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The Use of Selenium in the Treatment of Graves' Hyperthyroidism

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Permission

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Abstract

Multiple studies have found an association between subnormal thyroid stimulating hormone (TSH), elevated free thyroxine (FT4) and/or triiodothyronine (T3) and increased free radicals and reactive oxygen species (ROS). These findings are related to the development of Graves' disease. Graves' disease is an autoimmune disorder that causes hyperthyroidism and a hypermetabolic state. The use of selenium has been of interest in the treatment of Graves' hyperthyroidism. Selenium, an antioxidant that is concentrated in the thyroid gland, is essential for normal thyroid metabolism and function. Selenium is also thought to reduce oxidative stress and ROS. Studies and trials currently continue on the use of selenium in the treatment of thyroid disorders, and thus, more information and discoveries are being made to date. This paper will review literature on the pathophysiology of Graves' disease, the role of selenium, and the utilization of selenium in the treatment of Graves' hyperthyroidism and the associated common complication of orbitopathy.

Background

A 65-year-old Caucasian female came to the clinic with a chief complaint of "feeling tired but cannot sleep." Upon further investigation, patient reported a recent unexplained weight loss of 10 pounds, irritability, poor concentration, occasional heart fluttering sensations, and intermittent hot flashes. Patient's physical exam was normal besides an enlarged thyroid. Labs were obtained and patient had a low TSH, high T4, and high T3. The patient was diagnosed with hyperthyroidism. Treatment was initiation of a beta-blocker and a referral to endocrinology.

Graves' disease is the main cause of hyperthyroidism among adults. Nearly 3% of women and 0.5% of men suffer from Graves' hyperthyroidism (Wang et al., 2016). In Graves' disease, autoantibodies are activated against the TSH receptor, which leads to excessive thyroid hormone production. Genetic and environmental factors have been implicated in the disease process, as well as, an inflammatory response with an increased production of reactive oxygen species (ROS) and free radicals that sustain and perpetuate Graves' disease (Duntas, 2012). Additionally, thyroid-associated orbitopathy, an inflammatory disorder of the orbit, is the most common extra-thyroid complication of Graves' disease, with up to 50% of patients with hyperthyroidism developing orbitopathy. Oxidative stress and an increase in ROS are a major cause of orbitopathy in Graves' disease, which can result in corneal breakdown and loss of vision (Strianese, 2017).

Currently, treatment for Graves' hyperthyroidism may include the use of antithyroid medication, radioactive iodine, surgery, or a combination of these treatments, however none of

these treatment methods specifically target the underlying autoimmune process of Graves' disease. In the treatment of Graves' disease. the antithyroid medications used are propylthiouracil (PTU) and methimazole (MMI) (Dunphy, Winland-Brown, Porter, & Thomas, 2015). Selenium, a trace element that is an antioxidant, is currently being studied as a possible treatment for Graves' hyperthyroidism. An antioxidant decreases oxidative stress and free radical damage, thereby lessening the autoimmune response. According to Wang et al. (2016) "selenium is intensively involved in the immune response, and it also has important roles in maintaining the normal function of the thyroid" (p. 559). Selenium is essential for healthy thyroid gland function, hormone metabolism, and the degradation of ROS in the thyroid gland. Selenium also interferes with the inflammatory response that causes thyroid eye disease and is recommended for treatment in mild orbitopathy (Strianese, 2017). Due to selenium's role in the inflammatory and autoimmune response, the use of selenium as an important antioxidant to reduce the ROS damage in Graves' hyperthyroidism leading to an euthyroid state may be implicated in practice. Selenium, which can be bought over the counter as a supplement or ingested in foods, may have a role in the treatment of Graves' disease.

Case Report

D.M, 65-year-old Caucasian female

Chief Complaint: Patient reports to clinic with complaint that for the past 6 weeks she "can't sleep but feels tired during the day."

HPI: Patient said she has no trouble falling asleep, but after about 2-3 hours she awakens and is unable to fall back asleep, as it feels she can't "unwind" and her "body feels restless". Patient denied taking naps during the day, limits herself to 1 cup of coffee in the morning, is not falling asleep easily throughout the day, and her husband has not complained of her snoring at night.

