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Untangling thyroid autoimmunity through modeling and simulation

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1. ABSTRACT

Thyroid autoimmunity is characterized by a large number of identified factors, and determining the relative importance of genetics and environment, for instance, can be difficult. In addition, the definition and progression of the individual diseases can also be challenging, and questions such as “when to begin treatment” or even “should treatment be begun” can be problematic. One approach to handling situations in which there are many factors is utilizing mathematical modeling. In a model, quantities that are clinically measurable are related through equations, based on known and inferred relationships between the systems involved. *In situations* where these relationships are complicated, the resulting simulations can provide information not previously recognized as logically resulting from those relationships. One advantage of this approach is that patient-specific parameter estimates can be used to personalize disease monitoring and treatment. In this paper, models involving Hashimoto's (autoimmune) thyroiditis, Graves' disease, and the roles of leptin, vitamin D₃, and adipose tissue are described. In the case of Hashimoto's, a model consisting of a system of differential equations is presented which allows a patient specific description of the progression of the disease. The

conditions leading to Hashitoxicosis are also described through that model. The patient specific model of the treatment of Graves' disease is also described. Finally, the roles of the inflammatory adipokines, especially leptin, and vitamin D₃ is explored as it relates to the initiation of thyroid autoimmunity. The result of this approach is an enhanced view of the initiation and progression of autoimmunity in the thyroid.

2. INTRODUCTION

The thyroid gland plays a central role in metabolism and protein synthesis through the production of the thyroid hormones T₃ (triiodothyronine) and T₄ (thyroxine) This review will focus on the control of the production of these hormones through the hypothalamic-pituitary-thyroid (HPT) axis, the factors that influence that control, especially the disruption of control due to autoimmunity of the thyroid. The central importance of the thyroid and interaction with other systems and factors result in a complicated overall system in which causes and effects can be confused. The goal here is to present the system in a way that the initiation and effects of autoimmune thyroid disease can be understood.

There are two predominant autoimmune diseases found in the thyroid, Graves' disease, which results in loss of control of the production of the thyroid hormones and hyperthyroidism, and autoimmune (Hashimoto's) thyroiditis in which the ability of the thyroid to respond to control results in hypothyroidism. Together, autoimmunity in the thyroid are the most common human autoimmune diseases (1) Although the mechanisms resulting in these diseases are different, they both involve the breaking of tolerance to self-antigens found in the thyroid.

The breaking of tolerance has both genetic (2, 3) and environmental (4) aspects – and involves the interaction between the two (5) The control from the HPT axis, a negative feedback system in which blood levels of T₃ and T₄ are sensed in the hypothalamus, result in lowering production of the thyrotropin-releasing hormone (TRH) if thyroid hormone levels are high and increased TRH if levels are low. TRH in turn controls production of thyroid stimulating hormone (TSH) from the pituitary. TSH binds to the TSH receptor in the thyroid, stimulating the production of the thyroid hormones. As T₃ is the active thyroid hormone and the thyroid predominantly produces T₄ in humans, a process is required produce T₃ from T₄ and maintain functional levels. This is accomplished through the deiodinase system which consists of three enzymes (D1, D2, and D3) These enzymes act on T₄ to produce the active hormone T₃ (D2), or inactive thyroid hormones (D1 and D3) (6) D2 local action in the brain producing T₃ is necessary for correct HPT axis operation (7) The role of this system in autoimmune disease is expressed through selenium (8) via the selenoproteins which comprise the deiodinase system. A simplified version of the HPT axis is shown in [Figure 1](#).

The autoimmune conditions described above disrupt this effective control system. In Graves' disease, the presence of an autoantibody to the TSH receptor, whose binding mimics the presence of TSH, greatly stimulates thyroid hormone production. In Hashimoto's thyroiditis, inflammation caused by the autoimmune disease results in the thyroid being unable to respond to the TSH signal effectively, with the response progressively worsening due to progressive thyroid destruction.

The approach of this paper is to describe the application of mathematical models, simulation of these models, and systems approaches, to resolve the essential subsystems and patient-specific clinical aspects of thyroid autoimmunity.

