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MAGNESIUM AND THE THYROID AXIS: AN OVERLOOKED CONNECTION IN AUTOIMMUNE HYPOTHYROIDISM

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ABSTRACT

Autoimmune hypothyroidism, predominantly caused by Hashimoto's thyroiditis (HT), is one of the most common endocrine disorders worldwide. While iodine and selenium have traditionally been emphasized in thyroid physiology, emerging evidence suggests that magnesium plays a crucial but often overlooked role in thyroid function and immune regulation. Magnesium is an essential intracellular cation involved in more than 300 enzymatic reactions, including ATP synthesis, oxidative phosphorylation, mitochondrial stability, and regulation of inflammatory pathways. Since thyroid hormone synthesis, secretion, and peripheral conversion are energy-dependent processes, magnesium deficiency may adversely affect the hypothalamic-pituitary-thyroid axis and contribute to thyroid dysfunction. Recent clinical studies have demonstrated significant associations between low serum magnesium levels and hypothyroidism, elevated thyroid autoantibody titers, oxidative stress, and chronic inflammation. Magnesium deficiency has also been implicated in impaired mitochondrial energy metabolism, increased reactive oxygen species generation, immune dysregulation, and altered thyroid hormone metabolism, all of which may contribute to the pathogenesis and progression of autoimmune thyroiditis. Furthermore, magnesium interacts synergistically with other micronutrients such as selenium, zinc, and vitamin D in maintaining thyroid health and modulating immune responses. Several studies suggest that magnesium supplementation may improve thyroid morphology, reduce inflammatory activity, and support thyroid hormone metabolism, particularly when combined with other micronutrients. However, despite growing evidence, magnesium remains an underrecognized factor in autoimmune hypothyroidism, and large-scale randomized controlled trials are still limited. This review summarizes the current understanding of the relationship between magnesium and the thyroid axis, highlighting the potential role of magnesium deficiency in autoimmune hypothyroidism and emphasizing the need for further research into magnesium-based therapeutic strategies.

INTRODUCTION

Autoimmune hypothyroidism, predominantly caused by Hashimoto's thyroiditis (HT), is one of the most prevalent endocrine disorders worldwide. It is characterized by autoimmune-mediated destruction of thyroid follicular cells leading to impaired thyroid hormone synthesis and progressive thyroid dysfunction. Although iodine deficiency has historically been regarded as the principal nutritional factor affecting thyroid function, increasing evidence suggests that other micronutrients, including selenium, zinc, iron, and magnesium, play significant roles in thyroid physiology and immune regulation [7]. Among these, magnesium has remained relatively underexplored despite its essential role in cellular metabolism and enzymatic reactions.

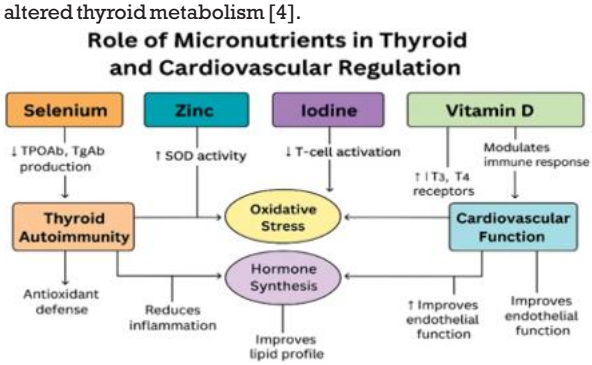
Magnesium is the second most abundant intracellular cation and serves as a cofactor for more than 300 enzymatic processes. It is involved in ATP synthesis, oxidative phosphorylation, nucleic acid stability, mitochondrial function, ion transport, and regulation of inflammatory pathways. Because thyroid hormone synthesis and secretion are highly energy-dependent processes, magnesium deficiency may adversely affect thyroid function and contribute to autoimmune thyroid disease [3,4].

Recent clinical and experimental studies have demonstrated significant associations between low magnesium levels and hypothyroidism, elevated thyroid autoantibody titers, oxidative stress, and chronic inflammation [1,2]. This review discusses the physiological relationship between magnesium and the thyroid axis and examines the possible role of magnesium deficiency in the pathogenesis and progression of autoimmune hypothyroidism.

Magnesium and Thyroid Physiology

The thyroid gland requires adequate energy production and optimal enzymatic activity for hormone synthesis, iodine uptake, thyroglobulin iodination, and hormone secretion. Magnesium is critically involved in these processes because biologically active ATP exists primarily as a magnesium-ATP complex. Consequently, magnesium deficiency can impair cellular energy metabolism and reduce thyroid hormone synthesis [3].

Magnesium also plays an important role in maintaining mitochondrial integrity and oxidative phosphorylation. Thyroid follicular cells possess high metabolic activity and depend heavily on mitochondrial ATP production. Impairment of mitochondrial function due to magnesium deficiency may result in decreased hormone production and altered thyroid metabolism [4].