Patient also has a recent, unexplained weight loss of 10 pounds. Additionally, patient had complaints of irritability and poor concentration, but denied forgetfulness. Patient stated concerns of "heart flutters" that occur during the day or night. She said the flutters last for about 5 minutes and will happen 2-3 times per week. Patient denied dizziness, diaphoresis, changes in vision, chest pain, jaw pain, shoulder/arm pain, nausea, headaches, or any other symptoms during her heart flutters. Patient denied a cardiac history. Patient will sit down and rest when heart flutters occur until they stop. Patient denied a pattern or any known exacerbating features, such as exercise, to her heart flutters. Patient said she has a history of "vertigo", but her symptoms are well controlled, and she can't even remember when she took her as needed medication. Patient also was concerned about intermittent hot flashes. Patient stated the hot flashes occur during the day, about 2 times per week, and will last "a couple minutes." Patient denied any of the prior accompanying symptoms or any other symptoms with her hot flashes. Patient said she is post-menopausal and went through menopause 12 years ago. Patient cannot recall any pattern to hot flashes or precipitating or exacerbating factors. Patient denied any recent medicine changes or supplement use. Patient has tried exercise, meditation, limiting caffeine, lavender lotion, dark room, shutting her door, distraction, and changing rooms to help alleviate her symptoms. Patient stated nothing has worked and that is why she is in the office today.

Past Medical History: benign positional vertigo, childbirth X2

Surgical History: none

Medications: Antivert PRN, multivitamin daily, calcium daily

Immunizations: up to date

Allergies: None

Family History: Mother: cardiac stent, Alzheimer's disease, Father: diabetes mellitus (unknown if type 1 or 2), Brother: prostate cancer, Brother: healthy, Brother: healthy, Sister: hypertension

Social History: Patient lives at home with husband. Patient has 2 adult children. Patient does not drink alcohol besides an "occasional 1 glass of wine", does not smoke, and does not use illicit drugs. Patient is retired but does volunteer work. Patient exercises 3 times per week.

Review of systems per chief complaint and history of present illness.

Objective:

Weight: 136 pounds, pulse: 96, respirations: 12, temperature: 99.4, BP: 124/74

Physical Exam:

65-year-old Caucasian female, alert, oriented, in no acute distress, well developed. Answers questions appropriately and able to provide a history. Exam was negative besides an enlarged thyroid palpated.

Plan:

Completed testing: CBC, CMP, TSH, T4, T3, EKG, UA.

All labs and EKG normal besides TSH was low and T3/T4 elevated. Patient started on a beta-blocker for heart rate control, heart flutter symptom control, and to possibly lessen restlessness and sleeplessness. A referral for endocrinology was placed for further management. Explained to patient the thyroid gland, its function, and the diagnosis of hyperthyroidism. Informed patient of different treatment options for hyperthyroidism and stated that endocrinology will further explain and help patient make the best decision for her. All patient's questions answered. Patient to follow-up in 6 weeks or per endocrinology recommendations.

Literature Review

A literature search was conducted through CINAHL, PubMed, textbooks, and GoogleScholar. The phrases "Graves' hyperthyroidism and selenium", "hyperthyroidism and selenium", "selenium and antithyroid medication", "selenium treatment in hyperthyroidism", "selenium and thyroid" and "Graves' disease and selenium" were used to generate articles. Articles were chosen between the years of 2012 and 2019.

Hyperthyroidism is a common condition that includes the excessive production and excretion of one or both of the thyroid hormones: thyroxine (T4) and triiodothyronine (T3). Graves' disease, an autoimmune disorder, is the most common cause of hyperthyroidism in the United States, accounting for 80-90% of all hyperthyroid cases (Dunphy et al., 2015). About 3% of women and 0.5% of men have Graves' hyperthyroidism. In Graves' disease, it is known that anti-TSH-receptor antibodies (TRAb) bind to TSH receptors. This binding of receptors causes thyroid hypertrophy and stimulates the production of thyroid hormones (Wang et al., 2016). The stimulation of thyroid hormone production leads to the increased T3 and T4, and the binding of receptors causing thyroid hypertrophy is consistent with the enlarged thyroid that may be palpated on exam, both findings commonly identified in Graves' disease. Anti-TSH-receptor antibodies are often used as an antibody marker for this disease.

Graves' hyperthyroidism is known to have genetic and environmental factors that trigger the autoimmune process in the disease. At a cellular and genetic level, a human leukocyte antigen (HLA), a gene complex that is responsible for regulating the immune system, develops a defect in suppressor T-lymphocyte function. This defect leads to decreased suppression of thyroid-directed T-lymphocytes. The subsequent proliferation of helper T-lymphocytes, as a result of decreasing suppressor T-lymphocytes, produces interferon and interleukin-1, which are cytokines that differentiate B cells to plasma cells and ultimately generate TRAb (Duntas, 2012).

