The Connection Between Emotional Stress and Developing Graves’ Disease

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**Abstract**

Graves’ disease is an autoimmune disease where the body’s immune system attacks the thyroid and causes the overproduction of thyroid hormone. It also causes hyperthyroidism where the thyroid is essentially in hyperdrive. This study aimed to identify the effects of long-term emotional stress on the development of Graves’ disease. More specifically, it looked to see if this type of stress triggered the overabundance of thyroid-stimulating immunoglobulins (TSIs), the antibodies that attack the thyroid, causing growth and the production of too much thyroid hormone. The expected outcome is that that the participants that have not been officially diagnosed with the disease and experience the symptoms of hyperthyroidism will have elevated levels of T3 and T4; therefore, the overabundance of TSIs.

**Introduction**

The thyroid is a small butterfly shaped gland located in the center of the neck. The thyroid is mainly in charge of the body’s metabolism and energy. However, it also plays a role in the body’s cardiovascular function and bone health (Panicker 2011). The most common thyroid issues deal with the production of the thyroid hormones. Too much of the hormones leads to an overactive thyroid (hyperthyroidism) and too little of the hormones leads to an underactive one (hypothyroidism). Unfortunately, a lot of thyroid issues, diseases, and even cancer are hereditary. There are a number of thyroid diseases that can be passed down from generation to generation within families around the world.

Autoimmune thyroid diseases are an organ specific autoimmune disease that mainly affects women ages 30 to 50 (Swain et al., 2005). In simple terms, it is the imbalance of apoptosis and cell proliferation happening in the thyroid (Castro de Vasconcelos et al., 2018). There are two major autoimmune thyroid diseases are prevalent around the world. Graves’ disease and Hashimoto’s thyroiditis affect up to about 1% to 5% of the population (Tomer 2014). Genetics and/or environmental factors can create an immune response that infiltrates the thyroid with lymphocytes and the production of autoantibodies in both diseases (Zaaber et al., 2016). Graves’ disease usually presents itself in adults ages 30 to 50 years old; however, children and adolescents can develop Graves’ too (Kus et al., 2019). Maternal relatives have been shown to have an increased incidence of Graves’ disease at a younger age (Brent 2008). However, the genetic background around pediatric Graves’ disease is unknown so it is difficult to predict whether the disease will present itself at a young age or at an older age (Kus et al., 2019). With Graves’ disease, the thyrotoxicosis produces stimulating antibodies to the TSH (thyroid-stimulating hormone). It causes the thyroid to be put into overdrive essentially, producing more thyroid hormones than needed. While, Hashimoto’s disease is where there is tissue destruction which results in hypothyroidism, too little hormones being produced (Campbell et al., 2016). To this day, endocrinologists, doctors, and researchers do not know the exact causes of Graves’ and Hashimoto’s disease (Hammerstad et al., 2013).

There are several environmental factors related to the development of autoimmune thyroid diseases. Smoking cigarettes, iodine intake, and viral infections are common ones that can play a role in the development of a thyroid disease (Swain et al., 2005). The iodine intake is an important environmental factor in regulating a healthy thyroid because it is needed to help regulate thyroid hormone synthesis (Swain et al., 2005). Human bodies do not make iodine so it should be an essential part of our daily diet. Dairy products, seafood, and vitamin supplements are good sources of iodine to keep the thyroid healthy.

 Overall, genetics play the main role in the development of autoimmune thyroid diseases (Hadj-Kacem et al., 2009). These diseases have been observed to cluster within families and there is a high number of autoantibodies found in relatives of both adults and children affected with the diseases (Kanga et al., 2006). Analysis of twin data studies have shown that around 79% of people are at risk of developing Graves’ disease through genetic factors (Hadj-Kacem et al., 2009). Several genome screenings done in the past have found evidence to show a link between autoimmune thyroid diseases’ inheritance and specific markers on fourteen different chromosomes (Hadj-Kacem et al., 2009). There have also been numerous studies done on looking at specific genes and their contributions to autoimmune thyroid diseases.

 In 2008, a study was done that investigated whether or not *p53* could be used as a genetic marker for predicting the development of autoimmune thyroid diseases (Chen et al., 2008). PCR (polymerase chain reaction) analysis was done for the C (CCC)/G (CGC) polymorphism at the *p53* codon 72 Proline/Arginine to find the genotypes of 107 Hashimoto’s thyroiditis, 90 Graves’ disease patients, and 105 normal patients (Chen et al., 2008). They found that HT patients had a greater amount of arginine homozygosity at the *p53* codon 72 than the normal control patients (Chen et al., 2008). GD patients showed no relationship between *p53* codon 72 polymorphism and an individual’s susceptibility to GD (Chen et al., 2008). They believe that the *p53* codon 72 proline/arginine polymorphism may possible be a genetic marker to predict a person’s susceptibility of developing HT (Chen et al., 2008).

 *TSHR* is another important gene that is associated with autoimmune thyroid diseases. *TSHR* plays a role in regulation the functions and growth of the thyroid (Pujol-Borrell et al., 2015). Activating a *TSHR* mutation is rare but not unheard of. It can cause a nonautoimmune hyperthyroidism (Patel et al., 2019). However, identifying patients with this mutation is difficult because it has the same symptoms as Graves’ disease (Patel et al., 2019). It can difficult to identify patients in routine clinical practice so it is necessary to get genetic testing done to confirm it is in fact the mutation and not Graves’ disease.