In addition to its role in thyroid hormone synthesis, magnesium may influence the hypothalamic-pituitary-thyroid (HPT) axis. Alterations in magnesium homeostasis can affect pituitary hormone secretion and thyroid hormone responsiveness at the cellular level. Duntas highlighted that magnesium and other trace elements are necessary for maintaining normal thyroid hormone metabolism and receptor activity [7].

Peripheral conversion of thyroxine (T4) to triiodothyronine (T3) is another energy-dependent process influenced indirectly by magnesium status. Reduced intracellular magnesium may impair deiodinase enzyme activity and mitochondrial function, thereby contributing to reduced T3 availability and hypothyroid manifestations.

Magnesium Deficiency and Hypothyroidism

Several studies have demonstrated altered magnesium levels in patients with thyroid dysfunction. Jain and Ducatman

observed significantly lower serum magnesium concentrations in individuals with hypothyroidism compared with euthyroid controls [8]. Similar findings were reported by Khatiwada et al., who demonstrated a significant association between thyroid dysfunction and serum magnesium imbalance [10].

Hypothyroidism is frequently associated with electrolyte disturbances due to reduced renal perfusion, altered tubular function, and impaired cellular metabolism. Suneel et al. identified magnesium imbalance as a common biochemical abnormality in hypothyroid patients [9]. These electrolyte abnormalities may contribute to several clinical manifestations of hypothyroidism, including fatigue, muscle weakness, lethargy, depression, and neuromuscular dysfunction.

One of the most significant studies evaluating magnesium and thyroid disease was conducted by Wang et al. in a large Chinese population [1]. The investigators reported that severely low serum magnesium levels were associated with increased risks of positive anti-thyroglobulin antibody status and overt hypothyroidism. Their findings strongly suggested that magnesium deficiency may not merely be a secondary consequence of thyroid dysfunction but may actively contribute to autoimmune thyroid disease development.

The association between magnesium deficiency and thyroid dysfunction may be explained by impaired ATP production, reduced thyroid hormone synthesis, altered hormone transport, and increased oxidative stress. Since thyroid hormone production requires substantial energy expenditure, inadequate magnesium availability may compromise multiple stages of thyroid physiology.

Magnesium and Autoimmune Thyroiditis

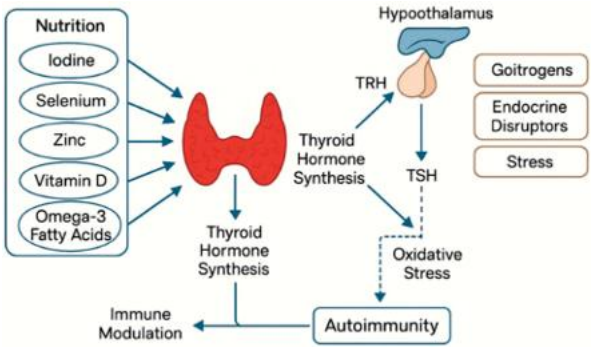
Hashimoto's thyroiditis is characterized by chronic lymphocytic infiltration of the thyroid gland accompanied by progressive follicular destruction and fibrosis. The disease is strongly associated with elevated anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin antibodies (TgAb). Although genetic susceptibility plays a major role in disease development, environmental and nutritional factors are increasingly recognized as important contributors to thyroid autoimmunity.

Magnesium has significant immunomodulatory properties and is involved in regulation of both innate and adaptive immune responses. Magnesium deficiency has been associated with chronic low-grade inflammation and increased production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha. Persistent inflammatory activation may contribute to autoimmune-mediated thyroid tissue injury [6].

Celik et al. evaluated serum magnesium levels in patients with Hashimoto's thyroiditis and observed that lower magnesium concentrations were associated with increased thyroid autoantibody positivity [2]. Their findings support the hypothesis that magnesium deficiency may contribute to autoimmune activation and progression of thyroid disease.

Oxidative stress is another critical factor involved in the pathogenesis of Hashimoto's thyroiditis. Excessive generation of reactive oxygen species can damage thyroid follicular cells and expose intracellular antigens to the immune system, thereby promoting autoantibody formation. Magnesium plays a vital role in antioxidant defense mechanisms and mitochondrial stability. Reduced magnesium levels impair antioxidant enzyme activity and increase oxidative cellular injury [11].

Allegra et al. emphasized the central role of oxidative stress in autoimmune thyroid diseases and highlighted the importance of antioxidant pathways in limiting thyroid tissue damage [11]. Since magnesium acts as an essential cofactor for numerous antioxidant enzymes, deficiency may exacerbate oxidative injury and inflammatory responses within the thyroid gland.



Mikulska et al. further demonstrated that micronutrient imbalance, including magnesium deficiency, contributes to metabolic dysregulation in Hashimoto's thyroiditis [5]. Magnesium deficiency may also interact synergistically with selenium and vitamin D deficiencies, thereby aggravating immune dysfunction and inflammatory activity.