According to Duntas (2012) interferon "modulates the autoimmune process and, by stimulating chemokine production by thyroid follicular cells, contributes to the maintenance of the autoimmune process" (p. 2). Thus, through genetic mutations on the HLA gene, suppressor T-lymphocytes are decreased allowing for the proliferation of helper T-lymphocytes. Helper T-lymphocytes, interferon, and interleukin-1 all work in conjunction that differentiate B cells to plasma cells and generate TRAb. As stated earlier, TRAb is an autoantibody that binds to TSH receptors and stimulates the production of T3 and T4, leading to hyperthyroidism. This increased thyroid hormone production may further reduce the number and function of suppressor T-lymphocytes and stimulate helper T-lymphocytes, which will perpetuate the cycle. Other factors known to contribute to Graves' hyperthyroidism are stress, age, smoking, and female gender (Calissendorff, Mikulski, Larsen, & Moller, 2015). It is also common for persons with Graves' disease to also have concurrent autoimmune disorders such as vitiligo, type I diabetes mellitus, or adrenal insufficiency (Dunphy et al., 2015).

Oxidative stress, through the release of free radicals and ROS, is thought to play a large role in the development of hyperthyroidism. When a patient suffers from hyperthyroidism, an increase of thyroid hormones causes the patient to be in a hypermetabolic state. This hypermetabolic state forms and releases a large amount of ROS in the peripheral tissues and the thyroid gland. Even the normal production of thyroid hormones causes ROS damage to the thyroid gland; thus, when the production is increased, as in the case of Graves' hyperthyroidism, even more thyroid hormone is produced, causing an increase in oxidative stress on the thyroid gland. It is believed that ROS elicits damage to the thyroid epithelial cells, resulting in exposure of autoantigens to the immune system, causing worsening of autoimmunity against the thyroid gland. The ROS that are generated in the peripheral tissues cause damage to those tissues,

contributing to various clinical manifestations of Graves' hyperthyroidism, including orbitopathy, anxiety, fine hand tremors, heat sensitivity, and weight loss (Marino, Menconi, Dottore, Leo, & Marcocci, 2018). Two major elements in the oxidative stress associated with Graves' hyperthyroidism are H_2O_2 and superoxide anion (O_2^-). Hyperthyroidism not only increases H_2O_2 , O_2^-, and oxidative stress, which contributes to tissue damage and continues the cycle of ongoing damage, but also decreases antioxidants, which leads to further oxidative stress. (Duntas, 2012). Because of this knowledge, an area of interest in treating Graves' hyperthyroidism is through the use of antioxidants. A goal of antioxidant therapy would be to reduce H_2O_2 to H_2O, and O_2^- to O_2, resulting in limiting the damage to the thyroid gland and peripheral tissue.

Selenium, a trace mineral, is important in thyroid health. The thyroid gland is characterized by a high tissue concentration of selenium. Selenium contributes to antioxidant defense in the thyroid by removing ROS generated during the production of thyroid hormones (Ventura, Melo, & Carrilho, 2017). It is a nonmetal mineral, trace element, and an essential micronutrient. In recent years there has been a growing interest in selenium, as it has been shown to be crucial in the role of maintenance of immune-endocrine function, metabolism, and cellular homeostasis. The selenoproteins, proteins made up of selenium, have important roles in antioxidant activity, contributes to the defense against oxidative stress, and removes the oxygen free radicals generated through the production of thyroid hormones (Ventura et al., 2017). Selenium is incorporated into selenoproteins as the 21st amino-acid, selenocysteine. The Selenoproteins have a wide range of important effects that include redox homeostasis, immunity, and the reproduction and metabolism of thyroid hormones. Selenoproteins important in thyroid function are glutathione peroxidase and thioredoxin reductases (Winther et al., 2014).