 Triiodothyronine (T3) and thyroxine (T4) are the thyroid hormones created by the thyroid that play a role in maintaining the body’s metabolism and heart rate. Thyroid stimulating hormone (TSH) secretion is turned off during stressful events through the activation of the hypothalamic-pituitary-adrenal axis (Ranabir & Reetu 2011). Also, glucocorticoids, steroid hormones, decline the TSH secretion in the body. Therefore, stress is correlated with decreases T3 and T4 levels (Falgarone et al., 2013). However, T3 and T4 increase the effects of glucocorticoids leading so mixed signals between axes and a disruption causing an excess amount of thyroid hormones to be produced in the body (Falgarone et al., 2013).

**Specific Aim**

After reviewing multiple studies on the genetics, mechanisms, and environmental factors of certain thyroid diseases, a new study should be done to see if there is a correlation between chronic emotional stress and developing an autoimmune thyroid disease, specifically Graves’ disease. This study aims to identify the effects of long-term emotional stress on the development of Graves’ disease. More specifically, looking to see if this type of stress triggers the overabundance of thyroid-stimulating immunoglobins (TSIs), the antibodies that attack the thyroid, causing growth and the production of too much thyroid hormone.

**Methodology**

*Subjects*

 For this comparative year-long study, I will need 50 participants who have been diagnosed with Graves’ disease, 50 participants who have been experiencing early signs and symptoms of hyperthyroidism, and lastly 50 people without any thyroid issues as a control group. All of subjects must complete and score higher than a 300 on the Holmes-Rahe Life Stress Assessment each month (Topcu et al., 2012). Some situations that are found on this assessment are loss of a relative, divorce, loss of a job, and long-term depression. Also, the participants will need to get an ultrasound of their thyroid to check to make sure that they do not have any form of thyroid cancer because that would make them ineligible for this study (Vita et al., 2009).

*Measurements*

 Each month blood will be withdrawn from patients to test their thyroid hormone levels and TSI levels. For T3 and T4, the free and total assays for both of them will measure the number of hormones in the blood stream (Tavares et al., 2017). For TSI, the Immulite 2000 assay will be used to determine the number of antibodies are found in the participants’ blood (Tavares et al., 2017).

*Data and statistical analysis*

 For data analysis, I want to get the means and standard deviations of T3, T4, and TSI of the three groups from each month and display the data in bar graph form. The bar graphs will be the best way to determine any patterns found in the data that may indicate that long-term emotional stress does in fact raise these hormone and antibody levels contributing to the development of Graves’ disease. An ANOVA (analysis of variance) can be performed on the means of the group to see if there is a significant (p < 0.05) difference in the means of the group.

**Potential Pitfalls**

One major pitfall that could arise when performing this study would concern the participants’ stress levels. This is a long-term study happening for a year. The participants need to keep a consistently high score on the Holmes-Rahe Life Stress Assessment each month before getting blood drawn. If their score were to suddenly decrease because the stressors in their life have gotten better, then that will definitely impact the data. The thyroid levels will most likely go back to normal if that situation were to happen.

 One way to combat that issue would be do very extensive background research with the people that are willing to participate in this study. It is important to find participants who under a lot of emotional stress constantly. They will need to be for at least a year for this study, so it is important to interview participants to see exactly what the stressors are in their lives. If it is something very short-term, then it would best to not have them participate in the study because they will risk skewing the data results.

 A second major pitfall that could occur in this study is the misdiagnosis of the early signs and symptoms of hyperthyroidism. A participant who actually has hypothyroidism will skew the data results, showing below normal results and T3 and T4. That is the opposite trend that this study is looking for. The similar symptoms that hyperthyroidism and hypothyroidism share are an enlarged thyroid gland, fatigue, muscle weakness, changes in menstrual patterns and hair thinning. The best way to combat that pitfall is to focus on the symptoms only patients with hyperthyroidism would experience when interviewing future participants. Those symptoms would be weight loss, heart palpitations, anxiety, sensitivity to heat, and tremors.

**Potential Conclusions**

Since no one has found an official cause of Graves’ disease, it is difficult to assume a hundred percent that these methods will yield any valuable results. There is one result will for sure be similar between the all participants and that is that the thyroid hormone levels found from the bloodwork will all be higher than normal range found in the control group. That is because Graves’ disease and hyperthyroidism have that in common: the overproduction of thyroid hormones.

The results that are questionable in this experiment will be whether or not the participants that show the early signs and symptoms of hyperthyroidism will have the TSIs like the Graves’ participants will have. It could be that some of the participants just have hyperthyroidism and not have the antibodies present in their bloodwork throughout the full year of the experiment. It could be that maybe some will not show any antibodies until halfway through the study and by chance, some participants will have the antibodies present right away at the beginning.

It is important that we study Graves’ disease and see what are the causes of it since it is unknown. Besides being predisposed to it through genetics, it important to figure what else causes the development of Graves’. If there is a correlation between stress and the development of Graves’ disease, preventative measures can be established to help people take care of their body in stressful times.

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