

The role of iodine vs selenium on the rising trend of autoimmune thyroiditis in iodine sufficient countries

Abstract

Iodine is a trace element that is essential for the synthesis of thyroid hormones in the thyroid gland. Evidence suggests that excess iodine intake exerts a triggering effect on the development of autoimmune thyroiditis (AT), with many studies reporting a rising incidence in iodine sufficient countries. Processing excess iodine in thyroid follicular cells, during thyroid hormone synthesis, may result in increased amounts of reactive oxygen species, leading to thyroid cell damage and the triggering of thyroid autoimmunity. Another trace element, selenium found in high amounts in the thyroid, is very important for thyroid physiology. Selenium is incorporated into selenoproteins that are involved in the protection of thyroid cells from oxidative damage, incurred by exposure to hydrogen peroxide (H_2O_2) originating during thyroid hormone synthesis. Population studies suggest an increased prevalence of thyroid autoimmunity in areas following iodine fortification, and a possible protective effect with selenium adequacy. In animal models, selenium has been shown to reverse the induction of autoimmune thyroiditis caused by excess iodine intake. It appears therefore, that an optimal balance between iodine and selenium is important for maintaining normal thyroid function, and that the loss of such balance in favor of iodine, may play a role for the rising trend of autoimmune thyroiditis, currently seen in iodine sufficient countries.

Keywords: iodine, selenium, autoimmune thyroiditis, thyroid autoimmunity

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Introduction

Autoimmune thyroiditis (AT) or Hashimoto's thyroiditis is an organ-specific autoimmune disease, characterized by infiltration of the thyroid gland by activated immune cells, leading to gradual destruction of thyroid cells, and eventually to hypothyroidism. In this condition, the activated T lymphocytes induce apoptosis of thyroid cells by the secretion of pro-inflammatory cytokines, whereas B lymphocytes produce antibodies against the thyroid auto-antigens, thyroid peroxidase (TPO), and/or thyroglobulin (Tg).^{1,2} Accumulating evidence suggests that the incidence of AT is increasing in iodine-sufficient countries. Especially, in formerly iodine deficient areas, the elimination of iodine insufficiency, following iodine prophylaxis programs or silent iodine prophylaxis, has been followed by a rise in the prevalence of AT.³⁻⁵ Iodine is an essential nutrient for thyroid function. It combines with thyroglobulin to produce the thyroid hormones thyroxine (T4) and tri-iodothyronine (T3) and so, normal thyroid function is dependent on adequate iodine intake.⁶ On the other hand, selenium is a mineral that is found in high concentrations in the thyroid, and the selenoproteins in the gland are involved in antioxidant defense. Selenium appears to protect thyroid cells from oxidative damage, incurred by exposure to hydrogen peroxide (H_2O_2), a byproduct during thyroid hormone synthesis from iodine.^{7,8} In the present opinion article, evidence is provided in support of the hypothesis that an optimal balance of iodine to selenium supply to the thyroid gland is important for maintaining a normal thyroid function. Loss of such balance in favor of iodine exerts a triggering effect on the induction of thyroid autoimmunity.

The role of iodine and the balancing effect of selenium on thyroid physiology

Iodine, a trace element found mostly in the soil of coastal areas in

the form of water soluble iodide ion (I^-), is essential for the production of thyroid hormones. Iodide is actively transported from the blood into the thyroid cell through a sodium/iodide (Na^+/I^-) symporter on the basolateral membrane. Subsequently, iodide is translocated across the apical membrane into the colloid of the follicular lumen. In the colloid, iodide is oxidized to iodine by TPO, with endogenously generated H_2O_2 as its substrate at the apical membrane. The generation of H_2O_2 is necessary for the iodination of tyrosine residues by TPO, as well as the coupling of iodinated tyrosines to thyroglobulin (TG), resulting in the production of the thyroid hormones T3 and T4. The iodination of TG and generation of H_2O_2 takes place in the luminal surface of the apical membrane of the thyroid cell, while any harmful H_2O_2 that diffuses into the cell is degraded by the intracellular antioxidant system.^{6,7} Under the action of thyroid stimulating hormone (TSH), iodinated Tg is reabsorbed into thyroid cells where it is digested by lysosomes, and the thyroid hormones T4 and T3, are released into the circulation. In the peripheral tissues, T4 is converted, through deiodination, into the active hormone T3. At least three deiodinases, each with unique expression in different organs, catalyze the deiodination reactions involved in the metabolism of T4.⁶⁻⁸ The recommended daily allowance of iodine is 150mg for adults. However, there is a relatively narrow interval of optimal iodine intake, and both iodine deficiency and iodine excess can result in increased prevalence of thyroid disorders. Thus, iodine intake in adequate amounts is required for normal thyroid function.⁷

