A 50-year Revisit of the Initiation and Associations of Hashimoto's Disease: Might Findings Conform to a Concept of Multifactorial Physiopathologic Transitions?

Tagoe, *et al* have comprehensively reviewed rheumatic disorders associated with autoimmune thyroid disease (AITD) in *The Journal*¹. The spectrum of AITD was defined as including Graves' disease and chronic (nonfocal) lymphocytic thyroiditis, which incorporates Hashimoto's disease (HD)². The review¹ rekindled long-past memories, and this commentary offers a personal historical perspective on some complex research questions and challenges persisting in HD and its associated conditions. Such issues had been posed some 2 generations ago^{2,3,4,5,6,7,8,9,10} (Table 1), but have not yet been adequately resolved.

Basic questions remain in interpreting the root of AITD. First, is a primary immunological dysregulation from genetic predisposition or environmentally related processes the cause of the observed antibodies and thyroid pathology as well as associated hyperthyroidism or hypothyroidism? Alternatively, is a primary thyroid cellular dysfunction from as-yet undiscovered physiological insufficiencies the cause of increased or modified cellular antigenic release, leading to secondary autoimmune serological and tissue reactions? Likely, the primary and secondary biological mechanisms are integrated in a complex way and are not clearly separated from each other. Nevertheless, evidence for the alternative initiation pathways can be investigated by their sequences of events, like genetic predisposition, initiation following triggering mechanisms, or whether particular early alterations (mild thyroid dysfunction vs minor elevated antibodies) are necessary in the beginning process or must progress for the disease to become manifest.

In the course of disease development, function may become disturbed before evidence of serological abnormalities or tissue pathological changes are manifest. A physiopathologic interpretation of disease focuses upon altered body function as related to the course of pathological alterations and mechanisms. In multifactorial diseases or when etiology is unknown, the predisposing or triggering mechanisms causing early dysfunctions are often obscure.

An organ like the thyroid, which begins to show physiological hyper- or hypofunction, may also incur alterations in its molecular pathways and cellular oxidative stress levels, if not microinjury. In turn, increased or modified cellular antigenic release may contribute to an amplified or abnormal autoimmune reactivity. Despite considerable research in HD over the past 5 decades, such questions of initiating or predisposing factors and sequential pathways of disease development and progression remain unanswered.

This commentary attempts to modernize perspectives from clinical-epidemiological investigations conducted 5 decades ago, which had remained dormant, until reawakened by the recent review¹. New research offers support for a multifactorial physiopathogenic concept of HD. Such a broadened framework includes the basis for documented ameliorating effects of thyroxine therapy, and enables questions that promise to increase understanding of host predisposing factors and associated medical disorders¹.

A primary question remains: is HD a primary thyroid dysfunction⁵ and does epithelial basement membrane injury^{4,9} precede the initiation of autoimmunity? The more popular alternative question is, does thyroid autoimmunity primarily cause chronic thyroiditis^{6,7,11}? A critical review concluded, "The underlying mechanisms responsible for initiating thyroid autoimmunity and promoting the progression of the disease remain unknown"¹². Personal clinical-epidemiological research from 1961 to 1967 included doctoral thesis studies of 539 cases of histologically diagnosed HD indexed in Baltimore city hospitals over the period 1948 to 1960^{13,14,15,16,17,18}, results of which conditioned a physiopathologic concept.

Hypothesis raised: Could thyroxine treatment diminish risk of autoimmune thyroiditis?

In longitudinal studies of thyroid autoimmunity^{19,20}, either

See Rheumatic manifestations of AITD, *J Rheumatol* 2012;39:1125

Table 1. The 1912 report of Hakaru Hashimoto (1881–1934) and mid-20th century articles on this disease*.

