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Vitamin D and Selenium in a Thyroid Eye Disease Population in Texas

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ABSTRACT

There is growing evidence of thyroid eye disease association with nutritional deficiencies including selenium and vitamin D. We conducted a retrospective chart review of all patients with clinical diagnosis of TED seen at our clinic from 2016 to 2017. Thirty-five patients met inclusion criteria and had serum 25-hydroxyvitamin D levels available, and 19 had selenium levels available. 7/35 (20%) patients had vitamin D deficiency, and 11 (31%) had vitamin D insufficiency, but none had selenium deficiency. Although both selenium and vitamin D supplementation have been recommended for TED, further investigation is necessary to justify supplementation for patients with TED.

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Background

Thyroid eye disease (TED) is an autoimmune disease characterized by the presence of autoantibodies directed against antigens in the thyroid gland that cross-react with orbital antigens (e.g., thyroid stimulating hormone receptor (TSH-R) or thyroperoxidase (TPO)). Key pathological features of TED include extraocular muscle or orbital fat expansion and soft tissue inflammation due to increased adipose tissue, oedema, and glycosaminoglycan (GAG) production in orbital tissue.[1] Left untreated, TED can cause photophobia, diplopia, pain, exposure keratopathy and proptosis. Compressive optic neuropathy threatening vision, however, is the feared complication.[1] Current therapeutic options include discontinuation of smoking, correction of any thyroid abnormalities, administration of non-steroidal or steroidal anti-inflammatory drugs, orbital low dose radiation therapy or surgery (e.g., orbital decompression).

Vitamin D regulates calcium and phosphorous levels in the human body, in addition to its role as an immunomodulatory.[2] Kriegel et al. suggested the role of vitamin D deficiency with various autoimmune diseases (e.g. multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis) and a similar mechanism may be at play in TED.[2] Although evidence is limited, supplementation may be a potential adjunct treatment strategy to slow disease progression due to its role in innate and adaptive immunity.[3,4]

Selenium is important in maintaining the body's immune function and metabolism, and is essential to thyroid function. In particular, the glutathione peroxidases protect the thyroid by removing excessive hydrogen peroxide produced there for thyroglobulin iodination. The normal thyroid gland contains a high concentration of selenium, which is incorporated into selenoproteins.[5] These selenoproteins have antioxidant properties, which function to neutralize oxygen free radicals, a byproduct of thyroid hormone production.[5,6] There is evidence from observational studies and randomized controlled trials that selenium/selenoproteins can reduce TPO-antibody titers and improve hypothyroidism and post-partum thyroiditis.[7]

Although prior studies have identified an association with these nutrient deficiencies in the context of other autoimmune diseases, the link to TED has not been well established. To our knowledge, this is the first such study to look at vitamin D and selenium levels in TED in an American population in the English language ophthalmic literature. We propose a further investigation into the therapeutic

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benefit of vitamin D or selenium supplementation for the treatment of thyroid eye disease.

Methods

Ethics statement

This retrospective chart review was conducted using the diagnosis codes for TED, Graves' ophthalmopathy and Hashimoto's orbitopathy. All patient records were de-identified and kept on an encrypted and password-protected device within the Houston Methodist Hospital. This study was approved by the Institutional Review Board (IRB) from Houston Methodist Hospital and conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion criteria

All charts of patients with the diagnosis of TED who presented to the Houston Methodist Hospital, Blanton Eye Institute between January 2016 and January 2017 were reviewed. Patients were included if they had the clinical diagnosis of TED defined by the presence of at least one sign of TED (e.g., lid retraction, lid lag, ophthalmoplegia, proptosis, periorbital oedema), evidence of thyroid autoimmune disease on blood tests (e.g., thyroid function studies and thyroid autoantibodies), and evidence of extraocular muscle enlargement seen on orbital ultrasound or other imaging. All patients had to have had a vitamin D or selenium level at the time of initial evaluation or within 5 months of neuro-ophthalmic evaluation.

Exclusion criteria

Patients without a clinical diagnosis of TED, confirmatory evidence of systemic autoimmune thyroid disease, imaging confirmation of the diagnosis, or vitamin D or selenium levels were excluded. Patients who were taking vitamin D or selenium supplementation prior to evaluation for TED were excluded.

Vitamin D and selenium analysis

Patient charts were reviewed for patient demographics, serum thyroid stimulating hormone, thyroperoxidase antibody, thyroid stimulating immunoglobulin, 25-hydroxy vitamin D, and selenium levels. All serum samples were collected from patients without vitamin D or selenium supplementation at the time of draw. Reference ranges used for vitamin D and selenium levels are 30–-150 ng/mL and 70–150 ug/L, respectively. Vitamin D and selenium laboratory values were collected within 5 months of the measured thyroid laboratory values and none of the patients were on supplementation.