Apart from iodine, selenium is the next most important trace mineral that plays a significant role in thyroid physiology. Its name derives from the Greek word "Σελήνη -Selene", that means "Moon" and refers to the bright-grey appearance of this mineral when it is melted. The thyroid contains high amounts of selenium in the form of selenocysteine, an amino acid incorporated into selenoproteins including glutathione peroxidases (GPx), thioredoxin reductases

(TRx), and iodothyronine deiodinases (IDD). These enzyme proteins play an important role in protecting thyroid cells from oxidative damage and, also, in thyroid hormone metabolism. The glutathione peroxidases, catalyze the conversion of H_2O_2 into water, which protects the thyroid gland from oxidative damage. GPx3 and GPx1 catalyze this reaction, and GPx4 removes excess lipid hydro peroxides in the mitochondria, protecting them from damage. The iodothyronine deiodinase enzymes catalyze the conversion of inactive T4 to the active thyroid hormone, T3. In particular, the deiodinases DIO1 and DIO2 activate T4 to T3 by removing the 5'-iodine. In contrast, DIO1 and DIO3 enzymes can prevent T4 from being activated, by converting it to reverse T3. A third selenoprotein enzyme is Selenoprotein S, that is involved in controlling the inflammatory response in the endoplasmic reticulum.^{9,10} It appears that iodine, in adequate amounts, is essential for thyroid hormone production by the thyroid gland. On the other hand, selenium is also important for the protection of the thyroid cells from oxidative damage during thyroid hormone synthesis from iodine.¹¹ Therefore, the iodine to selenium ratio in the thyroid gland should be kept optimal in order to maintain a normal thyroid function. The currently recommended dietary intake of selenium in humans ranges from 60 to 75 μ g per day. This is based on the amount of selenium intake, that is needed to induce the maximal activity of GPX in plasma or erythrocytes.¹⁰ The daily intake of selenium is variable according to geographical area. In general, reduced selenium levels are found in smokers, in the elderly, in subjects with major gut problems, and in those with high consumption of alcohol and coffee.¹⁰

The role of iodine to selenium imbalance in the induction of autoimmune thyroiditis

Autoimmune thyroiditis is a multi factorial disorder, with genetic and environmental risk factors contributing to its pathogenesis. It appears that, in genetically susceptible individuals, environmental factors exert a triggering effect on thyroid autoimmunity.² It is believed that certain environmental factors may increase immunogenicity of thyroid auto-antigens, enhance antigen presentation in the thyroid gland, and induce a breakdown of immune tolerance, leading to autoimmune reaction against thyroid-specific antigens. As a result, a large number of activated T lymphocytes as well as antibody producing B lymphocytes invade the thyroid gland. Th1 and Th17 immune responses predominate with increased production of pro-inflammatory cytokines by activated T lymphocytes, resulting in thyroid cell apoptosis and eventually in clinical hypothyroidism.^{1,2} Among the environmental factors, implicated in the development of thyroid autoimmunity, excess iodine intake and a relative selenium deficiency appear to play a predominant role.^{3,11} Although adequate iodine intake is essential for normal thyroid function, data from epidemiological and clinical studies suggest that excessive iodine intake is associated with increased prevalence of thyroid autoimmunity and hypothyroidism.³⁻⁵ On the other hand, in patients with AT and subclinical hypothyroidism, restricting iodine intake results in decreased TSH levels, further supporting the view, that iodine in excess can induce thyroid autoimmunity.¹² In addition, data from experimental animal studies suggest that excessive ingestion of iodine can act as an environmental trigger for AT. In genetically prone to thyroiditis animal models, excess iodine intake has been shown to increase the incidence and severity of the disease.¹³

Further studies have shown that iodine induces cytokine and chemokine-mediated lymphocytic infiltration in the thyroid parenchyma of autoimmune prone individuals, which is critical for the generation of thyroid auto- antibodies and thyroiditis.³ Excess iodine

