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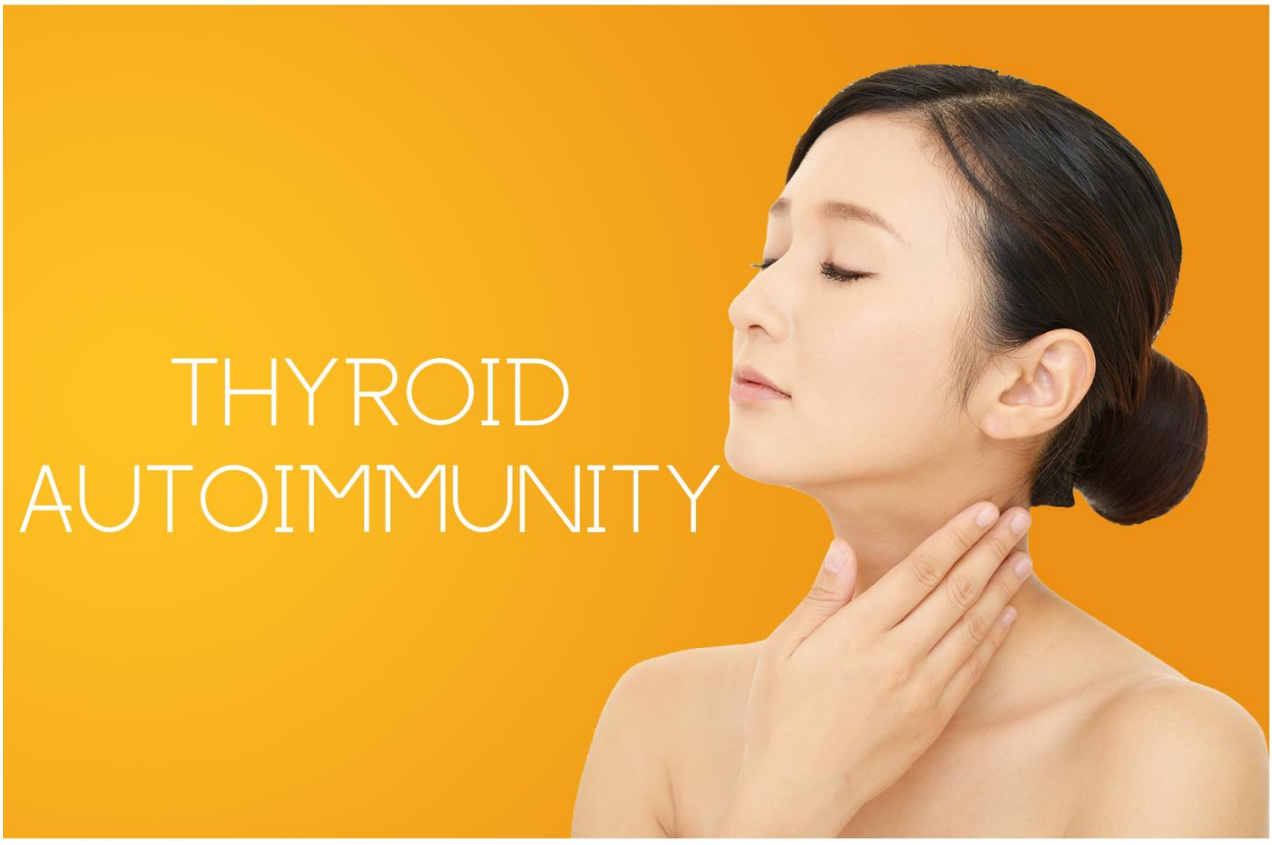

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Content

Introduction

Chronic autoimmune thyroiditis is an auto-immune disorder of the thyroid gland. It can occur in various forms: In Hashimoto's thyroiditis (HT), the commonest form, the body produces thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab). As a consequence of this, thyroid hormone production decreases substantially (thyroid hypofunction or hypothyroidism). Thyroid hypofunction results in weight gain, fatigue, and generally diminished performance, as well as sensitivity to cold, diminished ability to concentrate, and even depressive disorder. Its prevalence depends on age (more frequently appears between 45-55 years), gender (4-10 times more frequent in females than in males), and race (more common in whites than in blacks, hispanics and asians). The rarer Graves' disease is associated with the production of antibodies directed against a signaling molecule on the thyroid cells' surface. This causes the thyroid cells to produce an excessive amount of thyroid hormones (thyroid hyperfunction or hyperthyroidism). In the long run, however, many patients experience thyroid hypofunction as well. Thyroid hyperfunction is associated with symptoms such as sleeplessness, nervousness, hot flashes, rapid heartbeat and hair loss.
It is estimated that one in six women have a predisposition for autoimmune thyroiditis and up to ten per cent of them actually produce autoantibodies. However, it still is not clear which exact reasons and triggers are responsible for the onset of the disease. The literature on thyroid autoimmunity has identified many potential factors for the initiation and progression of autoimmune thyroid diseases. These include genetic susceptibility, environmental factors, some drugs, iodine and selenium, infection, molecular mimics, and immune system defects. Although the exact mechanism of progressive thyroid tissue destruction is not clear, HT is regarded as a disorder of T cell-mediated immunity, caused by an interaction between susceptibility genes and environmental factors. In most cases of patients with HT, lifelong levothyroxine (LT4) substitution, adjusting the dose to achieve normal circulating thyrotropin (TSH) levels, is required.

Autoimmune Thyroid Disease and Fertility

In infertile women, the prevalence of thyroid autoimmunity (TAI) is significantly higher compared to that in parous age-matched women. This is especially the case in women with endometriosis and the polycystic ovarian syndrome. It has been observed that TPO antibodies impair embryo quality (Weghofer et al, 2015, Andrisani et al, 2018) and pregnant women with thyroid autoimmunity have a significantly increased risk for miscarriage compared to women without TAI, even when euthyroidism was present before pregnancy (Poppe et al, 2006).

Pregnancy represents a major challenge for the thyroid gland, contributing to thyroid dysfunction in cases where the thyroid fails or is less able to adapt adequately to pregnancy-related changes. During pregnancy, there is an increased risk for obstetrical and fetal com-

plications (Abaloyich et al, 2002, Casey et al, 2005; Allan et al, 2000; Leung et al, 1993) and later for impaired neuropsychological development in children (Haddow et al, 1999).

Thyroid Autoimmunity and Nutrition

The management of thyroid autoimmunity depends on its clinical manifestations. In most cases of patients with Hashimoto's disease, lifelong levothyroxine substitution is required. The additional role of diet for the management of thyroid autoimmunity is often overlooked.
Beneficial effects have been recorded for a diet that takes into account the special requirements regarding iodine, selenium, iron, vitamin D, magnesium and gluten. In addition to that, certain micronutrients optimizing oocyte quality are helpful for patients with thyroid autoimmunity planning for pregnancy.

Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease.

Rayman MP.

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are examples of autoimmune thyroid disease (AITD), the commonest autoimmune condition. Antibodies to thyroid peroxidase (TPO), the enzyme that catalyses thyroid-hormone production and antibodies to the receptor for the thyroid-stimulating hormone, are characteristic of HT and GD, respectively. It is presently accepted that genetic susceptibility, environmental factors, including nutritional factors and immune disorders contribute to the development of AITD. Aiming to investigate the effect of iodine, iron and selenium in the risk, pathogenesis and treatment of thyroid disease, PubMed and the Cochrane Library were searched for relevant publications to provide a narrative review. Iodine: chronic exposure to excess iodine intake induces autoimmune thyroiditis, partly because highly-iodinated thyroglobulin (Tg) is more immunogenic. The recent introduction of universal salt iodisation can have a similar, although transient, effect. Iron: iron deficiency impairs thyroid metabolism. TPO is a haem enzyme that becomes active only after binding haem. AITD patients are frequently iron-deficient since autoimmune gastritis, which reduces iron absorption and coeliac disease which causes iron loss, are frequent comorbidities. In two-thirds of women with persistent symptoms of hypothyroidism despite appropriate levothyroxine therapy, restoration of serum ferritin above 100 µg/l ameliorated symptoms. Selenium: selenoproteins are essential to thyroid action. In particular, the glutathione peroxidases remove excessive hydrogen peroxide produced there for the iodination of Tg to form thyroidhormones. There is evidence from observational studies and randomised controlled trials that selenium, probably as selenoproteins, can reduce TPO-antibody concentration, hypothyroidism and postpartum thyroiditis. Appropriate status of iodine, iron and selenium is crucial to thyroid health.

Proc Nutr Soc. 2019 Feb;78(1):34-44. doi: 10.1017/S0029665118001192. Epub 2018 Sep 13.

Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease.

Wiersinga WM.