Author	Findings in Hashimoto's Disease (HD) and Interpretations
Hashimoto, 1912 ²	Lymphomatous firm diffuse goiters were found incidentally in 4 middle-aged women, their cause stated as . . . “probable that a chronic inflammatory process may have occurred” . . .
McConahey, 1954 ³	Thyroid extract therapy diminished the size of goiters in HD, but not adenomatous goiters.
Sommers and Meissner, 1954 ⁴	Basement membrane changes found in thyroid follicle epithelium were proposed to be the primary lesions in HD.
Skillern, 1956 ⁵	HD proposed to be a primary thyroid failure with compensatory thyroid enlargement.
Roitt, 1956 ⁶	Antithyroid precipitating antibodies were found in 6 patients with HD, but in none of 13 other thyroid disease patients, initiating the autoimmune theory of causation.
Doniach and Roitt, 1957 ⁷	Precipitating antibodies to purified thyroglobulin were found in sera of 25 of 30 HD patients, but in none of 105 thyrotoxic or 103 nontoxic nodular goiter patients.
Smart and Owen, 1961 ⁸	Confirmed that thyroid replacement therapy of HD patients for more than a year was associated with significantly lower serum antithyroid antibody titers.
Stuart and Allan, 1958 ⁹	Demonstrated a correlation between the extent of basement membrane damage and antithyroid antibody titers.
Becker, 1963 ¹⁰	A large patient sample report on the connective tissue disease and symptoms associated with Hashimoto's thyroiditis.

* Prominent reports on HD, before the author's doctoral studies and publications on this topic.

elevated serum thyroid-stimulating hormone (TSH) levels alone or positive antithyroid antibodies alone predicted subsequent development of hypothyroidism. Further, combined elevations of TSH and antibody levels were better predictors of hypothyroidism than each individual factor alone for both women and men²⁰. The hypothesis was raised, could prophylactic thyroxine treatment diminish risk of clinical autoimmune thyroiditis¹⁹?

Effects of L-thyroxine therapy on goiter size, serum TSH, and antithyroid antibody levels in HD

Since early studies in the 1950s (Table 1), a generation or longer elapsed before additional research confirmed that thyroxine treatment was associated with reduced thyroid size^{21,22} and decreased antithyroid antibody levels²¹ in either adult²¹ or juvenile²² patients with HD. A longitudinal study of goitrous HD and idiopathic myxedema²³ also found that L-thyroxine therapy for 2 to 4 years reduced goiter size ($p < 0.050$) as well as antibody levels ($p < 0.001$) in HD, in both hypothyroid HD and idiopathic myxedema, but not in patients with euthyroid HD.

A 1-year controlled study of thyroxine therapy in both euthyroid and hypothyroid HD patients found that thyroid antibody levels decreased in both subject groups²⁴. The thyroxine effects on thyroid function and its status were interpreted as having modulated autoimmunity expression in HD^{23,24}. The prophylactic effect of levothyroxine therapy in euthyroid HD patients was tested in a controlled 1-year study of 10 treated versus 11 untreated patients²⁵. Only the treated group had significantly ($p < 0.050$) decreased

thyroid peroxidase (microsomal) antibody levels²⁵. Fine-needle aspiration biopsy revealed significantly ($p < 0.050$) decreased percentages of thyroid-derived B lymphocytes only in the treated group²⁵. A subsequent longterm followup report of HD patients treated with levothyroxine and a review of such literature found that the mean antithyroid peroxidase levels had declined 45% after 1 year and 70% after 5 years of therapy²⁶.

Population prevalences of antithyroid antibodies

Positive thyroid peroxidase and thyroglobulin antibody concentrations were reported in a representative US population sample of 16,533 people aged 12 years or older without evident thyroid disease, goiter, or thyroid medication usage²⁷. In persons aged 60 years or older, positive concentrations of these antibodies were found in over 20% of females and over 10% of males²⁷. Notably, antithyroid peroxidase was significantly associated with chemical hypo- or hyperthyroidism, but not antithyroglobulin²⁷. Prevalences of positive antibodies increased continuously with age and were higher in whites than blacks²⁷. The age, sex, and race patterns of thyroid antibodies reported in this national population study²⁷ were fully complementary to the prevalences of HD personally found in the early community-wide hospital-based^{13,16} and autopsy¹⁵ studies. The question may be raised whether the serum thyroid antibodies detected are natural polyclonal immunoglobulins or pathogenic oligoclonal antibodies capable of initiating autoimmune thyroiditis²⁸.