Statistical analysis

Statistical analyses were conducted in Strata Version14 (College Station, TX). The median, interquartile range (25th and 75th), and normality were evaluated for vitamin D and selenium.

Results

Of the 86 patient charts with TED reviewed, 35 patients met inclusion criteria and had serum 25-hydroxyvitamin D levels available. Of these 35 included cases, 25 patients were females and 10 were males. Seven of the 35 patients had levels below 20 ng/mL consistent with vitamin D deficiency, and 11 patients had levels between 20 and 29 ng/mL indicating vitamin D insufficiency. Of the 86 patients, 19 had selenium levels available (6 males and 13 females) all showed normal values (70–150 ng/mL).

Stratification by gender demonstrated a higher incidence of vitamin D deficiency in females (7/25 female patients) compared to males (0/10 male patients), whereas vitamin D insufficiency was more prevalent in males (7/10 in males and 4/25 in female patients). Additionally, TED was more prevalent in females in our study. As for age, we found the highest prevalence of TED in patients over 65.

Discussion

Thyroid eye disease (TED) is an autoimmune disease that predominately affects women, with an annual incidence of 16 women per 100,000 persons in contrast to three men per 100,000.[1] TED is associated with autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis. Similar to our results, both conditions are

more prevalent in females. Graves' disease has an estimated incidence of 30.5 women per 100,000 persons per year compared to 8.0 men per 100,000. The incidence of Hashimoto's thyroiditis has steadily increased from 6.5 cases to 69 cases per 100,000 persons in women.[8]

The association between various autoimmune diseases and low levels of vitamin D has been identified, though a causative relationship has not been established.[3,4] Despite studies demonstrating the association of vitamin D deficiency and autoimmune conditions, evidence of vitamin D supplementation as a treatment remains inconclusive. This, in part, is explained by an inconsistency among studies to define vitamin D deficiency as the causative factor or effect of such diseases. In a prospective study, Simpson et al. demonstrated an association between vitamin D levels and decreased frequency of relapse in multiple sclerosis, an autoimmune disease.[9] However, other studies have shown a lack of evidence concerning vitamin D as a treatment for autoimmune diseases. The role of vitamin D in autoimmune thyroiditis was found to reduce T-cell inflammatory response and modulate circulating thyroid hormone levels via stimulation of the thyrotropin receptor.[3,10] Alhuzaim and Aljohani demonstrated that vitamin D deficient mice were more likely to develop persistent hyperthyroidism compared to controls that received adequate vitamin D.[3] A similar association in humans may support vitamin D supplementation in managing thyroid hormone levels in certain patients.

The National Health and Nutrition Examination Surveys published in 2006, showed two-thirds of the American population had sufficient vitamin D, about one-quarter were at risk of vitamin D inadequacy, and 8% were at risk of vitamin D deficiency. They also found that the risk of deficiency or inadequacy differed by age, sex, and race and ethnicity with groups at lower risk being children, males, non-Hispanic white persons, and pregnant or lactating women. However, Forrest and Stuhldreher reported a 41.6% overall prevalence of vitamin D deficiency in US adults over 65 years of age in a study involving 4495 participants, used for comparison as an age-matched control to our cohort.[11] According to a meta-analysis including 26 studies, a higher prevalence of vitamin D deficiency was found in patients with autoimmune thyroid disease compared to controls.[12] Yasuda et al. demonstrated that the prevalence of vitamin D deficiency in Graves' disease patients (65.4%, n = 26) was higher compared to control subjects (32.4%, n = 46).[6] Another study conducted by Kivity et al. revealed similar results with 92 participants: 72% of autoimmune thyroid disease patients had vitamin D deficiency compared to 30.6% of control patients with vitamin D deficiency.[13] In our study we found, the prevalence of vitamin D deficiency in thyroid eye disease patients to be 20% with the majority of our patients being over 65 years of age. As for selenium, Marcocci et al. demonstrated in a randomized double-blind placebo-controlled trial, the therapeutic benefit of selenium supplementation in TED. In that study, selenium administration significantly improved quality of life, reduced ocular involvement and slowed progression of the disease in patients with mild TED.[14] However, these authors did not measure the levels of selenium prior to giving supplementation. Adequate concentrations of selenium have been linked to a decrease in antithryoperoxidase antibody levels, which is associated with delayed progression of ocular dysfunction and improvement of thyroid function with improved quality of life.[5,14] Without selenium, thyrocyte damage, and eventual fibrosis may occur.[5] Wang et al. demonstrated that thyroglobulin and TSH levels decreased in patients supplemented with selenium compared to the placebo group and that patients showed improved quality of life and delayed progression of TED as well.[15] Khong et al., reported in a study from Australia lower selenium levels in patients with TED compared with Graves' disease without TED.[16] There are currently ongoing trials, GRASS (GRAves' disease Selenium Supplementation) trial and CATALYST (Chronic Autoimmune Thyroiditis Quality of Life Selenium) trial, that are enrolling patients with the purpose of exploring the benefit of addition of selenium to antithyroid drugs in decreasing antithyroid drug treatment failures, faster remission of the disease, and improved quality of life.[17,18] Both of those trials are European, as is most of the literature on selenium role in autoimmune thyroid disease. None of our patients showed selenium deficiency.