Genetic factors contribute for about 70% to 80% and environmental factors for about 20% to 30% to the pathogenesis of autoimmune thyroid disease (AITD). Relatives of AITD patients carry a risk to contract AITD themselves. The 5-year risk can be quantified by the so-called Thyroid Events Amsterdam-score, based on serum thyroid-stimulating hormone, thyroid peroxidase (TPO)-antibodies and family history. Subjects at risk may ask what they can do to pre-

vent development of AITD. This review summarizes what is known about modulation of exposure to environmental factors in terms of AITD prevention. To stop smoking decreases the risk on Graves disease but increases the risk on Hashimoto disease. Moderate alcohol intake provides some protection against both Graves and Hashimoto disease. Low selenium intake is associated with a higher prevalence of thyroid autoimmunity, but evidence that selenium supplementation may lower TPO antibodies and prevent subclinical hypothyroidism remains inconclusive. Low serum vitamin D levels are associated with a higher prevalence of TPO antibodies, but intervention studies with extra vitamin D have not been done yet. Stress may provoke Graves hyperthyroidism but not Hashimoto thyroiditis. Estrogen use have been linked to a lower prevalence of Graves disease. The postpartum period is associated with an increased risk of AITD. Taking together, preventive interventions to diminish the risk of AITD are few, not always feasible, and probably of limited efficacy.

Endocrinol Metab (Seoul). 2016 Jun;31(2):213-22. doi: 10.3803/EnM.2016.31.2.213. Epub 2016 May 13.

Influence of diet on the induction of experimental autoimmune thyroid disease.

Bhatia SK, Rose NR, Schofield B, Lafond-Walker A, Kuppers RC.

Immunization of CBA/J mice with thryoglobulin (Tg) emulsified in complete Freund's adjuvant induces experimental thyroiditis (EAT), a well-characterized model of Hashimoto's disease. Recent studies have suggested that dietary factors play a role in the modulation of the immune response and that diet can have a profound effect on the induction of autoimmune diseases. In this study, we examined the influence of diet on autoimmune thyroiditis in mice. EAT was induced in mice fed ad libitum one of the three diets, a standard maintenance chow (Agway H1000), Purina 5020 Breeding Chow, and Purina 5010 Autoclavable (unautoclaved) Diet. Tg-immunized mice fed the Agway 1000 diet were found to be resistant to the development of autoimmune thyroid disease, with only 4 out of 25 mice developing mild thyroiditis. In contrast, 16 out of 25 mice fed the Purina 5010 diet developed moderate to severe thyroiditis. Mice fed the 5020 diet were partly susceptible: 7 out of 25 developed a mild to moderate thyroiditis. Histologic examination of thyroid glands of diseased mice fed the 5010 and 5020 diets showed marked lymphocytic infiltration with destruction of follicles, compared with mice fed the Agway diet, the latter showing only mild infiltration with preservation of thyroid follicles. Titers of antibody to Tg did not differ among the groups, and there was no significant difference in the IgG isotype subclass usage. The results demonstrate that diet can markedly affect the severity of autoimmune disease in the EAT model. In contrast, diet has little effect on the humoral autoimmune response in this system. These results implicate diet as a factor in the severity of cell-mediated autoimmune destruction and suggest that dietary modification could decrease pathology in some forms of autoimmune disease.

Proc Soc Exp Biol Med. 1996 Dec;213(3):294-300.

Autoimmune Thyroiditis with Hypothyroidism Induced by Sugar Substitutes.

Sachmechi I, Khalid A, Awan SI, Malik ZR, Sharifzadeh M.

The use of sugar substitutes (artificial sweeteners or non-nutritive sweeteners) has increased dramatically in the past few decades. They have been used as a substitute for sucrose (table sugar) in various diet-related disorders. Their excessive use has been linked to hyperphagia and obesity-related disorders. Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is a disease that involves the immune-mediated destruction of the thyroid gland, gradually leading to its failure. Animal studies report that artificial sweeteners affect the immune system. Moreover, animal studies show that sucralose diminishes the thyroid axis activity. We are presenting

the case of a 52-year-old female with autoimmune thyroiditis with hypothyroidism (Hashimoto's thyroiditis) induced by an excessive intake of beverages containing non-nutritive sweeteners. She was ruled out for any other autoimmune disorder. The association between Hashimoto's thyroiditis and the excessive consumption of sugar substitutes is shown by the quick return of thyroid stimulating hormone and antibody levels to normal after eliminating the use of sugar substitutes. Thus, it suggests that the sugar substitutes were the culprit in the development of Hashimoto's thyroiditis in our patient.

Nutriti Cureus. 2018 Sep 7;10(9):e3268. doi: 10.7759/cureus.3268.

Changes in Glucose-Lipid Metabolism, Insulin Resistance, and Inflammatory Factors in Patients With Autoimmune Thyroid Disease

Yi Lei, Jun Yang, Hua Li, Haihua Zhong, Qin Wan

Background: Autoimmune thyroid disease (AITD) is a common organ-specific autoimmune disorder, and genetic, environmental, and endogenous factors are responsible for initiation of thyroid autoimmunity. Some AITD patients suffer from a certain degree of glucose-lipid metabolism disorder. This study aims to explore the changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with AITD.

Methods: A total of 91 patients with Hashimoto's thyroiditis were retrospectively analyzed and divided into hypothyroidism group (n = 42) and normal thyroid group (n = 49), while 50 healthy people were selected as control group. The changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in each group were compared, and their correlations with the thyroid function were analyzed.

Results: The levels of serum interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), IL-12, IL-10, (FINS), and homeostasis model assessment of insulin resistance (HOMA-IR) were gradually declined in sequence of hypothyroidism group, normal thyroid group, and control group ($P < 0.05$). In hypothyroidism group, the levels of serum-free triiodothyronine (FT3), free thyroxine (FT4), (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) were significantly lower than those in normal thyroid group ($P < 0.05$), while the level of serum thyroid stimulating hormone (TSH) was significantly higher than that in normal thyroid group ($P < 0.05$). However, the fasting blood glucose and 2-hour postprandial blood glucose levels had no statistically significant differences among the three groups ($P > 0.05$).

Conclusion: Autoimmune thyroid disease patients are prone to fat metabolism disorder, and the serum thyroid hormone level has a close correlation with blood lipid metabolism, insulin metabolism, and inflammatory factors.

J Clin Lab Anal. 2019 Sep;33(7):e22929.

A concise review of Hashimoto thyroiditis (HT) and the importance of iodine, selenium, vitamin D and gluten on the autoimmunity and dietary management of HT patients. Points that need more investigation.

Liontiris MI, Mazokopakis EE.

Hashimoto's thyroiditis (HT) is a chronic autoimmune thyroid disease caused by an interaction between genetic factors and environmental conditions, both of which are yet to be fully understood. The management of HT depends on its clinical manifestations, commonly including diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism and permanent hypothyroidism. However, in most cases of patients with HT, lifelong levothyroxine substitution is required. The additional role of diet for the management of HT is usually overlooked. A literature search regarding the importance and the influence of iodine, selenium, vitamin D and gluten on HT was conducted. In HT careful supplementation of possible deficiencies is recommended for the dietary management of these patients. The use of a diet low in gluten among HT patients with or without celiac disease (CD) is discussed.

Hell J Nucl Med. 2017 Jan-Apr;20(1):51-56. doi: 10.1967/s002449910507. Epub 2017 Mar 20.

Excess iodine promotes apoptosis of thyroid follicular epithelial cells by inducing autophagy suppression and is associated with Hashimoto thyroiditis disease.

Xu C, Wu F, Mao C, Wang X, Zheng T, Bu L, Mou X, Zhou Y, Yuan G, Wang S, Xiao Y.

The incidence of the autoimmune thyroid disease Hashimoto thyroiditis (HT) has increased in recent years, and increasing evidence supports the contribution of excess iodine intake to thyroid disease. In this study, we examined the status of autophagy and apoptosis in thyroid tissues obtained from patients with HT, and we determined the effects of excessive iodine on the autophagy and apoptosis of thyroid follicular cells (TFCs) in an attempt to elucidate the effects of excess iodine on HT development. Our results showed decreases in the autophagy-related protein LC3B-II, and increases in caspase-3 were observed in thyroid tissues from HT patients. Interestingly, the suppression of autophagy activity in TFCs was induced by excess iodine in vitro, and this process is mediated through transforming growth factor-β1 downregulation and activation of the Akt/mTOR signaling pathway. In addition, excess iodine induced autophagy suppression and enhanced reactive oxygen species (ROS) production and apoptosis of TFCs, which could be rescued by the activation of autophagy. Taken together, our results demonstrated that excess iodine contributed to autophagy suppression and apoptosis of TFCs, which could be important factors predisposing to increased risk of HT development.

J Autoimmun. 2016 Dec;75:50-57. doi: 10.1016/j.jaut.2016.07.008. Epub 2016 Jul 21.

The Role of Iodine and Selenium in Autoimmune Thyroiditis.

Duntas LH.

