMI), smoking, iodine supplementation, radiation exposure, sociodemographic index, family history of cancer, time elapsed between detection of thyroid functional alteration and pharmacological intervention, and/or surgical and other associated comorbidities) [94-96].

These aspects have made it difficult to establish "causality" in the continuum of the pathogenesis between AITD and DTC; furthermore, the relationship could also be argued to be non-causal, and that what really happens is the coexistence between two independent and highly prevalent entities, with enormous ease of early identification through laboratory tests, thyroid ultrasound, and thyroid cytology [97-99].

Accordingly, it must be considered that the over-screening of thyroid functional evaluation (or imaging evaluation) and for TC can be potential confounders when evaluating the possible association between AITD and DTC (a phenomenon of overestimation of the association, with overdiagnosis and, potentially, overtreatment) [97-101].

In summary, different observational studies, meta-analyses, and systematic reviews have found an association between thyroid functional abnormalities, thyroid autoimmunity, and DTC; however, the characteristics and designs of the studies evaluated do not yet allow a causal relationship between the

two entities to be established.

On the other hand, the biological plausibility between AITD and DTC has been evaluated in studies in humans and in animals, finding in general that the inflammatory phenomenon seems to be an inherent and common finding in both GBD and HT. However, in mouse models of AIT, the inflammatory infiltrate in the thyroid has been found to possibly have a tumor "controlling" effect (in experimental iodine-exacerbated thyroiditis), in contrast to those who synchronously developed thyroiditis and PTC, suggesting that the tumor phenotype differs depending on the moment in which AIT develops [102, 103].

These findings may explain (at least in part) the discrepancy between observational studies trying to find an association between HT and DTC in humans. Similarly, the true role of TRAbs and TSH levels on DTC risk has yet to be established, but to date, the results have been conflicting, and the available evidence is scant (especially with TRAbs).

The effect of cytokines on the establishment of the inflammatory infiltrate and its potential impact on the development of DTC should also be explored, as well as the expression of other oncogenes and mutations other than *RET*/PTC and *BRAF*V600E, respectively.

Besides, certain genetic factors should also be explored, for example, the influence and interaction between susceptibility genes for both entities, epigenetic factors, and the role of non-genetic factors such as infectious agents (viruses, bacteria, parasites, and intestinal microbiota, among others); nutritional aspects (obesity, as well as consumption of iodine, iron, vitamin D, selenium, gluten, and other micronutrients), smoking, alcohol intake and, finally, the effect of psychological stress and other thyroid endocrine disruptors [102-106].

As a final reflection, and taking into account that the ultrasound-guided fine-needle aspiration (FNA) is the method of choice for the initial approach to thyroid nodules (with subsequent cytological evaluation using the Bethesda System for Reporting Thyroid Cytopathology (BSRTC)), clearly accepting the low potential for malignancy in Bethesda II category (and high potential in categories V and VI), with well-established treatment and follow-up guidelines [107-110].

However, the malignancy risk categories (III and IV) have been classified as "indeterminate" and constitute a real clinical challenge, especially in surgical decision making, since the potential for malignancy in these nodules is variable, and management depends on the presence of other risk factors (family history of TC, high TSH levels, ultrasonographic characteristics (presence of calcifications, shape, echogenicity, vascularity, regular borders, size, among others)) [111-113].

In these "indeterminate" categories, management usually consists of strict follow-up without intervention, performing periodic cytological controls or in some cases, surgical management (lobectomy/thyroidectomy) [114].

However, the available evidence about the malignant potential of thyroid nodules in this category is widely variable and has been modified according to the reclassifications of some thyroid neoplasms, (which may have implications when classifying the risk of malignancy (ROM)), because only a minority of Bethesda III - IV cases undergo excision, estimating the ROM based on histological follow-up alone overestimates the risk (due to selection bias) [115-118].

This is demonstrated in studies carried out in different parts of the world where the malignancy potential of Bethesda III nodules varies from 15.7% to 54.6% (and that of Bethesda IV nodules from 16.8% to 72.4%), which contrasts with the generalized concept of that the malignancy rate in Bethesda III and IV nodules is 5-15% and 15-30%, respectively [119-122].

Therefore, in those individuals with AITD in whom the presence of thyroid nodules has been documented (and who have been evaluated with FNA) there may evidently be a "misclassification" phenomenon by interpreting a significant proportion of said cytology as "malignant" when they really are not [123, 124].

These findings should broaden the horizon in the search for other strategies that allow better classification and stratification of this group of patients, for example, by means of "molecular markers" or also by complementing thyroid ultrasound with elastography [125-128].

In this review, some strengths can be identified, such as the fact that AITD has been differentiated into its two extremes of phenotypic presentation (GBD and HT) in order to separately analyze the available information on the possible association between both entities and DTC. Finally, some limitations can be identified; for example, the potential effect that thyroid autoimmunity may have on the risk of recurrence of the DTC and on mortality was not taken into account; moreover, the association between AITD and other types of TC (MTC and ATC, among others) was not evaluated either.

Conclusions

The pathophysiological link between AITD and DTC is intriguing. Observational studies have found a possible association between AITD and the risk of DTC (especially for PTC); however, the design of these studies does not allow the establishment of causality. On the other hand, the biological plausibility between GBD, HT, and TC has been described; in this sense, the common denominator (biological and molecular) is inflammation; however, at the interface between thyroid autoimmunity and DTC, the interaction between genetic, epigenetic, and environmental factors, among others, is necessary.

Acknowledgments

None to declare.

Financial Disclosure

The author declares that he does not have a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

Conflict of Interest

None to declare.

Author Contributions

The author designed the search strategy, the synthesis of the information and wrote the final manuscript.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

Abbreviations

AIT: autoimmune thyroiditis; AITD: autoimmune thyroid disease; ATC: anaplastic carcinoma; BSRTC: Bethesda System for Reporting Thyroid Cytopathology; CLT: chronic lymphocytic thyroiditis; DTC: differentiated thyroid carcinoma; FNA: fine-needle aspiration; FTC: follicular carcinoma; GBD: Graves-Basedow disease; HT: Hashimoto's thyroiditis; MTC: medullary carcinoma; PI3K: phosphatidylinositol 3-kinase; PTC: papillary carcinoma; TC: thyroid cancer; TL: T lymphocytes; TMG: toxic multinodular goiter; TSH: thyrotropin; TUG: toxic uninodular goiter; UTNG: unspecified toxic nodular goiter; VEGF: vascular endothelial growth factor

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