-induced oxidative stress and consequential oxidative cell injury has been proposed as a potential trigger for this lymphocytic response.¹⁴ Excessive iodine may also alter the conformation of thyroglobulin, and augment the antigenicity of the molecule by increasing the affinity of its determinants for the T-cell receptor.¹⁵ Thus, excess iodine intake will eventually induce a breakdown of immune tolerance leading to an autoimmune reaction against thyroid auto-antigens and the development of AT. On the other hand, recent evidence suggests that adequate selenium status is protective against iodine-induced thyroid autoimmunity.¹⁶ A recent study from China, compared two countries differing in selenium intake and found that thyroid autoimmunity was lower in the country with adequate selenium intake. Moreover, higher serum selenium was associated with lower odds of developing AT. Both countries had a higher than adequate iodine intake, which presumably accounted for the high prevalence of thyroid disease.¹⁷ In short, these data indicate, that adequate selenium status may be protective against thyroid autoimmunity resulting from high iodine intake. Further studies have shown that, people living in areas with low selenium content in the soil, are more likely to develop AT.¹⁸ Furthermore, in patients with thyroid autoimmunity, serum selenium levels tended to be lower compared with healthy controls.¹⁹

Apart from the clinical data, above, data from animal studies also support the concept that selenium supplementation may prevent iodine-induced thyroiditis in animal models of autoimmune thyroid disease.²⁰ Interestingly, it has been shown that, apart from protecting the thyroid cells against oxidative damage, selenium supplementation increased the frequency of T regulatory cells (Treg), that were reduced by high iodine intake.²¹ It is believed that Treg cells establish and maintain self -tolerance by suppressing response to self-antigens and preventing excessive immune responses to the host. On the other hand, deficits in Treg cell numbers or function may lead to autoimmune diseases.²² This information implies that an optimal iodine to selenium balance is also needed to maintain proper Treg cell populations, and that selenium supplementation may restore normal regulation of autoimmunity. While adequate selenium status is protective against iodine- induced AT, in the case of combined iodine and selenium deficiency, normalizing selenium without prior iodine supplementation may aggravate hypothyroidism.²³ This may occur through an increase in thyroid metabolism via selenium containing deiodinases, exaggerating further the hypothyroxinemia. It appears that an imbalance in the iodine to selenium ratio in favor of iodine may play an important role in the mechanism of iodine-induced AT. In light of the above information, studies in humans have examined the efficacy of selenium supplementation in modifying the autoimmune process in patients with chronic AT. Overall, these studies have shown that selenium supplementation may cause a decline in anti-TPO antibody titers and an improvement in thyroid echogenicity.²⁴ Promising are also preliminary data showing that selenium administration may have a protective role in pregnant women with AT.²⁵ However; the clinical significance of such intervention is not yet established. Further studies are awaited to determine the role of selenium supplementation in modifying the natural history of AT.

Conclusions and future perspectives

Evidence from clinical research suggests that excess iodine intake can act as an environmental risk factor for the development of autoimmune thyroid disease in populations of iodine sufficient countries. Similarly, in animal studies high iodine intake may exacerbate a pre-existing autoimmune thyroiditis. It is believed that redundant H_2O_2 are generated during oxidation and organification of

excessive iodine in thyroid cells, leading to elevated oxidative stress and resulting in oxidative cell damage. However, this may occur only if selenium is deficient. Optimal selenium intake exerts a protective effect against iodine-induced oxidative cell damage by enhancing glutathione peroxidase activity and providing antioxidant protection to the thyroid cell. It appears, that selenium status may play an important role in preventing iodine-induced AT, and that an optimal balance between iodine and selenium is important for maintaining normal thyroid function. It can, therefore, be concluded that an iodine to selenium imbalance, in favor of iodine, may be responsible for the rising trend of AT in iodine sufficient countries. At a clinical level, studies have shown that selenium administration may improve autoimmune laboratory parameters in patients with established AT.²⁴ Further studies are awaited to demonstrate the impact of such intervention in modifying the natural course of thyroid autoimmunity. It is tempting to speculate that, the real impact of selenium would be in preventing the manifestation of AT in those individuals at high risk of developing the condition, after exposure to high iodine intake. Thus, in implementing future iodine prophylaxis programs, balancing the effect of iodine with concurrent selenium administration, is expected to have a favorable outcome on the risk of AT.

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Conflict of interest

The author declares no conflict of interest.

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