The selenoproteins glutathione peroxidases and thioredoxin reductase have a critical role in a complex defense mechanism that maintains normal thyroid function by protection the gland from H_2O_2 and ROS. They are shown to have of benefit in autoimmune thyroid disease by slowing down the autoimmune process (Watt et al., 2013). Since Graves' disease is an autoimmune process that involves free radical and ROS damage, the damage further perpetuates thyroid dysfunction and continues the disease process and hyperthyroid state. Since selenium is known to blunt the autoimmune process and is heavily saturated in the thyroid gland, this trace mineral is researched as a treatment option for Graves' hyperthyroidism (Leo et al., 2016) This is meaningful because the current conventional treatments of anti-thyroid medications, radioactive iodine, and surgery only treat the thyroid gland but not the autoimmune process. In addition to the autoimmune protection of decreasing oxidative stress, selenium supplementation has shown to decrease helper T-lymphocytes and upregulate suppressor T-lymphocytes, which puts a brake on the immune response. Through this mechanism with selenium, T-lymphocyte levels may be normalized. There is also a correlated increase in glutathione peroxidase levels with selenium intake, which has a protective role in the defense mechanism (Kahaly, Riedl, Konig, Diana, Schomburg, 2017).

To further explain the selenoproteins, glutathione peroxidase has an enzymatic function, in which selenium is located on the catalytic site. This is important in the antioxidant action of the enzyme, as catabolism breaks down a substance. Glutathione peroxidase protects the thyroid gland from oxidative stress by reducing H_2O_2 into H_2O (Leo et al., 2017). Thioredoxin reductase is induced by stress. It has strong redox activities, thus decreasing oxidative stress. Thioredoxin reductase has also been implicated in the regulation of the production T3 in Graves' disease (Duntas, 2012). Furthermore, glutathione peroxidase is found in other tissues, which helps

explain the extra-thyroid clinical manifestations that occur with Graves' hyperthyroidism. All of the glutathione peroxidases have an antioxidant defense and protects the tissues where it is concentrated. Thioredoxin reductase has a cytosolic function that acts as a main antioxidant at the cellular level and a mitochondrial function that regulates cell proliferation. Lastly, there is another selenoprotein, iodothyronine deiodinase that is active in the conversion of T4 to reverse T3, which is the inactive metabolite (Ventura et al., 2017). These are the main groups of selenoproteins that are found in the thyroid gland and are important in the normal function of the thyroid gland.

Selenium is available in organic compounds known as selenomethionine and selenocysteine, or in inorganic compounds known as selenite and selenate. The organic form is known to have better absorption and is the preferable formula for supplementation and treatment. Selenomethionine is found in vegetables sources (Ventura et al., 2017). Supplements containing selenomethionine have the highest bioavailability of selenium. The amount of selenium a person consumes varies by region and is also dependent on the soil and water concentration in that area. It is commonly found in animal food sources such as fish, ham, beef, cottage cheese, and eggs. Other food sources of selenium are pasta, rice, bread, and cereal. Reduced selenium levels have also been found in smokers, elderly, large consumption of white rice, alcohol use, and consumption of coffee (Ventura et al., 2017). The daily recommended intake of selenium is 53 micrograms in women and 60 micrograms in men. Since selenium is found in a wide variety of foods, diet restrictions or preferences do not largely impact the consumption of selenium. The variance of selenium concentration in the environment plays a larger role in plasma selenium levels, which can influence if a person will suffer from a selenium deficiency and subsequent disease states. If the environment is known to be deficient in selenium, a person may have to take

a prepared selenium supplement to assist in controlling the autoimmune process and oxidative stress in Graves' disease; otherwise, it is best if a person obtains selenium through diet.

Due to antioxidant properties, selenium has been used as part of the treatment for Graves' hyperthyroidism and hyperthyroidism orbitopathy. The use of the mineral is controversial, and more research is being conducted to support or discredit selenium in the treatment of hyperthyroidism. In a study performed by Zheng et al., (2018) there was a decrease in free T3 levels in patients taking the anti-thyroid medication methimazole (MMI) and selenium. A decrease in free T3 and a difference between the selenium and control group was noted in the three-month group, but not at the nine-month mark. There was also a decrease, higher in the patients taking MMI and selenium versus patients just taking MMI, in the free T4 levels at three months and six months, but not at nine months. Selenium supplementation with MMI showed a higher TSH level at six months but did not display an increase at three months or nine months. Lastly, TRAb levels were also evaluated in these patients. Patients taking MMI with selenium had a decrease of TRAb levels at six months but not at nine months (Zheng et al., 2018). It is interesting to note that the patients did have measurable benefits while taking MMI with selenium. The patients had a significantly faster decrease in free T3, T4, and TRAb, while having an increase in TSH. This study showed that patients reached a euthyroid state faster when utilizing selenium with MMI than just with MMI. Additionally, the use of only anti-thyroid medication is associated with a high rate of recurrence. Wang et al. (2016) noted that "about 50% patients will achieve remission after receiving ATDs [anti-thyroid drugs] therapy for about 12-18 months, but there is a high prevalence of recurrence in those patients with remission, ranging from 30 to 70% in published studies" (p. 559). Thus, the use of selenium was of particular interest in treating Graves' hyperthyroidism and recurrent hyperthyroidism, since a second round