Large twin cohorts offer promise to evaluate genetic susceptibility and early stages of HD

In a Danish twin registry study²⁹ of 38 healthy twin siblings of twins with AITD, multiple antithyroid antibodies were found to be more frequently concordant ($p = 0.006$) in 8 (53%) of 15 monozygotic (MZ) versus 2 (9%) of 23 dizygotic (DZ) subjects. Among a total of 1378 healthy Danish twins³⁰, antithyroid antibodies were found in 98 (7.1%) subjects, more frequently among females (15.3%) than males (6.8%). Greater age ($p = 0.010$), female sex ($p < 0.001$), higher serum TSH ($p = 0.011$), and lower free T3 ($p = 0.001$) were highly correlated with antibody positivity³⁰. Proband-wise concordance of either thyroid peroxidase or thyroglobulin antibodies within twin-pair zygosity groups was nonsignificantly ($p = 0.221$) greater in 7 (29.2%) of 24 MZ than in 3 (8.3%) of 36 DZ twin pairs³⁰. Thus, a genetic influence on the presence of thyroid antibodies was demonstrated. However, such immunogenetic variation might not be equivalent to the variation of heredity risk in developing AITD³⁰, raising the importance of investigating other host¹³ and environmental^{12,31} factors. Prospective followup of healthy twins and family members in national registers promises to identify susceptibility genes³² and the sequence of early-stage alterations in antibody or thyroid metabolic status.

Personal studies of HD

The accumulated literature on HD is vast. One of our early reports¹⁸ was the first reference in a detailed review of disease associations in AITD³³, used to cite their text statement, "The many potential problems that beset studies of disease associations were clearly described over 30 years ago¹:" Space limitations do not permit a review of the numerous potential design faults in association studies^{13,16,17,18}, particularly Berkson's bias³⁴, which could apply to the large number of putative associations with HD^{1,10,33,35}. Our early detailed clinical and pathological study of 74 autopsied cases of HD (including diffuse chronic thyroiditis) failed to show a higher overall association with additional autoimmune disorders than a carefully matched set of postmortem patients¹⁷. Further, no overall excess of autoimmune disorders was found in 170 clinically detected and histologically confirmed cases of HD compared to 340 matched control female patients at Johns Hopkins Hospital, from 1948 to 1963¹⁸. However, the possibility of a previously reported excess of rheumatoid arthritis (RA) in HD¹⁰ was recognized and not excluded.

A 2006 systematic review³⁶ of autoimmune (Hashimoto) thyroiditis co-occurring with RA in individuals and within family members indicated no consistent trend for individuals to have both associated diseases, in 4 controlled studies. No family study in which the index case had HD satisfied eligibility criteria to analyze the comorbidity of autoimmune diseases within families³⁶. However, a 2009

report³⁷ based on the Swedish national multigeneration register database indicated standardized incidence ratios (SIR) of RA in a family member, when the proband's disease was Hashimoto thyroiditis/hypothyroidism. The SIR of RA was modestly elevated in 73 observed parents, 1.54 (95% CI 1.21–1.94), but was not quite significant in 23 observed siblings, 1.71 (95% CI 0.76–3.62).

Considerations of priority issues for future research directions in HD

1. Immunological effects of antigen/ligand escape from degeneration or discontinuities of cellular/tissue barriers, like the follicular epithelial basement membrane^{4,9,13,16}.
2. Role of thyroid cellular/molecular antigen-driven stimulation in the immune response^{11,12,28}.
3. Evidence of altered autogenous antigen/epitope or foreign antigen stimulation in the immune response^{11,12,28,38,39}.
4. Acquired or multigenic polymorphisms regulating immune tolerance to thyroid antigen/epitope-specificities^{7,38,39}.
5. Direct or interacting effects of environmental toxins or infectious agents in HD^{12,38,39}.

One may hypothesize that the greater the extent to which HD may be initiated by a primary thyroid dysfunction^{4,5,8,9}, the less frequently might associated autoimmune disorders be expected. Assuming HD is caused primarily by an immune dysregulation^{6,7,28}, the more frequently other associated autoimmune disorders might be expected.

Future studies of disease associations in HD remain promising to provide insights into autoimmune processes¹. Proper methodology requires critical investigations, incorporating unbiased or matched controls^{13,16,34}. Preferably, studies should incorporate longitudinal or prospective associations or risks, rather than only cross-sectional designs^{1,10,29,35}. Future investigations of HD warrant a broader and more balanced conceptual basis regarding its initiation and pathways of progression. The deciphering of alternative constructs and systems pathways resulting from a primary dysfunction in the thyroid target organ vis-à-vis an innate immune dysregulation promises improved understanding of the predisposing and initiating events in HD. In turn, its truly associated disorders can be more accurately identified and quantified in future critical investigations. This perspective supports the recent *Journal* proposal¹ that a focus on AITD and HD can offer a better understanding of autoimmune diseases. This goal can be expected, if future genetic, endocrinological, immunological, and epidemiological studies are critically designed, translated, and interpreted to address the basic and multifactorial questions in AITD and Hashimoto's disease.

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