Iodine and selenium (Se) are both essential elements to thyroid hormone economy, while they represent key players in the development of autoimmune thyroiditis. Chronic

high iodine intake has been associated in various studies with increased frequency of autoimmune thyroiditis. In susceptible individuals, iodine excess increases intra-thyroid infiltrating Th17 cells and inhibits T regulatory (TREG) cells development, while it triggers an abnormal expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in thyrocytes, thus inducing apoptosis and parenchymal destruction. As was shown in a mouse model, high iodine supply leads to changes in the immunogenicity of the thyroglobulin molecule, upregulation of vascular intercellular adhesion molecule-1 (ICAM-1), and reactive oxygen species (ROS) generation in the thyrocytes. Serum Se levels were found decreased in Hashimoto thyroiditis and especially in Graves' disease as well as in thyroid-associated ophthalmopathy patients, the levels being related to the pathogenesis and outcome. Selenium is strongly involved, via the variable selenoproteins, in antioxidant, redox, and anti-inflammatory processes. Selenium enhances CD4+/CD25 FOXP3 and T regulatory cells activity while suppressing cytokine secretion, thus preventing apoptosis of the follicular cells and providing protection from thyroiditis. Selenium supplementation may be useful in autoimmune thyroid diseases, though, while usually well-tolerated, it should not be universally recommended, and it is also likely to be helpful for those with low Se status and autoimmunity. Broadly speaking, the achievement and maintenance of "selenostasis" as well as adequate urinary iodine excretion are mandatory to control disease, while, putatively, they may additionally be critical to preventing disease

Horm Metab Res. 2015 Sep;47(10):721-6. doi: 10.1055/s-0035-1559631. Epub 2015 Sep 11.

Selenium and Iodine in Autoimmune Thyroiditis

Edoardo Guastamacchia, Vito Angelo Giagulli, Brunella Licchelli, Vincenzo Triggiani

Selenium and iodine are essential for thyroid hormone synthesis and function. Selenium, in form of selenocysteine, is found either in the catalytic center of enzymes involved in the protection of the thyroid gland from free radicals originating during thyroid hormone synthesis, and in three different iodothyronine deiodinases catalyzing the activation and the inactivation of thyroid hormones. Iodine is an essential constituent of thyroid hormones and its deficiency causes different disorders that include goiter, hypothyroidism, reduced fertility and alteration in growth, physical and neurological development. These two micronutrients could be involved in the pathogenesis of autoimmune thyroid diseases, a spectrum of pathological conditions including Hashimoto's thryoiditis, post-partum thyroiditis, the so-called painless thyroiditis, Graves' disease and Graves' ophtalmopathy. Aim of this paper is to review the role played by selenium and iodine in autoimmune thyroiditis.

Endocr Metab Immune Disord Drug Targets. 2015;15(4):288-92.

Iodine excess.

Bürgi H.

Several mechanisms are involved in the maintenance of normal thyroid hormone secretion, even when iodine intake exceeds physiologic needs by a factor of 100. The sodium-iodide symporter system contributes most to this stability. Faced with an iodine excess, it throttles the transport of iodide into the thyroid cells, the rate-limiting step of hormone synthesis. Even before the iodine symporter reacts, a sudden iodine overload paradoxically blocks the second step of hormone synthesis, the organification of iodide. This so-called Wolff-Chaikoff effect requires a high (>or=10(-3) molar) intracellular concentration of iodide. The block does not last long, because after a while the sodium-iodide symporter shuts down; this allows intracellu-

lar iodide to drop below 10(-3) molar and the near-normal secretion to resume. In some susceptible individuals (e.g., after radio-iodine treatment of Graves' disease or in autoimmune thyroiditis), the sodium-iodide symporter fails to shut down, the intracellular concentration of iodide remains high and chronic hypothyroidism ensues. To complicate matters, iodine excess may also cause hyperthyroidism. The current explanation is that this happens in persons with goitres, for example, after long-standing iodine deficiency. These goitres may contain nodules carrying a somatic mutation that confers a 'constitutive' activation of the TSH receptor. Being no more under pituitary control, these nodules overproduce thyroid hormone and cause iodine-induced hyperthyroidism, when they are presented with sufficient iodine. These autonomous nodules gradually disappear from the population after iodine deficiency has been properly corrected. More recent studies suggest that chronic high iodine intake furthers classical thyroid autoimmunity (hypothyroidism and thyroiditis) and that iodine-induced hyperthyroidism may also have an autoimmune pathogenesis.

Best Pract Res Clin Endocrinol Metab. 2010 Feb;24(1):107-15. doi: 10.1016/j.beem.2009.08.010.

Selenium in Thyroid Autoimmunity

Selenium supplementation in patients with subclinical hypothyroidism affected by autoimmune thyroiditis: Results of the SETI study.

Pirola I, Rotondi M, Cristiano A, Maffezzoni F, Pasquali D, Marini F, Coperchini F, Paganelli M, Apostoli P, Chiovato L, Ferlin A, Cappelli C.

OBJECTIVE:
The purpose of this prospective study was to assess the effects of selenium supplementation on TSH and interferon-γ inducible chemokines (CXCL9, CXCL10 and CXCL11) levels in patients with subclinical hypothyroidism due to Hashimoto's thyroiditis.

PATIENTS AND METHODS:
Patients with subclinical hypothyroidism due to Hashimoto thyroiditis were prospectively enrolled in the SETI study. They received 83mcg of selenomethionine/day orally in a soft gel capsule for 4 months with water after a meal. No further treatment was given. All patients were measured thyroid hormone, TPOAb, CXCL9, CXCL10, CXCL11, iodine, and selenium levels at baseline and at study end.

RESULTS:
50 patients (43/7 female/male, median age 43.9±11.8 years) were enrolled, of which five withdrew from the study. At the end of the study, euthyroidism was restored in 22/45 (48.9%) participants (responders), while 23 patients remained hypothyroid (non-responders). There were no significant changes in TPOAb, CXCL9, CXCL10, CXCL11, and iodine levels from baseline to the end of the study in both responders and non-responders. TSH levels were re-tested six months after selenomethionine withdrawal: 83.3% of responding patients remained euthyroid, while only 14.2% of non-responders became euthyroid.

CONCLUSIONS:
The SETI study shows that short-course supplementation with selenomethionine is associated to a normalization of serum TSH levels which is maintained 6 months after selenium withdrawal in 50% of patients with subclinical hypothyroidism due to chronic autoimmune thyroiditis. This TSH-lowering effect of selenium supplementation is unlikely to be related to changes in humoral markers of autoimmunity and/or circulating CXCL9.

Endocrinol Diabetes Nutr. 2020 Jan;67(1):28-35. doi: 10.1016/j.endinu.2019.03.018. Epub 2019 Jun 10.

Multiple Nutritional Factors and Thyroid Disease, With Particular Reference to Autoimmune Thyroid Disease

Margaret P Rayman

Hashimoto's thyroiditis (HT) and Graves' disease (GD) are examples of autoimmune thyroid disease (AITD), the commonest autoimmune condition. Antibodies to thyroid peroxidase (TPO), the enzyme that catalyses thyroid-hormone production and antibodies to the receptor for the thyroid-stimulating hormone, are characteristic of HT and GD, respectively. It is presently accepted that genetic susceptibility, environmental factors, including nutritional factors and immune disorders contribute to the development of AITD. Aiming to investigate the effect of iodine, iron and selenium in the risk, pathogenesis and treatment of thyroid disease, PubMed and the Cochrane Library were searched for relevant publications to provide a narrative review. Iodine: chronic exposure to excess iodine intake induces autoimmune thyroiditis, partly because highly-iodinated thyroglobulin (Tg) is more immunogenic. The recent introduction of universal salt iodisation can have a similar, although transient, effect. Iron: iron deficiency impairs thyroid metabolism. TPO is a haem enzyme that becomes active only after binding haem. AITD patients are frequently iron-deficient since autoimmune gastritis, which reduces iron absorption and coeliac disease which causes iron loss, are frequent co-morbidities. In two-thirds of women with persistent symptoms of hypothyroidism despite appropriate levothyroxine therapy, restoration of serum ferritin above 100 µg/l ameliorated symptoms. Selenium: selenoproteins are essential to thyroid action. In particular, the glutathione peroxidases remove excessive hydrogen peroxide produced there for the iodination of Tg to form thyroid hormones. There is evidence from observational studies and randomised controlled trials that selenium, probably as selenoproteins, can reduce TPO-antibody concentration, hypothyroidism and postpartum thyroiditis. Appropriate status of iodine, iron and selenium is crucial to thyroid health.

Proc Nutr Soc. 2019 Feb;78(1):34-44.doi: 10.1017/S0029665118001192. Epub 2018 Sep 13.

A Pilot Study on the Beneficial Effects of Additional Selenium Supplementation to Methimazole for Treating Patients With Graves' Disease

Bin Xu , Di Wu, Hong Ying, Ying Zhang

Background/aim: The aim of this study was to assess the effect of a combination use of methimazole (MMI) and selenium (Se) in the treatment of Graves' disease (GD).

Materials and methods: A total of 103 newly diagnosed hyperthyroidism patients were randomized to MMI and MMI + Se combination groups. After treatment for 6 months, the levels of triiodothyronine (FT3), free thyroxine (FT4), thyrotropin receptor antibody (TRAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb) were observed. An in vitro culture model of thyroid cells was established and the protein expression and mRNA levels of TRAb, TPOAb, and TGAb were determined by western blot and RT-PCR.

Results: A significant decrease in the levels of FT3, FT4, TRAb, TPOAb, and TGAb were observed in both groups along with a marked increase in TSH levels. Furthermore, the in vitro experiments showed that the protein expression and mRNA levels of TRAb, TPOAb, and TGAb decreased significantly. Also, compared to the MMI group, there was a greater improvement of these indices in the MMI + Se group.

Conclusion: We suggest that the combined use of MMI and Se could improve the thyroid activity in patients, which may provide an effective therapy for the treatment of GD in clinical settings.