of anti-thyroid medication is less likely to induce and maintain an euthyroid state, and the only other treatment methods are radioactive iodine and surgery. In patients with recurrent Graves' hyperthyroidism, selenium was added to MMI therapy to possibly enhance the effectiveness of the MMI and induce euthyroid. In the group treated with selenium and MMI, the concentration of free T4, free T3, and TRAb decreased faster than those treated with just MMI at the two-month follow-up, with higher TSH levels noted at the two month follow up, as well (Wang et al., 2016).

In recurrent Graves' hyperthyroidism, 52.3%, were able to attain and maintain a euthyroid state when taking selenium with MMI. Only 25% of patients taking only MMI were able to attain remission. Overall, higher remission rates in Graves' hyperthyroidism are associated with selenium use, as well as, a faster response to anti-thyroid medication (Wang et al., 2016).

Reaching a euthyroid state is often noted to be quicker in patients receiving selenium with MMI than patients taking only MMI. In further support of this role of antioxidant use, the TRAb levels correlated with the levels of free T3, free T4, and TSH. Early on in the studies TRAb levels dropped quicker with the use of selenium when compared to those without selenium use. As the TRAb levels dropped, the free T3 and T4 levels dropped and the TSH levels increased. These findings support the positive impact combining selenium and MMI may have in autoimmunity and faster control and normalization of the thyroid gland (Ventura et al., 2017). Additionally, the patients taking selenium therapy consistently had lower levels of free T3, T4 and TRAb, and higher level of TSH at each of the follow-ups: two months, three months, six months, and 12 months. (Wang et al., 2016). This evidence is continually backed by other studies including ones performed by Zheng et al. (2018), Wang et al. (2016), Calissendorff et al.

(2015), and Ventura et al. (2017). Calissendorff et al. (2015) concluded that after an addition of selenium to MMI therapy there was a reduction in free T4 and increase in TSH at 18 and 36 weeks. Calissendorff et al. (2015) stated "Se [selenium] is important for initiating and enhancing immunity but is also involved in regulating excessive immune responses, which is crucial for preventing responses that may lead to autoimmunity or chronic inflammation" (p. 97).

Patients taking selenium have been able to take a lower dose of an MMI and were less likely to discontinue the medication than the patients taking only an MMI (Wang et al., 2016). A larger difference in TSH was noted when patients in the selenium group were increased from 60 micrograms daily to 90 micrograms daily, suggesting that higher doses of selenium may correspond with a greater TSH response (Calissendorff et al., 2015). Higher remission rates of Graves' hyperthyroidism were noted in patients receiving 200 micrograms/day and MMI than patients receiving 166 micrograms/day and MMI. There was also a larger decrease in TRAb levels in the patients with 200 micrograms daily versus 166 micrograms daily (Winther, Bonnema, and Hegedus, 2017). The patient's initial selenium status may play a role in the dosing of selenium. Patients may be more prone to selenium deficiency in areas where there is less selenium in the environment and foods. Knowing that certain regions that have less selenium in the environment, a higher dose of selenium supplementation may be warranted. Most persons upper tolerable level of selenium intake is 400 micrograms/day but it is tolerated in short-term doses up to 10,000 micrograms/day. An excessive amount of selenium can lead to gastrointestinal discomfort, hair and nail formations or loss, peripheral neuropathy, fatigue, dizziness, and even more rarely cardiovascular collapse and respiratory distress (Watt et al., 2013).