3. AUTOIMMUNITY IN THE THYROID

The mechanisms of Hashimoto's and Graves' disease are complicated, involving the production of autoantibodies and the lymphocytic infiltration of the thyroid (9, 10) The precise onset and development of both autoimmune disorders is unknown but have strong associations with genes, environment and inheritability

(3, 11) Autoantibodies are clinical biomarkers of thyroid autoimmunity. In Hashimoto's thyroiditis, the immune system inhibits the production of thyroid hormones (T3 and T4) through autoantibodies, thyroid peroxidase antibody (TPOAb) and the thyroglobulin antibody (TGAb), binding to thyroid peroxidase (TPO) and thyroglobulin (TG) in the gland. This may lead to abnormal thyroid size (goiter or atrophic) and thyroid function, progressing through a sequential clinical state, euthyroidism (normal thyroid), subclinical hypothyroidism (mildly underactive) and hypothyroidism (underactive thyroid), although autoimmune disease may be present without goiter or glandular atrophy. In Graves' disease, the immune system stimulates the production of thyroid hormones through autoantibody, thyroid receptor stimulating antibody (TRAb) binding with unstimulated TSH receptors on the gland. This leads to abnormal thyroid size and function, progressing through sequential clinical states, euthyroidism, subclinical hyperthyroidism (mildly overactive) and hyperthyroidism (overactive thyroid)

3.1. Clinical Presentations

The current incidence rate of Hashimoto's thyroiditis is estimated to be 300 - 500 cases per 100,000 individuals per year whereas the incidence rate of Graves' disease is estimated to be 20 - 30 cases per 100,000 individuals per year and are mostly seen in women between 30 and 50 years old (12, 13) This rate has been increasing in Western countries (14) possible due to environmental pollution (15) The diagnosis of Hashimoto's thyroiditis includes the tests for serum TPOAb, TGAb, TSH and free T4 whereas the diagnosis of Graves' disease includes the tests for serum TRAb, TSH, free T3 and free T4. Not all Hashimoto's patients produce anti-thyroid antibody, though. The values of TSH and free T4 indicate the status of thyroid function, such as hypothyroidism or hyperthyroidism while presence and nature of serum autoantibodies indicate Hashimoto's or Graves' disease. Approximately, the typical normal reference limits of TSH and free T4 are 0.4 - 4 mU/L and 7 -18 pg/mL respectively (16) Reference levels are quite different during pregnancy (17) This is due to placental human chorionic gonadotropin (HCG) binding to the TSH receptor – stimulating thyroid hormone production as well as estradiol-induced thyroxine binding globulin levels and hemodilution.

Assuming autoantibodies are detected in the serum, if patients' serum TSH and free T4 measurement falls within the normal reference limit, then the status of thyroid function at that time point is clinically euthyroid. If patients' serum TSH low or high and free T4 values are normal, then the status of thyroid function at that time point is mildly abnormal and clinically labeled as subclinical hyperthyroidism or subclinical hypothyroidism, depending on the nature of the autoantibodies. If patients' serum TSH high and free T4 are low, that indicates thyroid status at that time point is hypothyroidism. If patients' serum TSH is very low or undetectable and free T4 values are high, that indicates thyroid status at that time point is hyperthyroidism (16, 18) Accuracy and sensitivity of the thyroid evaluation is very important to determine the exact status of thyroid function since rarely the sudden thyroid burst can happen during Hashimoto's thyroiditis which increases serum free T4 and suppresses serum TSH levels mimicking Graves' disease; it can lead to misdiagnosis, so this is one caveat in the clinical thyroid evaluation (19)