Turk J Med Sci. 2019 Jun 18;49(3):715-722. doi: 10.3906/sag-1808-67.

Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis.

Wichman J, Winther KH, Bonnema SJ, Hegedüs L.

BACKGROUND:
Selenium supplementation may decrease circulating thyroid autoantibodies in patients with chronic autoimmune thyroiditis (AIT), but the available trials are heterogenous. This study expands and critically reappraises the knowledge on this topic.

METHODS:
A literature search identified 3366 records. Controlled trials in adults (≥18 years of age) with AIT, comparing selenium with or without levothyroxine (LT4), versus placebo and/or LT4, were eligible. Assessed outcomes were serum thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) autoantibody levels, and immunomodulatory effects. After screening and full-text assessment, 16 controlled trials were included in the systematic review. Random-effects meta-analyses in weighted mean difference (WMD) were performed for 3, 6, and 12 months of supplementation in two different populations: one receiving LT4 therapy and one newly diagnosed and LT4-untreated. Heterogeneity was estimated using I2, and quality of evidence was assessed per outcome, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

RESULTS:
In LT4-treated populations, the selenium group had significantly lower TPOAb levels after three months (seven studies: WMD = -271 [confidence interval (CI) -366 to -175]; $p < 0.0001$; I2 = 45.4%), which was consistent at six months (three studies) and 12 months (one study). TgAb decreased at 12 months, but not at three or six months. In LT4-untreated populations, the selenium group showed a decrease in TPOAb levels after three months (three studies: WMD = -512 [CI -626 to -398]; $p < 0.0001$, I2 = 0.0%), but not after 6 or 12 months. TgAb decreased at 3 months, but not at 6 or 12 months. Quality of evidence was generally assessed as low. Study participants receiving selenium had a significantly higher risk than controls of reporting adverse effects ($p = 0.036$).

CONCLUSIONS:
Selenium supplementation reduced serum TPOAb levels after 3, 6, and 12 months in an LT4-treated AIT population, and after three months in an untreated AIT population. Whether these effects correlate with clinically relevant measures remains to be demonstrated.

Thyroid. 2016 Dec;26(12):1681-1692. Epub 2016 Nov 2.

Selenium supplementation for autoimmune thyroiditis: a systematic review and meta-analysis.

Fan Y, Xu S, Zhang H, Cao W, Wang K, Chen G, Di H, Cao M, Liu C.

Many studies have reported that selenium (Se) has a close relationship with autoimmune thyroiditis (AIT). The therapeutic effect of Se supplementation in AIT treatment remains unclear.

The objective of the present study was to determine the efficacy of Se supplementation for the treatment of AIT. A structured literature search was undertaken to identify all randomized controlled trials conducted in patients with AIT receiving Se supplementation or placebo. Nine studies enrolling a total of 787 patients were included. The results showed that Se supplementation with duration 6 months significantly dropped the TPOAb titers but did not decrease the TgAb titers. Patients assigned to Se supplementation for 12-month duration showed significantly lower TPOAb titers and TgAb titers. Patients after Se supplementation had a higher chance to improve the mood or well-being compared with controls. Se supplementation is associated with a significant decrease in TPOAb titers at 6 and 12 months; meanwhile, the TgAb titers can be dropped at 12 months. After Se supplementation treatment, patients had a higher chance to improve the mood without significant adverse events.

Int J Endocrinol. 2014;2014:904573. doi: 10.1155/2014/904573. Epub 2014 Dec 11.

Trace element levels in Hashimoto thyroiditis patients with subclinical hypothyroidism.

Erdal M, Sahin M, Hasimi A, Uckaya G, Kutlu M, Saglam K.

The present study was conducted to evaluate the serum copper, zinc, magnesium, and selenium levels in patients with subclinical hypothyroidism in the iodine-rich region of Ankara, Turkey. The effects of hormone replacement therapy on these elements were also studied in these patients. Basal levels of selenium and iron in patients were significantly lower than control group (67.7 +/- 10.4 vs. 83.7 +/- 17.3 microg/dl, p = 0.02; 55.7 +/- 38 vs 275.7 +/- 24, P = 0.03 microg/dl). Serum magnesium levels were significantly higher in patient group (2.16 +/- 0.31 vs 1.95 +/- 0.13 mg/dl, P < 0.0001). There was a correlation between selenium levels with hsCRP (r = -0.408, p = 0.007). HsCRP levels in patients with selenium levels <80 microg/l (n = 31) was significantly higher than hsCRP levels in patients with selenium levels >80 microg/l (n = 12; 1.99 +/- 1.0; 1.02 +/- 0.9, p = 0.014). None of these biochemical risk factors and trace elements have changed after euthyroidism in patients with SH when compared to pretreatment levels. Selenium deficiency may contribute to cardiovascular disease risk in these patients

Biol Trace Elem Res. 2008 Summer;123(1-3):1-7. doi: 10.1007/s12011-008-8117-8. Epub 2008 Mar 6.

Selenium and the Thyroid.

Köhrle J.

PURPOSE OF REVIEW:

This article provides an update on the role of the essential trace element selenium and its interaction with the other trace elements iodine and iron that together contribute to adequate thyroid hormone status. Synthesis, secretion, metabolism and action of thyroid hormone in target tissues depend on a balanced nutritional availability or supplementation of these elements. Selenium status is altered in benign and malignant thyroid diseases and various selenium compounds have been used to prevent or treat widespread diseases such as goiter, autoimmune thyroid disease or thyroid cancer.

RECENT FINDINGS:

Several studies, most with still too low numbers of cases, indicate that selenium administration in both autoimmune thyroiditis (Hashimoto thyroiditis) and mild Graves' disease improves clinical scores and well-being of patients and reduces thyroperoxidase antibody titers. However, published results are still conflicting depending on basal selenium status, dose, time and form of selenium used for intervention. Evidence for sex-specific selenium action, lack of beneficial effects in pregnancy and contribution of genetic polymorphisms (selenoprotein S) has been presented.

SUMMARY:
Adequate nutritional supply of selenium that saturates expression of circulating selenoprotein P, together with optimal iodine and iron intake, is required for a healthy and functional thyroid during development, adolescence, adulthood and aging.

Curr Opin Endocrinol Diabetes Obes. 2015 Oct;22(5):392-401. doi: 10.1097/MED.0000000000000190.

Thyroid Autoimmunity and Gluten

Celiac disease and endocrine autoimmunity - the genetic link.

Kahaly GJ, Frommer L, Schuppan D.

Celiac disease is a small intestinal inflammatory disease with autoimmune features that is triggered and maintained by the ingestion of the storage proteins (gluten) of wheat, barley and rye. The prevalence of celiac disease is increased in patients with monoglandular and/or polyglandular autoimmunity and their relatives. Between 10 and 30% of patients with celiac disease are thyroid and/or type 1 diabetes antibody positive, while around 5 to 7% of patients with autoimmune thyroid disease and/or type 1 diabetes are IgA anti-tissue transglutaminase antibody positive. The close relationship between celiac disease and endocrine autoimmunity is largely explained by sharing a common genetic background. The HLA antigens DQ2 (DQA1*0501-DQB1*0201) and/or DQ8 (DQA1*0301-DQB1*0302), that are tightly linked to DR3 and DR4, respectively, are the major common genetic predisposition. Moreover, functional single nucleotide polymorphisms of various genes that are involved in immune regulation have been identified as "overlap" susceptibility genes for both celiac disease and monoglandular or polyglandular autoimmunity. While plausible, it remains to be established how far a gluten free diet may prevent or ameliorate glandular autoimmunity. In conclusion, all patients with celiac disease should be screened for type 1 diabetes and/or autoimmune thyroid disease. Conversely, patients with the above autoimmune endocrine disorders should be also screened for celiac disease.

Autoimmun Rev. 2018 Dec;17(12):1169-1175. doi: 10.1016/j.autrev.2018.05.013. Epub 2018 Oct 12.

Celiac Disease and Glandular Autoimmunity.

Kahaly GJ, Frommer L, Schuppan D.

Celiac disease is a small intestinal inflammatory disease with autoimmune features that is triggered and maintained by the ingestion of the storage proteins (gluten) of wheat, barley, and rye. Prevalence of celiac disease is increased in patients with mono- and/or polyglandular autoimmunity and their relatives. We have reviewed the current and pertinent literature that addresses the close association between celiac disease and endocrine autoimmunity. The close relationship between celiac disease and glandular autoimmunity can be largely explained by sharing of a common genetic background. Further, between 10 and 30% of patients with celiac disease are thyroid and/or type 1 diabetes antibody positive, while around 5⁻7% of patients with autoimmune thyroid disease, type 1 diabetes, and/or polyglandular autoimmunity are IgA anti-tissue transglutaminase antibody positive. While a gluten free diet does not reverse glandular autoimmunity, its early institution may delay or even prevent its first manifestation. In conclusion, this brief review highlighting the close association between celiac disease and both monoglandular and polyglandular autoimmunity, aims to underline the need for prospective studies to establish whether an early diagnosis of celiac disease and a prompt gluten-free diet may positively impact the evolution and manifestation of glandular autoimmunity.

Nutrients. 2018 Jun 25;10(7). pii: E814. doi: 10.3390/nu10070814.