Not all studies cite a clinical benefit of response on TSH in those who concurrently use selenium supplementation as part of their treatment, but the initial selenium status of the patient may be a major reason why no benefit was seen. In a study of 70 patients by Kahaly et al. (2017), no significant changes in free T3, T4, TRAb, and TSH were noted between selenium and control groups. The relapse rate was also the same between the two groups. A positive correlation was noted between selenium status and SELENOP (the protein that carries selenium throughout the body) and TSH. It was hypothesized that the lack of response may have been related to unknown initial selenium levels of the patients, as well as, small study size and short study duration (Kahaly et al., 2017). The fact that there was a positive relation between selenium levels and TSH is promising, as it demonstrates that selenium does have an effect on TSH. Kahaly et al. (2017) further explains "these divergent results indicate that a direct comparison of the currently available Se supplementation studies in GD [Graves' disease] is hampered by the differences in Se compound, dosage, and time of supplementation chosen, by the baseline Se status of the patient, which is not always determined…" (p. 4339). In a study where selenium status was established, all patients were within normal plasma selenium range. When thyroid hormones and TSH were compared between the 2 groups, there was no difference in the speed of remission or thyroid levels (Leo et al., 2016). The use of selenium has shown to be of benefit to patients that are selenium deficient, though; and, since organic selenium is known for better absorption within the body, the type of supplementation may also play a role in treating Graves' disease (Ventura et al., 2017).

Selenium supplementation has also shown to decrease the clinical manifestations associated with hyperthyroidism. Patients taking selenium reported a lower degree of depression. Furthermore, there was also a positive correlation in recovery from the symptoms of

hyperthyroidism and selenium use (Calissendorff et al., 2015). There are studies underway, particularly one that should be published soon by Winther et al. (2014), looking at the quality of life and treatment with selenium in thyroid disease. The primary outcome of this study is a patient's reported quality of life with selenium versus no selenium supplementation, with the hope that selenium will further support improved quality of life. One of the most studied areas that pertain to quality of life and Graves' hyperthyroidism is orbitopathy, since thyroid eye disease is the most common extra-thyroid problem in Graves' disease.

Selenium supplementation has been implicated in the treatment of Graves' orbitopathy, a common consequence affecting approximately 50% of Graves' patients (Strianese, 2017). Oxidative stress and ROS in Graves' disease are shown to contribute to orbitopathy. This inflammatory process leads to an increased number of orbital fibroblasts, consequently increasing the volume of orbital structures and causing the clinical manifestations of Graves' orbitopathy (Marino et al., 2018). The clinical manifestations of thyroid eye disease include eyelid retraction, proptosis, ocular motility disturbances, dry eyes, foreign body sensations, and tearing (Strianese, 2017). Through oxidative stress and ROS damage the etiology of the Graves' hyperthyroidism and Graves' orbitopathy are very similar; thus, the importance of selenium in Graves' orbitopathy has been researched.

Treatment with selenium in the cases of orbitopathy was associated with improved quality of life, less eye involvement, and delayed progression of eye disease at six months and 12 months when compared to treatment with pentoxifylline, a common prescription medication used for Graves' orbitopathy. Selenium was found to be of most benefit to patients with mild to moderate orbitopathy. Additionally, the organic form of selenium, selenomethionine, had more advantages in treating orbitopathy than the inorganic forms (Ventura et al., 2016). Strianese

(2017) found that "the antioxidant effect of selenium, which may interfere with TED progression, represents an advance in TED therapy, particularly for mild disease" (p. 511). The findings that selenium can improve quality of life and decrease the clinical manifestations of ocular involvement in thyroid disease will be helpful in treating the disease, since selenium has the potential to treat not only the thyroid but also Graves' orbitopathy.

Winther et al.'s (2017) study found that selenium supplementation improved quality of life and ophthalmological status after only 6 months of treatment, concluding that treatment with selenium for 6 months improves Graves' orbitopathy. The study also discovered an association between selenium deficiency and the development of orbitopathy, hypothesizing selenium deficiency may be an independent risk factor for Graves' orbitopathy (Winther et al., 2017). Additionally, Marino et al. (2018) found that 12 months after withdrawal of selenium treatment, patients still had improved ocular status, indicating a persistence of benefits of selenium supplementation. Due to the unvarying findings of the benefits of selenium in Graves' orbitopathy and the lasting benefits of supplementation, it has been recommended that patients with mild ocular involvement start selenium supplementation for 6 months, especially patients that are selenium deficient (Marino et al., 2018).

Key Points

- Graves' hyperthyroidism is a common autoimmune disease that accrues damage from oxidative stress and ROS affecting an estimated 10 million Americans each year.

- Selenium, which is highly concentrated in the thyroid gland, is an antioxidant that helps decrease oxidative stress and ROS involvement in the body; and, may be clinical useful in reducing the autoimmune response that occurs in Graves' hyperthyroidism.
- Selenium, in addition to methimazole, has been shown to help a patient attain an euthyroid state faster and maintaining the euthyroid state better than just methimazole alone.

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