Both autoimmune disorders show physical signs and/or symptoms. The physical signs and symptoms of Hashimoto's hypothyroidism may include fatigue, increased sensitivity to cold, constipation, dry skin, a puffy face, brittle nails, hair loss, joint pain and stiffness, muscle weakness, depression, excessive bleeding and memory lapses. The physical signs and symptoms of Graves' hyperthyroidism may include anxiety, difficulty in sleeping, fatigue, weight loss, palpitations and eye swelling, diffused goiter, increased pulse pressure, tremor, warm moist palms and tachycardia. Treatment of Hashimoto's and Graves' disease depend on the degree of severity, thyroid size, the levels of serum thyroid hormones, and the choice of a patient. Hashimoto's hypothyroidism is generally treated with levothyroxine, the synthetic form of natural T4, to restore euthyroidism. Graves' hyperthyroidism is generally treated with one of three approaches, namely use of anti-thyroid drugs (thionamides) to restore euthyroidism, destruction of thyroid via radioactive iodine, or removal of the thyroid via surgery (20)

3.2. Leptin and Vitamin D

Several systems interact with and affect the operation of the HPT axis. Of interest here is the effect of inflammatory molecules, the adipokines, produced predominantly in white adipose tissue (WAT) The most important for this report is leptin. Leptin was discovered in 1994 (21) as a hormone involved in appetite control. The adipokines have been shown to affect the operation of the HPT axis (22) by altering TRH (23) In addition, leptin levels correlate with body fat and differ in males and females due to differences in fat storage and possibly other reasons (24, 25) Also the adipokines, which also include TNF-alpha and IL-6, serve to raise the general level of inflammation – lowering the barrier to breaking immunological tolerance.

Vitamin D₃ is a fat-soluble vitamin predominately produced in the skin in response to ultraviolet-B (UVB) radiation. The primary role of vitamin D is in calcium homeostasis, which also involves the parathyroid in a feedback loop. Effects of vitamin D are expressed through the vitamin D receptor (VDR) which is found in many cells including those of the immune system and the thyroid (26, 27) A role of vitamin D in autoimmunity is somewhat controversial, but evidence is mounting (28) It is also possible that one must consider both WAT and vitamin D together to understand its role (25) The interaction between vitamin D and WAT in autoimmunity is an emerging story (29, 30)

4. MATHEMATICAL DYNAMIC MODELS AND SIMULATION – USE AND LIMITATIONS

The use of computational mathematical models in biology and medicine have been used for at least a century. Mathematical biology and medicine is considered a tool of scientific investigation that complements and augments data gathered in laboratories and clinics. In immunology, for instance, computational models have been used for at least a century (31)

Creating a model necessarily requires a simplification of the system under study. This means that important aspects are kept, while those deemed less important are not considered in the model. In diagrams presented here, this process can be seen. It is hoped that the essential information in the system is captured through these important aspects. A second step in the modeling process is to identify those important components that are measurable and which are not available or measurable. Assumptions based on current understanding, along with numerical fitting of the model, is then used to estimate parameters not available. This entire process, as a result, has the ability to provide insight not directly present in the data, and expose the logical consequence of current understanding.

A computational model is more than a presentation of data gathered through graphs and tables, and more than descriptive statistical quantities, such as the mean and standard deviation computed from data. The use of a computational model involves an attempt to use both data gathered, and assumptions and knowledge of the system under study to infer additional information regarding the system. For instance, a computer simulation of the model could be used to show that the data gathered is consistent or inconsistent with a particular hypothesis. The implications arising from the data and assumptions are predictions made by the model based on the assumptions and data used to construct the model. If the assumptions are true and the model was carefully constructed, the predictions should be eventually observed – this validates the model and its assumptions. These predictions are a natural way in which new experiments are suggested as part of the scientific method. Note that verifying the predictions does not prove that the assumptions are true, only that they may not be inconsistent with observations.

In models describing a normal operation of a system, such as the HPT system in the case of the thyroid, an accurate model can be constructed whose behavior mimics the behavior of normal operation. This is made possible by large patient population data sets as seen in (32) In the case of disruption of normal control due to

disease, a model of the normal operation is often not directly useful. If in addition, the model is to describe not a population of individuals, but the natural history of a single individual for therapeutic insight, a different approach, which recognizes how the system can be affected by disease is needed. Validation of such a model involves being able to fit data from each individual independently. Models of this type must be simple, as the data is limited, and dynamically more complicated, as the pathological system is being described.