The Effect of Gluten-Free Diet on Thyroid Autoimmunity in Drug-Naïve Women with Hashimoto's Thyroiditis: A Pilot Study.

Krysiak R, Szkróbka W, Okopień B.

BACKGROUND:
Autoimmune thyroid disease is often accompanied by celiac disease.

OBJECTIVE:
The purpose of this study was to investigate whether a gluten-free diet affects thyroid autoimmunity, hypothalamic-pituitary-thyroid axis activity and thyroid function tests in women with Hashimoto's thyroiditis and incidentally found positive anti-tissue transglutaminase antibodies.

METHODS:
The study included 34 women with autoimmune thyroiditis divided into two group. The patients belonging to the first one (group A, n=16) complied with the gluten-free diet for 6 months, while the remaining patients (group B, n=18) remained without any dietary treatment. Serum titers of thyroid peroxidase and thyroglobulin antibodies, as well as serum levels of thyrotropin, free thyroid hormones and 25-hydroxyvitamin D were measured at the beginning of the study and 6 months later. Based on thyrotropin and free thyroid hormone levels, Jostel's thyrotropin index, the SPINA-GT index and the SPINA-GD index were calculated.

RESULTS:
All patients completed the study protocol. In group B, serum thyrotropin and free thyroid hormones levels, serum 25-hydroxyvitamin D levels as well as the calculated indices remained at the similar levels. The gluten-free diet reduced thyroid antibody titers, as well as slightly increased 25-hydroxyvitamin D levels and the SPINA-GT index. In group A, the impact on TPOAb and TgAb titers correlated with the changes in the SPINA-GT index, whereas the impact on TPOAb with the changes in 25-hydroxyvitamin D levels.

CONCLUSIONS:
The obtained results suggest that the gluten-free diet may bring clinical benefits to women with autoimmune thyroid disease.

Exp Clin Endocrinol Diabetes. 2018 Jul 30. doi: 10.1055/a-0653-7108. [Epub ahead of print]

Thyroid Autoimmunity, Inflammation and Oxidative Stress

Increased Interleukin-23 in Hashimoto's Thyroiditis Disease Induces Autophagy Suppression and Reactive Oxygen Species Accumulation.

Zheng T, Xu C, Mao C, Mou X, Wu F, Wang X, Bu L, Zhou Y, Luo X, Lu Q1, Liu H, Yuan G, Wang S, Chen D, Xiao Y.

Hashimoto's thyroiditis (HT) represents the most common organ-specific autoimmune disease. Inflammatory factors and reactive oxygen species (ROS) play detrimental roles during the pathogenesis of HT. In this study, we found that thyroid follicular cells (TFCs) from HT patients expressed an elevated level of interleukin-23 (IL-23), which contributed to autophagy suppression and ROS accumulation. Additionally, IL-23-induced autophagy suppression and ROS accumulation in human TFCs was attributed to AKT/mTOR/NF-κB signaling pathway activation. Inhibition of either IL-23 by a specific neutralization antibody, or mTOR by rapamycin, or NF-κB by IKK-16, significantly reversed the autophagy suppression and ROS accumulation. These results demonstrate a key role for IL-23 in HT pathogenesis and provide a potential therapeutic strategy against IL-23 or its signaling pathway in HT.

Front Immunol. 2018 Jan 29;9:96. doi: 10.3389/fimmu.2018.00096. eCollection 2018.

Dietary Factors Associated with Plasma Thyroid Peroxidase and Thyroglobulin Antibodies.

Matana A, Torlak V, Brdar D, Popović M, Lozić B, Barbalić M, Perica VB, Punda A, Polašek O9, Hayward C, Zemunik T.

The knowledge about dietary habits and their influence in the development of autoimmune thyroid disease is insufficient. The aim of this study was to analyse the association of dietary factors and plasma thyroid peroxidase antibodies (TPO-Ab) and/or thyroglobulin antibodies (Tg-Ab). The study enrolled 1887 participants originating from the South Croatia. Participants with elevated plasma TPO-Ab and/or Tg-Ab were defined as cases (n = 462) and those with TPO-Ab and/or Tg-Ab within referent values were defined as controls (n = 1425). Dietary intake was evaluated according to a food frequency questionnaire containing 58 food items. Principal component analysis was used to group food items into dietary groups. We used logistic regression analysis to examine dietary groups associated with positive plasma TPO-Ab and/or Tg-Ab. The results indicate that the dietary group with frequent consumption of animal fats and butter is associated with positive plasma TPO-Ab and/or Tg-Ab ($p = 0.01$). The dietary group with frequent consumption of vegetables as well as the dietary group with high consumption of dried fruit, nuts, and muesli are associated with negative findings of TPO-Ab and/or Tg-Ab ($p = 0.048$ and $p = 0.02$, respectively). We showed that the anti-inflammatory dietary groups are associated with the negative findings of plasma TPO-Ab and/or Tg-Ab.

Nutrients. 2017 Oct 28;9(11). pii: E1186. doi: 10.3390/nu9111186.

The relationship between oxidative stress and autoimmunity in Hashimoto's thyroiditis.

Ates I, Yilmaz FM, Altay M, Yilmaz N, Berker D, Güler S.

OBJECTIVE:

We have aimed to study the relation between Hashimoto's thyroiditis (HT) and thyroid autoantibodies and oxidative stress parameters in euthyroid, subclinical and overt hypothyroid stages.

DESIGN AND METHODS:

A total of 124 patients were included in the study; 93 of whom were newly diagnosed with HT (31 patients in each of the euthyroid, subclinical hypothyroid and overt hypothyroid subgroups), aged over 18 and had not received any prior treatment and 31 of whom were healthy volunteers.

RESULTS:

Total oxidant status (TOS) and oxidative stress index (OSI) levels were higher, and total antioxidant status (TAS) and total thiol and arylesterase levels were lower in the overt hypothyroid group compared to other groups. TOS and OSI levels increased, and TAS levels decreased significantly in each phase from euthyroid, subclinical hypothyroid, to overt hypothyroid subgroups among HT patients. There was a negative correlation between TAS, log (paraoxonase1) and paraoxonase1/HDL and anti-thyroid peroxidase and a negative correlation between anti-thyroglobulin and total thiol. It was also determined that overt hypothroidism was an individual predictor that effects all of the oxidative stress parameters, but not total thiol, levels.

CONCLUSION:

Our results suggest that oxidative stress increases continuously during the development of subclinical hypothyroidism and overt hypothyroidism in patients with HT. To determine whether this is a cause or result, randomized, controlled trials that study the effect of antioxidant treatment on the development of overt hypothyroidism and its consequences, e.g., increase in total cholesterol levels, may be performed in euthyroid and/or subclinical hypothyroid patients with HT.

Eur J Endocrinol. 2015 Dec;173(6):791-9. doi: 10.1530/EJE-15-0617. Epub 2015 Sep 4.

The effect of oxidative stress on the progression of Hashimoto's thyroiditis.

Ates I, Arikan MF, Altay M, Yilmaz FM, Yilmaz N, Berker D, Guler S.

OBJECTIVE:

We aimed to investigate the effects of oxidative stress in the pathogenesis and progression of Hashimoto's thyroiditis (HT).

METHODS:

Forty euthyroid and 40 subclinical hypothyroid patients older than 18 years and not yet had received treatment were enrolled in the study.

RESULTS:

In the 9 months follow-up, 14 of the HT patients developed overt hypothyroidism. The mean total oxidant status (TOS) and oxidative stress index (OSI) were higher in patients who developed overt hypothyroidism than those who did not ($p < .001$). And no significant difference was found between the two groups in terms of paraoxanase-1 and arylesterase ($p > .05$). Multivariable Cox regression model showed thyroid stimulating hormone level (HR = 1.348, $p < .001$), free-thyroxine level (HR = 0.481, $p = .017$) and OSI ratio (HR = 2.349, $p < .001$) to be

independent predictors of development of overt hypothyroidism. OSI level, being over 2.96 with 92.9% sensitivity and 62.5% specificity, predicts the risk of hypothyroidism.

CONCLUSION:
Oxidative stress may be an effective risk factor in the development of overt hypothyroidism in HT.

Arch Physiol Biochem. 2018 Oct;124(4):351-356. doi: 10.1080/13813455.2017.1408660. Epub 2017 Nov 29.

Enhanced oxidative stress in Hashimoto's thyroiditis: inter-relationships to biomarkers of thyroid function.

Rostami R, Aghasi MR, Mohammadi A, Nourooz-Zadeh J.

OBJECTIVES:
Oxidative stress has been implicated in the pathogenesis of several inflammatory and immune-mediated disorders including Hashimoto's thyroiditis (HT). The objectives of the present cross-sectional investigation were to estimate serum glutathione (GSH) status and the activities of its recycling enzymes in HT and to explore their interrelationships with biomarkers of autoimmunity and thyroid function.

DESIGN AND METHODS:
Newly diagnosed females with HT (n=44) and 58 matched control subjects were recruited. Thyroid hormone profile, anti-thyroperoxidase anti-body (TPO-AB), anti-thyroglublin anti-body (Tg-AB), thyroid volume (Tvol), urinary iodine excretion (UIE), GSH and the activities of glutathione peroxidase (GPx), glutathione reductase and gamma-glutamyltransferase were assessed.