The main limitations of our study were a relatively small sample size (n = 35 for vitamin D analysis and n = 19 for selenium analysis), absence of a clinical activity score at presentation, lack of an unaffected control group and absence of long-term follow up data succeeding supplementation. Currently, patients

rarely receive health insurance coverage for selenium testing and this limited the number of included cases. Further study is necessary to determine the role of supplementation in TED and the differential risks for deficiencies as well as the excess of vitamin D and selenium in the American populations.

Conclusion

In our retrospective pilot study, we found 20% prevalence of vitamin D deficiency and no selenium deficiency in TED. Future larger studies will be necessary to confirm the rationale and efficacy of vitamin D or selenium supplementation in TED.

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References

1. Xia N, Ye X, Hu X. Simultaneous induction of Graves' hyperthyroidism and Graves' ophthalmopathy by TSHR genetic immunization in BALB/c mice. *PLoS One*. 2017;12(3):e0174260. doi:10.1371/journal.pone.0174260.
2. Kriegel MA, Manson JE, Costenbader KH. Does vitamin D affect risk of developing autoimmune disease?: a systematic review. *Semin Arthritis Rheum*. 2011;40(6):512–531.e8. doi:10.1016/j.semarthrit.2010.07.009.
3. Alhuzaim ON, Aljohani N. Effect of vitamin D3 on untreated Graves' disease with vitamin D deficiency. *Clin Med Insights Case Rep*. 2014;7:83–85. doi:10.4137/CCRep.S13157.
4. Wawrzyniak S, Mikolajewska E, Kuczko-Piekarska E, Niezgodzinska-Maciejek A, Goch A. Association of vitamin D status and clinical and radiological outcomes in a treated MS population in Poland. *Brain Behav*. 2017;7(2):e00609. doi:10.1002/brb3.609.
5. Ventura M, Melo M, Carrilho F. Selenium and thyroid disease: from pathophysiology to treatment. *Int J Endocrinol*. 2017;2017:1297658. doi:10.1155/2017/1297658.
6. Yasuda T, Okamoto Y, Hamada N. Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. *Endocrine*. 2012;42(3):739–741. doi:10.1007/s12020-012-9679-y.
7. Hu S, Rayman MP. Multiple nutritional factors and the risk of Hashimoto's thyroiditis. *Thyroid*. 2017;27(5):597–610. doi:10.1089/thy.2016.0635.
8. McLeod DS, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012;42(2):252–265. doi:10.1007/s12020-012-9703-2.
9. Simpson S Jr., Taylor B, Blizzard L. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. *Ann Neurol*. 2010;68(2):193–203. doi:10.1002/ana.22043.
10. Borgogni E, Sarchielli E, Sottili M. Elocalcitol inhibits inflammatory responses in human thyroid cells and T cells. *Endocrinology*. 2008;149(7):3626–3634. doi:10.1210/en.2008-0078.
11. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;31(1):48–54. doi:10.1016/j.nutres.2010.12.001.
12. Xu MY, Cao B, Yin J, Wang DF, Chen KL, Lu QB. Vitamin D and Graves' disease: a meta-analysis update. *Nutrients*. 2015;7(5):3813–3827. doi:10.3390/nu7053813.
13. Kivity S, Agmon-Levin N, Zisappl M. Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol*. 2011;8(3):243–247. doi:10.1038/cmi.2010.73.
14. Marcocci C, Kahaly GJ, Krassas GE. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med*. 2011;364(20):1920–1931. doi:10.1056/NEJMoa1012985.
15. Wang L, Wang B, Chen SR. Effect of selenium supplementation on recurrent hyperthyroidism caused by Graves' disease: a prospective pilot study. *Horm Metab Res*. 2016;48(9):559–564. doi:10.1055/s-0042-110491.
16. Khong JJ, Goldstein RF, Sanders KM. Serum selenium status in Graves' disease with and without orbitopathy: a case-control study. *Clin Endocrinol (Oxf)*. 2014;80(6):905–910. doi:10.1111/cen.12392.
17. Winther KH, Watt T, Bjorner JB. The chronic autoimmune thyroiditis quality of life selenium trial (CATALYST): study protocol for a randomized controlled trial. *Trials*. 2014;15:115. doi:10.1186/1745-6215-15-115.
18. Watt T, Cramon P, Bjorner JB. Selenium supplementation for patients with Graves' hyperthyroidism (the GRASS trial): study protocol for a randomized controlled trial. *Trials*. 2013;14:119. doi:10.1186/1745-6215-14-59.