5. PATIENT-SPECIFIC MODEL OF HASHIMOTO'S AUTOIMMUNE THYROIDITIS

In order to predict the clinical course of Hashimoto's thyroiditis, we have constructed a patient-specific differential equations model using the clinical variables, concentration of TSH (in mU/L), concentration of free T4 (in pg/mL), concentration of anti-thyroid peroxidase antibodies (TPOAb, in U/mL) and the functional (active) size of thyroid gland (in L) (33) Only TSH, free T4, and TPOAb are measurable in the serum. The functional size of thyroid gland is considered as a hidden variable that can be obtained through the relationship of other three variables. We list the key assumptions made on the clinical variables while developing this model.

1. The hypothalamus-pituitary function is intact.
2. Total TSH receptors concentration does not change during Hashimoto's thyroiditis.
3. Serum TSH stimulates the growth of functional thyroid and the production and secretion of thyroid hormones.
4. The immune system uses serum TPOAb to attack the thyroid and those titers can be used as a biomarker for the level of the anti-thyroid immune activity.
5. The patient does not demonstrate central or peripheral resistance to thyroid hormone.

The model is nonlinear with four equations, eleven parameters and continuous in time (33) The rate of change of serum TSH over time is the secretion rate of TSH minus elimination rate of TSH. The rate of change of serum free T4 over time is the secretion rate of free T4 minus elimination rate of free T4. The rate of change of the functional size over time is the growth rate minus destruction rate. The rate of change of serum TPOAb over time is the production rate of TPOAb minus elimination rate of TPOAb. Serum TSH changes on a faster time scale with a half-life of 1 hour, serum free T4 changes on an intermediate slower time scale with half-life of 7 days and serum TPOAb changes on a slower time scale with half-life of 20 days respectively. On the other hand, the thyroid functional size affected by Hashimoto's thyroiditis changes on even much slower time scale of months or years. Using two time scale assumption and slow dynamics, we can describe the clinical mechanisms in patients with Hashimoto's thyroiditis typically observed by the treating physicians: euthyroid → euthyroid, euthyroid → subclinical hypothyroidism, and euthyroid → subclinical hypothyroidism → hypothyroidism.

One of the main results while analyzing the model (33): there is a key patient parameter that corresponds to the production of thyroid peroxidase antibodies, which explains the clinical progression of Hashimoto's disease while other parameters are fixed during simulation. When this parameter value is below or equal to the threshold value, the patient would remain in the euthyroid state. When this parameter value is above the threshold value, the patient would progress to subclinical hypothyroid or hypothyroid state. See the simulations in Figures 2A, 2B and 3A for a hypothetical patient with initial state of TSH = 2.2. mU/L, free T4 = 12.5. pg/mL, TPOAb = 16 U/mL and the functional size = 0.0.15 L. In Figure 2A, the parameter value is exactly equal to threshold value. In Figures 2B and 3A, the parameter value is above the threshold value.

We have data from 119 individual Hashimoto patients with information on serum TSH, free T4, TPOAb, TGAb and levothyroxine. So, we can fit the model to an untreated patient data and describe or predict their long-term clinical progression of Hashimoto's thyroiditis (see Figure 3B) As another application of the model, we developed a chart with TSH curves over time for different values of that key parameter to monitor the clinical progression (see Figure 4A) The chart has several generated curves that represent TSH values remaining same, TSH values

changing from euthyroid state to subclinical hypothyroid state and TSH values changing from euthyroid state to hypothyroid state via subclinical hypothyroid state. The motivation for the development of a chart came from the pediatrics growth chart and since TSH is used as the baseline measurement for the function of negative feedback system of the HPT axis. Euthyroid individuals show variability with TSH values within the physiological range, so we can move the TSH chart in accordance with the patients' first clinical visit TSH measurement and then observe the progression.