RESULTS:
Median UIE in HT was slightly but not significantly higher than that of controls. HT group exhibited higher levels of TSH, TPO-AB, Tg-AB and larger Tvol when compared with controls ($P<0.001$). The means of GSH and GPx in HT patients were significantly different from those of controls ($P<0.001$). In HT subjects, significant associations were seen between Tvol on TSH, GSH on TPO-AB, GSH on TSH and TPO-AB titers on TSH, respectively.

CONCLUSIONS:
This is the first study to demonstrate a substantial reduction in GSH status in HT subjects. Secondly, the interrelationship between the GSH contents and TPO-AB titers in HT provides a preliminary data to support the notion that GSH diminution is a hallmark of in the events leading to oxidative stress activation and the development of immunological intolerance in HT. Further studies are required to elucidate the role of GSH in the etiology of down-regulation of thyroid function.

Clin Biochem. 2013 Mar;46(4-5):308-12. doi: 10.1016/j.clinbiochem.2012.11.021. Epub 2012 Dec 4.

Thyroid Peroxidase Antibody is Associated with Plasma Homocysteine Levels in Patients with Graves' Disease.

Li F, Aji G, Wang Y, Lu Z, Ling Y.

PURPOSE:
Homocysteine is associated with cardiovascular, inflammation and autoimmune diseases. Previous studies have shown that thyroid peroxidase antibody is associated with homocysteine levels in hypothyroidism. The relationship between thyroid antibodies and homocysteine in hyperthyroidism remains unclear. In this study, we aimed to investigate the association of thyroid antibodies with homocysteine in patients with Graves' disease.

METHODS:
This was a cross-sectional study including 478 Graves' disease patients who were consecutively admitted and underwent radioiodine therapy. Homocysteine, thyroid hormones, thyroid antibodies, glucose and lipids were measured.

RESULTS:
Patients with homocysteine levels above the median were older and had unfavorable metabolic parameters compared to patients with homocysteine levels below the median. Thyroglobulin antibody or thyroid peroxidase antibody was associated with homocysteine levels (β=0.56, 95%CI 0.03-1.08, p=0.04; β=0.75, 95%CI 0.23-1.27, p=0.005). The relationship between thyroid peroxidase antibody and homocysteine remained significant when additionally adjusting for free triiodothyronine (β=0.76, 95%CI 0.24-1.28, p=0.004). The presence of a homocysteine level above the median increased significantly with increasing thyroid peroxidase antibody quartiles in the logistic regression (OR=1.74, 95%CI 1.27-2.39, P for trend=0.001). Homocysteine levels increased significantly with increasing thyroid peroxidase antibody quartiles (p=0.005). Thyroid peroxidase antibody had no significant effect on other traditional cardiovascular risk factors.

CONCLUSIONS:
Thyroid peroxidase antibody is independently and positively associated with homocysteine levels in patients with Graves' disease. Thyroid peroxidase antibody may be associated with the cardiovascular risk of patients with Graves' disease through its effect on homocysteine.

Exp Clin Endocrinol Diabetes. 2018 Jul 2. doi: 10.1055/a-0643-4692. [Epub ahead of print]

Hyperhomocysteinemia and hypercholesterolemia associated with hypothyroidism in the third US National Health and Nutrition Examination Survey.

Morris MS, Bostom AG, Jacques PF, Selhub J, Rosenberg IH.

Hypothyroid (thyroid stimulating hormone (TSH)> or =20 mIU/l; N=32) participants in the third National Health and Nutrition Examination Survey, Phase 2 (1991-1994) were compared with non-hypothyroid subjects (0.5 mIU/l<TSH<20 mIU/l; N=6490) to examine the relationship between hypothyroidism and hyperhomocysteinemia (serum total homocysteine>12 micromol/l) and hypercholesterolemia (serum total cholesterol>6.2 mmol/l). After controlling for age, gender, and race ethnicity, the odds ratios (95% confidence interval (CI)) relating hypothyroidism to hyperhomocysteinemia and high total cholesterol were 4.9 (1.8-14.0) and 8.0 (2.9-21.9), respectively. Based on 26 hypothyroid and 5811 non-hypothyroid subjects with tri-

glyceride concentration < or =2.82 mmol/l, the odds ratio for the relationship between hypothyroidism and high low-density lipoprotein (LDL)-cholesterol (>4.6 mmol/l by the Friedewald equation) was 5.3 (95% CI, 1.3-20.9). Adding additional terms to the multivariate logistic regression model had little effect on the odds ratios relating hypothyroidism to high total or LDL-cholesterol, but adding terms for serum creatinine concentration >123.8 micromol/l and for red blood cell folate and serum vitamin B-12 concentrations resulted in an attenuated, but still significant (P<0.05), odds ratio relating hypothyroidism to hyperhomocysteinemia (2.5; 95% CI, 1.0-6.1). Controlling for cigarette smoking, heart attack/stroke history, body mass index, and serum albumin concentration did not affect the odds ratios. Hyperhomocysteinemia and hypercholesterolemia could help to explain the increased risk for arteriosclerotic coronary artery disease in hypothyroidism.

Atherosclerosis. 2001 Mar;155(1):195-200.

Hyperhomocysteinemia in acute iatrogenic hypothyroidism: the relevance of thyroid autoimmunity.

Cicone F, Santaguida MG, My G, Mancuso G, Papa A, Persechino R, Virili C, Brusca N, Tofani A, Scopinaro F, Centanni M.

PURPOSE:
Hyperhomocysteinemia is a known cardiovascular risk factor and a key player in the inflammatory activation of autoimmune diseases. Hashimoto's thyroiditis (HT) is the leading cause of hypothyroidism which, in itself, has been associated with a significant raise of homocysteine (Hcy) levels and increased cardiovascular risk. Our aim was to assess the impact of HT on Hcy levels in patients with acute hypothyroidism.

METHODS:
We prospectively enrolled 121 patients (mean age: 46 years, F/M = 102/19) with acute post-surgical hypothyroidism. Based on the presence of anti-thyroid antibodies and the histological description of an inflammatory infiltrate, 26 and 95 patients were classified as HT and non-HT, respectively. Several parameters including thyroid-stimulating hormone (TSH), levels of serum free T3 and free T4, weight, glucose levels, total cholesterol, creatinine, vitamin B12, ferritin and erythrocyte sedimentation rate were obtained from all patients and correlated with Hcy levels.
RESULTS:
Median Hcy level in the whole cohort was 16.8 µmol/L (normal values: < 12 µmol/l). Among all parameters analysed, only Hcy levels were significantly different between HT and non-HT patients (median Hcy = 19.7 vs 16.2 µmol/L, respectively; p = 0.018, Mann-Whitney U test). Analysis of covariance showed the presence of HT to be the strongest predictor of Hcy levels (coefficient = 0.25534, p = 0.001). Serum TSH was not significantly associated with Hcy levels (p = 0.943).

CONCLUSION:
In patients with iatrogenic hypothyroidism, those with HT have significantly higher Hcy levels than those without HT. The increase of Hcy levels appears to be mainly determined by the HT-related immune-inflammatory condition.

J Endocrinol Invest. 2018 Jul;41(7):831-837. doi: 10.1007/s40618-017-0811-y. Epub 2017 Dec 29.

Plasma total homocysteine levels in hyperthyroid and hypothyroid patients.

Nedrebø BG, Ericsson UB, Nygård O, Refsum H, Ueland PM, Aakvaag A, Aanderud S, Lien EA.

We found a higher plasma concentration of total homocysteine (tHcy), an independent risk factor for cardiovascular disease, in patients with hypothyroidism (mean, 16.3 micromol/L; 95% confidence interval [CI], 14.7 to 17.9 micromol/L) than in healthy controls (mean, 10.5 micromol/L; 95% CI, 10.1 to 10.9 micromol/L). The tHcy level of hyperthyroid patients did not differ significantly from that of the controls. Serum creatinine was higher in hypothyroid patients and lower in hyperthyroid patients than in controls, whereas serum folate was higher in hyperthyroid patients compared with the two other groups. In multivariate analysis, these differences did not explain the higher tHcy concentration in hypothyroidism. We confirmed the observation of elevated serum cholesterol in hypothyroidism, which together with the hyperhomocysteinemia may contribute to an accelerated atherogenesis in these patients.

Metabolism. 1998 Jan;47(1):89-93.

Prevalence and evaluation of B12 deficiency in patients with autoimmune thyroid disease.

Ness-Abramof R, Nabriski DA, Braverman LE, Shilo L, Weiss E, Reshef T, Shapiro MS, Shenkman L.

BACKGROUND:
Patients with autoimmune thyroid disease (AITD) have a higher prevalence of pernicious anemia compared with the general population. Clinical signs of B12 deficiency may be subtle and missed, particularly in patients with known autoimmune disease. We assessed the prevalence of vitamin B12 deficiency in patients with AITD and whether their evaluation may be simplified by measuring fasting gastrin levels.

METHODS:
Serum B12 levels was measured in 115 patients with AITD (7 men and 108 women), with a mean age of 47 +/- 15 years. In patients with low serum B12 levels (< or =133 pmol/L), fasting serum gastrin and parietal cell antibodies (PCA) were measured.