Mechanisms Linking Magnesium Deficiency with Thyroid Autoimmunity

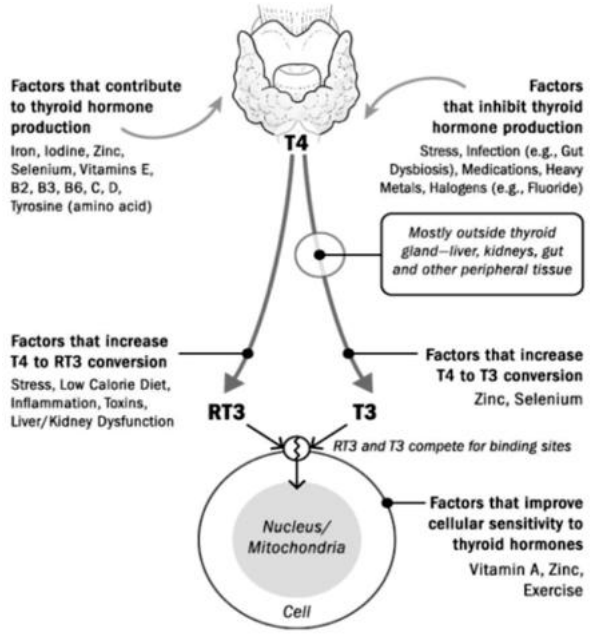


FIGURE 4: FACTORS THAT AFFECT THYROID FUNCTION

Multiple mechanisms may explain the relationship between magnesium deficiency and autoimmune hypothyroidism.

Impaired Cellular Energy Metabolism

Magnesium is indispensable for ATP synthesis and mitochondrial energy production. Reduced magnesium availability impairs energy-dependent thyroid hormone synthesis and secretion, thereby contributing to hypothyroidism [3,4].

Increased Oxidative Stress

Magnesium deficiency promotes oxidative stress by reducing antioxidant defense mechanisms and increasing reactive oxygen species generation. Oxidative injury to thyroid follicular cells may trigger autoimmune responses and chronic inflammation [11].

Immune Dysregulation

Magnesium regulates T-cell activation, cytokine production, and inflammatory signaling pathways. Deficiency can result

in immune imbalance and enhanced autoantibody production against thyroid tissue [2,6].

Altered Hormone Conversion

Peripheral conversion of T4 to T3 depends on adequate enzymatic and mitochondrial function. Magnesium deficiency may impair these processes and reduce active thyroid hormone availability [7].

Interaction with Other Micronutrients

Magnesium works synergistically with selenium, zinc, and vitamin D in maintaining thyroid health. Concurrent deficiencies may amplify oxidative stress and autoimmune activity [5,7].

Therapeutic Implications

Emerging evidence suggests that magnesium supplementation may have beneficial effects in patients with autoimmune hypothyroidism. Moncayo and Moncayo proposed that magnesium supplementation, particularly when combined with selenium and coenzyme Q10, may improve thyroid morphology and metabolic function [3,4]. Their studies demonstrated improvement in thyroid ultrasound patterns and symptomatic relief following correction of magnesium deficiency.

Kravchenko and Zakharchenko emphasized the importance of mineral balance in immunocorrection of autoimmune thyroid disorders [6]. Restoration of adequate magnesium levels may help reduce inflammatory activation, improve mitochondrial function, and support thyroid hormone metabolism.

Dietary magnesium is obtained primarily from green leafy vegetables, legumes, nuts, seeds, and whole grains. However, modern dietary patterns, chronic stress, gastrointestinal disorders, and certain medications may contribute to magnesium depletion. Clinical evaluation of magnesium deficiency remains challenging because serum magnesium reflects only a small fraction of total body magnesium stores.

Although current evidence is promising, large randomized controlled trials evaluating magnesium supplementation in Hashimoto's thyroiditis remain limited. Further research is necessary to determine optimal supplementation strategies, dosage, duration, and long-term clinical outcomes.

Future Perspectives

Magnesium remains an underrecognized factor in thyroid disease despite increasing evidence linking magnesium deficiency with hypothyroidism and autoimmune thyroiditis. Most available studies are observational and do not establish direct causality. Future investigations should focus on intracellular magnesium assessment, molecular mechanisms of immune regulation, and the therapeutic efficacy of magnesium supplementation in autoimmune hypothyroidism.

Additionally, studies examining the combined role of magnesium with selenium, zinc, and vitamin D may provide better insight into integrated micronutrient therapy for thyroid disorders. Understanding the relationship between magnesium and thyroid autoimmunity may lead to improved preventive and therapeutic approaches in endocrine practice.

CONCLUSION

Magnesium plays a crucial yet often overlooked role in thyroid physiology and immune regulation. Increasing evidence indicates that magnesium deficiency is associated with hypothyroidism, elevated thyroid autoantibody levels, oxidative stress, and chronic inflammation. Through its involvement in ATP production, mitochondrial function, enzymatic activity, and immune modulation, magnesium may significantly influence the thyroid axis and the pathogenesis of Hashimoto's thyroiditis. Although further clinical trials are required, assessment and correction of magnesium deficiency may represent a valuable adjunctive strategy in the management of autoimmune hypothyroidism.

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