6. HASHITOXICOSIS

In Hashimoto's thyroiditis, the thyroid burst associated with Hashitoxicosis can occur at any clinical state, euthyroidism, subclinical hypothyroidism or overt hypothyroidism which sometimes creates a transient hyperthyroidism. Thyrotoxicosis leads to leakage of thyroid hormones from the gland, a phenomenon called Hashitoxicosis. Using the homoclinic orbit from the patient-specific model of Hashimoto's thyroiditis, we can explain the thyroid burst occurring at different states, or the natural history of Hashitoxicosis. Homoclinic orbit is a special solution to the patient-specific model. To obtain a homoclinic orbit, we have used a two time-scale assumption, rewritten the model to a singularly perturbed initial value problem and defined a slow manifold (34) The slow manifold is a three dimensional surface in four dimensional space, where the functional size of the gland and thyroid peroxidase antibodies are free clinical variables. Basically, the slow manifold provides the functional relationship among clinical variables not previously recognized.

There are two steady states in the model, one is a diseased-free state and another is diseased state. Both steady states appear on the slow manifold for appropriate values of the key parameter (different from the parameter discussed in section 5) while other parameters are fixed during simulation. When this key parameter value is close to zero and less than the threshold value, diseased state is saddle as a solution to the model, which forms a homoclinic orbit. Needless to say, when this key parameter value is greater than or equal to the threshold value, the diseased-free state is asymptotically stable and homoclinic orbit is not possible. Since we are interested in homoclinic orbit, we focused in the diseased state. In [Figures 5A, 5B](#) and [6A](#), we show the simulations for a hypothetical patient when the thyroid burst occurs at the euthyroid state, subclinical hypothyroid state and hypothyroid state respectively. The yellow surface in [Figures 5A, 5B](#) and [6A](#) is the slow manifold.

By combining the orbits from [Figures 5A, 5B](#) and [6A](#), we developed a two dimensional clinical tool consisting of only homoclinic orbits indicating thyroid burst at early, middle and late state for patients with Hashimoto's thyroiditis (see [Figure 6B](#)) This tool may help with monitoring or describing patients' clinical progression in the event of a sudden burst of thyroid hormones. Although the diseased state lives on the slow manifold, the homoclinic orbit does not live on the slow manifold but approximately stays close to the manifold, which may be observed in [Figure 6B](#).

7. MODEL OF THE TREATMENT OF GRAVES' DISEASE

In Graves' disease, serum anti-thyroid receptor antibodies (TRAb) mimic the action of TSH and stimulate the thyroid hormone receptor (TSHR) Consequently, this results in hyperthyroidism and goiter. In order to predict the clinical course of hyperthyroidism treatment with Methimazole (MMI), we have developed a patient-specific treatment model using differential equations. The model has four clinical variables, namely concentration of free T4 (in pg/mL), concentration of MMI (in mg/L), concentration of TRAb (in U/mL) and the functional size of thyroid gland (in L) with thirteen parameters. We made the following key assumptions with the construction of the model (35)

1. The hypothalamus-pituitary function is intact.
2. Thyroid intakes MMI from the serum which inactivates the functional growth of the gland.

3. MMI absorption happens instantaneously from gut to serum.
4. Serum TRAb mimics the action of serum TSH and stimulates the growth of functional thyroid and the production and secretion of thyroid hormones.
5. This model does not consider the goitrogenic effect of long-term MMI use.

The model is nonlinear and continuous in time. All differential equations are written based on the physical principles. For instance, the rate of change of concentration of MMI over time is MMI dosing rate minus the MMI uptake rate and the elimination rate. The MMI dosing rate is modeled with the oral intake of MMI per day per liter of body volume. The uptake rate is modeled with the saturation kinetics while the elimination rate is modeled with first order kinetics. The rate of change of free thyroxine over time is the secretion rate minus elimination rate of free T4. The rate of change of the functional size over time is the growth rate minus inactivation rate of the functional size due to MMI intake. The rate of change of TRAb over time is the production rate of TRAb minus the elimination rate of TRAb.