RESULTS:
Thirty-two patients (28%) with AITD had low B12 levels. Fasting serum gastrin was measured in 26 and was higher than normal in 8 patients. PCA were also measured in 27 patients with B12 deficiency and were positive in 8 patients. Five patients with high gastrin levels underwent gastroscopy with biopsy, and atrophic gastritis was diagnosed in all. The prevalence of pernicious anemia as assessed by high serum gastrin levels in patients with low B12 was 31%.

CONCLUSIONS:
Patients with AITD have a high prevalence of B12 deficiency and particularly of pernicious anemia. The evaluation of B12deficiency can be simplified by measuring fasting serum gastrin and, if elevated, referring the patient for gastroscopy.

Am J Med Sci. 2006 Sep;332(3):119-22.

Prevalence of vitamin B-12 deficiency among patients with thyroid dysfunction.

Collins AB, Pawlak R.

Due to the non-specificity of symptoms and possibly severe consequences of untreated vitamin B-12 deficiency, screening is important for at-risk patients to ensure the prompt delivery of treatment. In this review, studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction are evaluated to determine whether regular vitamin B-12 screening is necessary. A literature search was conducted using multiple electronic data-

bases. Only original studies assessing the prevalence of vitamin B-12 deficiency in thyroid dysfunction that reported their findings as percentages of the sample were eligible for inclusion. From a total of 7091 manuscripts generated, 6 were included in this review. The prevalence of vitamin B-12 deficiency in hypothyroidism was reported as 10, 18.6, and 40.5% in three separate studies. The prevalence of deficiency in autoimmune thyroid disease was reported as 6.3, 28, and 55.5% in three studies. The prevalence of vitamin B-12deficiency in hypothyroidism and autoimmune thyroid disease are reflective of the nutrition status of the population. Autoimmune thyroid disease is also associated with the autoimmune disorders pernicious anemia and atrophic gastritis which may lead to malabsorption of vitamin B-12. Vitamin B-12 screening is recommended upon initial diagnosis with autoimmune thyroid disease and then periodically thereafter. There is not enough evidence to recommend regular screening for patients with hypothyroidism unless the underlying cause is autoimmune thyroid disease.

Asia Pac J Clin Nutr. 2016;25(2):221-6. doi: 10.6133/apjcn.2016.25.2.22.

Vitamin D

Does severe vitamin D deficiency impact obstetric outcomes in pregnant women with thyroid autoimmunity?

Bozdag H, Akdeniz E.

PURPOSE:
Vitamin D plays an important role in the modulation of the immune system and anti-autoimmune activities. Autoimmune thyroiddiseases related to endocrine disorders are associated with poor obstetric outcomes in pregnancy. Herein, we aimed to investigate the contribution of vitamin D hypovitaminosis to poor pregnancy outcomes in pregnant women with the positive autoimmune antibody.

MATERIALS AND METHODS:
This was a prospective case-control study that enrolled pregnant women at their first trimester. The pregnant women were divided based on thyroid antibody (TA) status (TA-positive pregnant group (TAs (+)) and negative group (TAs (-)). Vitamin D status was categorized as sufficient, insufficient, and deficient (severe and moderate).

RESULTS:
A total of 283 pregnant women were enrolled in this study. A total of 219 pregnant women were assigned to the TAs (-) group and 64 to the TAs (+) group. The rate of vitamin D insufficiency was 8.7, and 7.8% in the pregnant with TAs (-), and the pregnant with TAs (+) groups, respectively. Vitamin D deficiency was highly prevalent in all groups. Specifically, the prevalence rate was 91 and 92% in the pregnant with TAs (-) and the pregnant with TAs (+) groups, respectively. Admission to the neonatal intensive care unit (NICU) was more prevalent in the pregnant with TAs (+) group than in the pregnant with TAs (-) group (40.6 versus 25%; p = .0187; effect size (ES) = 0.134). The rate of gestational diabetes mellitus (GDM) was significantly higher in the pregnant women with TAs (+) group than that in the pregnant women with TAs (-) group (12.5 versus 4.1%; p = .03; ES =0.13). The rate of NICU admission and GDM was significantly higher in the severe vitamin D-deficient pregnant group with TAs (+) than that in the severe vitamin D-deficient pregnant group with TAs (-) (47 versus 23%; p = .007; ES =0.207 and 19.4% versus 4.1%; p = .006; ES =0.214, respectively).

CONCLUSIONS:
Severe vitamin D deficiency may contribute to increase the prevalence of GDM and need for NICU admission in pregnant women with positive TA.

J Matern Fetal Neonatal Med. 2018 Sep 25:1-11. doi: 10.1080/14767058.2018.1519017. [Epub ahead of print]

Vitamin D and autoimmunity.

Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y.

OBJECTIVES:
To review and evaluate the role of vitamin D in autoimmune diseases based on current studies.

METHOD:
We searched PubMed using keywords such as 'vitamin D', 'autoimmune disease', and 'autoimmunity'. We compiled and reviewed various studies including prospective cohorts, cross-sectional studies, longitudinal evaluations, genetic studies, and experimental models that investigated the role of vitamin D in autoimmune diseases.

RESULTS:
There is evidence based on these various studies that several key autoimmune diseases are modulated by vitamin D. These diseases include, but are not limited to, multiple sclerosis (MS), scleroderma or systemic sclerosis (SSc), autoimmune thyroid diseases, rheumatoid arthritis (RA), and primary biliary cirrhosis (PBC).

CONCLUSIONS:
Although there is evidence for vitamin D as a factor in the pathophysiology of autoimmune diseases, the mechanism for this association has yet to be elucidated. Additional data are needed to corroborate these findings.

Scand J Rheumatol. 2016 Nov;45(6):439-447. Epub 2016 May 18.

Vitamin D and autoimmunity: is vitamin D status an environmental factor affecting autoimmune disease prevalence?

Cantorna MT.

The environment in which the encounter of antigen with the immune system occurs determines whether tolerance, infectious immunity, or autoimmunity results. Geographical areas with low supplies of vitamin D (for example Scandinavia) correlate with regions with high incidences of multiple sclerosis, arthritis, and diabetes. The active form of vitamin D has been shown to suppress the development of autoimmunity in experimental animal models. Furthermore, vitamin D deficiency increases the severity of at least experimental autoimmune encephalomyelitis (mouse multiple sclerosis). Targets for vitamin D in the immune system have been identified, and the mechanisms of vitamin D-mediated immunoregulation are beginning to be understood. This review discusses the possibility that vitamin D status is an environmental factor, which by shaping the immune system affects the prevalence rate for autoimmune diseases such as multiple sclerosis, arthritis, and juvenile diabetes.

Proc Soc Exp Biol Med. 2000 Mar;223(3):230-3.

Magnesium deficit? overlooked cause of low vitamin D status?

Zittermann A.

Like vitamin D deficit, magnesium deficit is considered to be a risk factor for cardiovascular disease. Several steps in the vitamin D metabolism, such as vitamin D binding to its transport protein and the conversion of vitamin D into the hormonal form 1,25-dihydroxyvitamin D by hepatic and renal hydroxylation, depend on magnesium as a cofactor. A new analysis of two National Health and Nutrition Examination Surveys data sets, published in BMC Medicine, investigated potential interactions between magnesium intake, circulating 25-hydroxyvitamin

D, which is the generally accepted indicator of vitamin D status, and mortality. Data indicate a reduced risk of insufficient/deficient vitamin D status at high magnesium intake and an inverse association between circulating 25-hydroxyvitamin D and mortality, particularly cardiovascular mortality, among those with magnesium intake above the median. The study provides important findings concerning potential metabolic interactions between magnesium and vitamin D and its clinical relevance. However, results should be considered preliminary since biochemical data on individual magnesium status were lacking, confounding cannot be excluded and questions on the dose/response relationship still remain to be answered.

BMC Med. 2013 Oct 24;11:229. doi: 10.1186/1741-7015-11-229.

Magnesium in the gynecological practice: a literature review.

Parazzini F, Di Martino M, Pellegrino P.

A growing amount of evidence suggests that magnesium deficiency may play an important role in several clinical conditions concerning women health such as premenstrual syndrome, dysmenorrhea, and postmenopausal symptoms. A number of studies highlighted a positive correlation between magnesium administration and relief or prevention of these symptoms, thus suggesting that magnesium supplementation may represent a viable treatment for these conditions. Despite this amount of evidence describing the efficacy of magnesium, few and un-systematize data are available about the pharmacological mechanism of this ion for these conditions. Herein, we review and systematize the available evidence about the use of oral magnesium supplementation in several gynecological conditions and discuss the pharmacological mechanisms that characterize these interventions. The picture that emerges indicates that magnesium supplementation is effective in the prevention of dysmenorrhea, premenstrual syndrome, and menstrual migraine and in the prevention of climacteric symptoms.

Magnes Res. 2017 Feb 1;30(1):1-7. doi: 10.1684/mrh.2017.0419.

Mitochondrial Function

Applying a systems approach to thyroid physiology: Looking at the whole with a mitochondrial perspective instead of judging single TSH values or why we should know more about mitochondria to understand metabolism.

Moncayo R, Moncayo H.

Classical thinking in endocrine physiology squeezes our diagnostic handling into a simple negative feedback mechanism with a controller and a controlled variable. In the case of the thyroid this is reduced to TSH and fT3 and fT4, respectively. The setting of this tight notion has no free space for any additions. In this paper we want to challenge this model of limited application by proposing a construct based on a systems approach departing from two basic considerations. In first place since the majority of cases of thyroid disease develop and appear during life it has to be considered as an acquired condition. In the second place, our experience with the reversibility of morphological changes makes the autoimmune theory inconsistent. While medical complexity can expand into the era of OMICS as well as into one where manipulations with the use of knock-outs and -ins are common in science, we have preferred to maintain a simple and practical approach. We will describe the interactions of

iron, magnesium, zinc, selenium and coenzyme Q10 with the thyroid axis. The discourse will be then brought into the context of ovarian function, i.e. steroid hormone production. Finally the same elemental players will be presented in relation to the basic mitochondrial machinery that supports the endocrine. We propose that an intact mitochondrial function can guard the normal endocrine function of both the thyroid as well as of the ovarian axis. The basic elements required for this function appear to be magnesium and iron. In the case of the thyroid, magnesium-ATP acts in iodine uptake and the heme protein peroxidase in thyroid hormone synthesis. A similar biochemical process is found in steroid synthesis with cholesterol uptake being the initial energy-dependent step and later the heme protein ferredoxin 1 which is required for steroid synthesis. Magnesium plays a central role in determining the clinical picture associated with thyroid disease and is also involved in maintaining fertility. With the aid of 3D sonography patients needing selenium and/or coenzyme Q10 can be easily identified. By this we firmly believe that physicians should know more about basic biochemistry and the way it fits into mitochondrial function in order to understand metabolism. Contemplating only TSH is highly reductionistic.

BBA Clin. 2017 Apr 4;7:127-140. doi: 10.1016/j.bbacli.2017.03.004. eCollection 2017 Jun.

Risk of Deficiency: Zinc and Iron

Zinc is one of the essential trace minerals, which means that the body cannot produce it itself, but it has to be supplied via the diet. It has been found that zinc deficiencies are quite frequent even in western countries, which might be due to the fact that the body is not able to store zinc.

Yet zinc plays a crucial role in the metabolism of carbohydrates, fats and proteins alike. In addition to that the immune and hormone systems as well as important antioxidative enzymes need zinc for their work. Furthermore it is crucial for the synthesis of the nucleic acids DNA and RNA, which are essential during cell division, tissue repair and embryo development.

Last not least zinc is needed for thyroid hormone metabolism.

Metabolic disorders and nutritional status in autoimmune thyroid diseases.

Kawicka A, Regulska-Ilow B, Regulska-Ilow B.

In recent years, the authors of epidemiological studies have documented that autoimmune diseases are a major problem of modern society and are classified as diseases of civilization. Autoimmune thyroid diseases (ATDs) are caused by an abnormal immune response to autoantigens present in the thyroid gland - they often coexist with other autoimmune diseases. The most common dysfunctions of the thyroid gland are hypothyroidism, Graves-Basedow disease and Hashimoto's disease. Hashimoto's thyroiditis can be the main cause of primary hypothyroidism of the thyroid gland. Anthropometric, biochemical and physicochemical parameters are used to assess the nutritional status during the diagnosis and treatment of thyroid diseases. Patients with hypothyroidism are often obese, whereas patients with hyperthyroidism are often afflicted with rapid weight loss. The consequence of obesity is a change of the thyroid hormones' activity; however, weight reduction leads to their normalization. The activity and metabolic rate of thyroid hormones are modifiable. ATDs are associated with abnormalities of glucose metabolism and thus increased risk of developing diabetes mellitus type 1 and type 2. Celiac disease (CD) also increases the risk of developing other autoimmune diseases. Malnutrition or the presence of numerous nutritional deficiencies in a

patient's body can be the cause of thyroid disorders. Coexisting deficiencies of such elements as iodine, iron, selenium and zinc may impair the function of the thyroid gland. Other nutrient deficiencies usually observed in patients suffering from ATD are: protein deficiencies, vitamin deficiencies (A, C, B6, B5, B1) and mineral deficiencies (phosphorus, magnesium, potassium, sodium, chromium). Proper diet helps to reduce the symptoms of the disease, maintains a healthy weight and prevents the occurrence of malnutrition. This article presents an overview of selected documented studies and scientific reports on the relationship of metabolic disorders and nutritional status with the occurrence of ATD.

Postepy Hig Med Dosw (Online). 2015 Jan 2;69:80-90. doi: 10.5604/17322693.1136383.

A post-publication analysis of the idealized upper reference value of 2.5 mIU/L for TSH: Time to support the thyroid axis with magnesium and iron especially in the setting of reproduction medicine.

Moncayo R, Moncayo H.

Laboratory medicine approaches the evaluation of thyroid function mostly through the single determination of the blood level of thyroid stimulating hormone (TSH). Some authors have suggested an upper reference value for TSH of 2.5 mIU/L. This suggestion has not been confirmed by recent clinical studies. These studies have delivered a clinically valid reference range going from 0.3 to 3.5 mIU/L. These values are valid for both for the general population as well as in the setting of fertility and pregnancy. Current biochemical evidence about the elements required to maintain thyroid function shows that these not only include dietary iodine but also magnesium, iron, selenium and coenzyme Q10. Iron is important for the synthesis of thyroid peroxidase; magnesium-ATP contributes to the active process of iodine uptake; iodine has to be sufficiently present in the diet; selenium acts through selenoproteins to protect the thyroid cell during hormone synthesis and in deiodination of thyroxine; coenzyme Q10 influences thyroid vascularity. As a consequence, good clinical practice requires additional biochemical information on the blood levels of magnesium, selenium, coenzyme Q10 as well as iron status. Since these elements are also important for the maintenance of reproductive function, we postulate that they constitute the connecting link between both endocrine systems

BBA Clin. 2017 Mar 19;7:115-119. doi: 10.1016/j.bbacli.2017.03.003. eCollection 2017 Jun.

The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy.

Li S, Gao X, Wei Y, Zhu G, Yang C.

Previous studies have identified an association between iron deficiency and thyroid function. We aimed to determine if there is a relationship between iron deficiency and thyroid function during the first trimester of pregnancy. Two thousand five hundred eighty-one pregnant women who presented for the first prenatal care were enrolled and divided into three groups, the mild iron deficiency (MID) group, iron deficiency anemia (IDA) group and normal control (NC) group, according to serum ferritin and hemoglobin levels. The former two groups can be merged into one iron deficiency (ID) group. Thyroid function parameters were compared among the three groups, including free thyroxine (FT4), thyroid stimulating hormone (TSH), total thyroxine (TT4) and thyroid peroxidase antibodies (TPOAb). Moreover, the rates of thyroid dysfunction were also compared. Our results show that pregnant women in the MID and IDA groups have higher TSH and lower FT4 status than those in the NC group ($p<0.01$), and the difference between the IDA group and MID group is significant ($p<0.05$). TPOAb in

the IDA group is higher than in the MID group and NC group. Meanwhile, the rate of hypothyroidism or subclinical hypothyroidism in the IDA group was significantly higher than in the MID group and NC group ($p<0.01$). And the positive rate of TPOAb is also higher in the IDA group than MID group and NC group ($p<0.05$). Iron deficiency is related to thyroid function and could lead to hypothyroidism during early pregnancy, which could be explained by thyroid autoimmunity.

J Nutr Sci Vitaminol (Tokyo). 2016;62(6):397-401. doi: 10.3177/jnsv.62.397.

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Dietary Supplementation Improves Blastocyst Number and Ongoing Pregnancy Rate of IVF Patients with Hashimoto Thyroiditis

Johannes Wogatzky, Birgit Schechinger, Dietmar Spitzer and Nicolas Herbert Zech

In Assisted Reproduction Techniques (ART), autoimmune disorders of the thyroid gland present as common concomitant diseases. Hypothyroidism caused by autoimmune thyroiditis can impair fertility and pregnancy. Hashimoto thyroiditis (HT) is the most common autoimmune thyroid disease (AITD). Patients with HT undergoing IVF/ICSI using the long protocol are thought to benefit from a broad therapeutic concept. We compared the outcome of two different therapeutic schemes for HT patients presenting at our fertility clinic and compared the outcome to ART patients without thyroiditis. TSH level was adjusted to under 2 µIU/mL using L-thyroxine, as required. Concurrent medication from the time of oocyte puncture included daily administration of fragmin (dalteparin) and acetylsalicylic acid (ASA), as well as prednisolone in increasing dosage. One group of these HT patients (group1, n=56) had additionally highly-dosed folic acid, another group (group 2, n=50, referred to as the supplemented group) was alternatively supplemented with a micronutrient preparation containing selenium, high-dose folic acid, B-vitamins, antioxidants and iron. We compared the number of oocytes, fertilization rate, blastocyst formation rate, pregnancy- and ongoing pregnancy rate between the two groups. Also, the ART outcomes of both groups were compared to ART results of non-HT patients within the same age group. We observed a significant increase in the blastocyst rate and demonstrated a substantial rise in ongoing pregnancy rate of the supplemented patients. These also needed less L-thyroxine to achieve optimal TSH level. The outcome of the micronutrient supplemented patients corresponded to the average of healthy IVF patients without HT at our clinic.

Wogatzky et al., J Food Nutr Disor 2013, 2:4

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