Using a parameter from the model that corresponds to MMI dosage rate or treatment, we show the hyperthyroidism treatment dynamics. More precisely, when MMI treatment is not given or this parameter value is zero, the patient remains untreated and stays at the hyperthyroid state (see [Figure 7A](#)) After the initiation of MMI treatment, the patient progress from hyperthyroid state to euthyroid via subclinical hyperthyroid state (see [Figure 7B](#)) Actually, there is a monotonic decreasing curve as a function of the treatment parameter on which the hyperthyroid state moves towards the euthyroid state. The treatment parameter value can be calculated on the basis of dosage schedule and body volume of a patient. The dosage schedule starts with loading doses that bring the thyroid hormones within the physiological range in a time period of month and half and subsequently maintenance doses are administered to control or keep thyroid hormones within the range. Usually, the Graves' hyperthyroidism treatment with MMI lasts for about 12 – 18 months. Suppose the MMI is withdrawn after treatment; some patients undergo the relapse of hyperthyroidism and some patients achieve remission with treatment. Too much MMI loading or maintenance doses sometimes induce hypothyroidism or overshooting (see [Figure 8A](#)) On the other hand, too few MMI doses induce subclinical hyperthyroidism or undershooting (see [Figure 8B](#))

The model can be used to carry out experiments on dosage schedules that include loading and maintenance dosages and relapse prediction (see [Figure 9A](#)) Experiments on the optimal dosage schedule can help with decision-making on oral intake of MMI and control free T4 levels within the normal reference range for a longer period of time by avoiding the overshooting or undershooting (see [Figure 9B](#)) Relapse prediction, will be useful for the individuals with high risk of developing hyperthyroidism after the withdrawal of MMI treatment. With the relapse prediction, one can plan for the approximate follow-up date with their physician or to plan for a second course of MMI treatment in advance.

8. LEPTIN AND INFLAMMATION IN THE THYROID

Leptin and the other adipokines provide a level of general inflammation in the thyroid ([36](#)) that makes the breaking of tolerance more likely (much like a catalyst in a chemical reaction) ([24](#)) The jump to autoimmunity also requires a trigger, akin to the adjuvant necessary in animal models ([37](#)) In the thyroid, this aspect can be supplied by the ability of thyrocytes to respond to pathogen-associated molecular patterns (PAMP) through Toll-like and other receptors ([38](#)) as well as stress ([39](#)) These PAMP receptors have been recognized as “adjuvant receptors” ([40](#)) The stage to the final jump to autoimmunity is now prepared, and molecular mimics are the likely next actors. The list of identified mimics is very large ([24, 41](#)) and varied. The need to have the stage set before the mimic acts, explains why the list is so long. An immune response to a mimic in this setting results in a response to a self-antigen and potentially autoimmunity ([42](#)) Autoimmunity also needs a sustained response,

not just a transient response to a self-antigen. This aspect can be seen in pregnancy (17) Note that the placenta is a large non-adipose producer of leptin (43, 44) The steps leading to autoimmunity in the thyroid are summarized in Figure 10.

9. CONCLUSIONS

Thyroid autoimmunity initiation and the clinical natural history reflects the central role of the thyroid hormones and interactions with many systems. A case can be made that describes the thyroid as the most sensitive organ for autoimmunity – in other words, if autoimmunity is present anywhere, it is likely also to be present in the thyroid – and was probably there first (24) In this review, models were constructed of the period after the autoimmune process had been established. In this way, a limited number of components and their interactions can be considered. In the case of Hashimoto's autoimmune thyroiditis, a central aspect was the declining size of the functional thyroid, and a single patient-specific aspect, the rate of production of thyroid peroxidase antibodies, was identified and simulations provided. Conditions were identified that would make possible Hashitoxicosis – again with patient-specific parameters. In Graves' disease, patient-specific description of disease treatment was portrayed through simulations. In each case, the patient-specific parameters and fit to data validated the models presented.

In the initiation of thyroid autoimmunity, one must look outside the thyroid to WAT and vitamin D. The disruption of the HPT axis and increased inflammation, especially in a low vitamin D environment, helps to set the stage for the action of the innate immune system (Toll-like receptors) and environment (mimics) to trigger an autoimmune reaction.

By looking at the complicated interactions, and selecting those aspects that are likely to be most important, the features of thyroid autoimmunity are revealed.

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