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ORIGINAL PAPER

Immunological harmony: the role of magnesium in the development of euthyroid Hashimoto's thyroiditis

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Abstract

Magnesium is a trace element that is closely linked to thyroid function and autoimmune thyroiditis. Numerous chronic disorders are also linked to low serum magnesium levels; however, it is unclear how its level relates to the development of autoimmune thyroiditis. In the present study, we evaluated the relationship between Hashimoto's thyroiditis (HT) and serum magnesium levels in 104 patients: 52 with low and 52 with normal serum magnesium levels. Patient records were retrospectively evaluated and the demographic data, serum levels of thyroid-stimulating hormone, anti-thyroid peroxidase antibody (TPOAb), anti-thyroglobulin antibody (TGAb) and serum magnesium levels were recorded. Patients with low magnesium levels were found to have higher levels of TPOAb, TGAb and radiological evidence of HT when compared to those with normal magnesium levels ($P = 0.001$, $P = 0.007$, and $P = 0.001$, respectively). In logistic regression analysis, ultrasonographic HT findings were found to be significantly more common in the magnesium deficient group ($P = 0.001$). The serum magnesium level of 0.72 mmol L^{-1} was determined to be the appropriate cut-off point for the presence of HT ultrasonographic findings with 68.9% sensitivity and 64.4% specificity. As a result, in the present study, low serum magnesium levels were found to be associated with significantly higher incidence of ultrasonographic findings of HT, which may suggest that adequate magnesium supplementation may be an independent protective factor against Hashimoto's Thyroiditis.

Keywords: serum magnesium, Hashimoto's thyroiditis, TPOAb positivity, TGAb positivity

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INTRODUCTION

Autoimmune thyroid diseases, Hashimoto's thyroiditis and Graves' disease are the conditions in which the immune system attacks the thyroid gland, leading to either a hypoactive (hypothyroidism) or overactive (hyperthyroidism) thyroid tissue. Autoimmune thyroiditis is a common endocrine disorder caused by a variety of environmental factors and dependent on genetic susceptibility. The most common autoimmune thyroid disorder is Hashimoto's thyroiditis. In Hashimoto's thyroiditis, the most important laboratory findings indicating autoimmunity are the presence of thyroid peroxidase (TPOAb) and thyroglobulin antibody (TGAb) in the serum. A range of trace elements are related to the pathogenesis of autoimmune thyroiditis. There are few studies on the relationship between magnesium and thyroid disease. This condition affects millions of people worldwide, with women being more commonly affected than men (Luty et al. 2019). Magnesium is a mineral that is present in large amounts in the body. It can be found naturally in a variety of foods, as well as in various pharmaceuticals and food products. Magnesium is a cofactor for numerous enzyme systems that control a variety of biochemical processes in the body, including protein synthesis, the health of muscles and nerves, the regulation of blood sugar, and the control of blood pressure. Magnesium is required for glycolysis, oxidative phosphorylation and energy production. In addition to being essential for the production of DNA, RNA and the antioxidant glutathione, it also aids in the structural development of the bone. Additionally, magnesium participates in the active transport of calcium and potassium ions across cell membranes, which is crucial for the transmission of nerve impulses, the contraction of muscles, and a regular heartbeat (Mazur et al. 2007, Fiorentini et al. 2021). Studies have found that people with autoimmune thyroid disorder, particularly Hashimoto's thyroiditis, tend to have lower levels of serum magnesium than healthy individuals. One study involving patients with Hashimoto's thyroiditis revealed that magnesium supplementation significantly reduced the levels of anti-thyroid antibodies in the blood (Moncayo, Moncayo 2015). How does magnesium play a role in the prevention of autoimmune thyroid disease? One possibility is that magnesium deficiency could contribute to inflammation in the body, which is thought to play a role in the development of autoimmune diseases (Figure 1). In one study, researchers found that magnesium deficiency led to an increase in the production of pro-inflammatory cytokines, which are molecules involved in the immune responses. Magnesium is also involved in the production and regulation of thyroid hormones (Sahni et al. 2010, Li et al. 2011, Kuras et al. 2012, Shahi et al. 2019). While the evidence linking magnesium and autoimmune thyroid disorder is promising, more research is required to fully understand the relationship between these two. In this study, we aimed to investigate the relationship between serum magnesium concentrations and thyroid

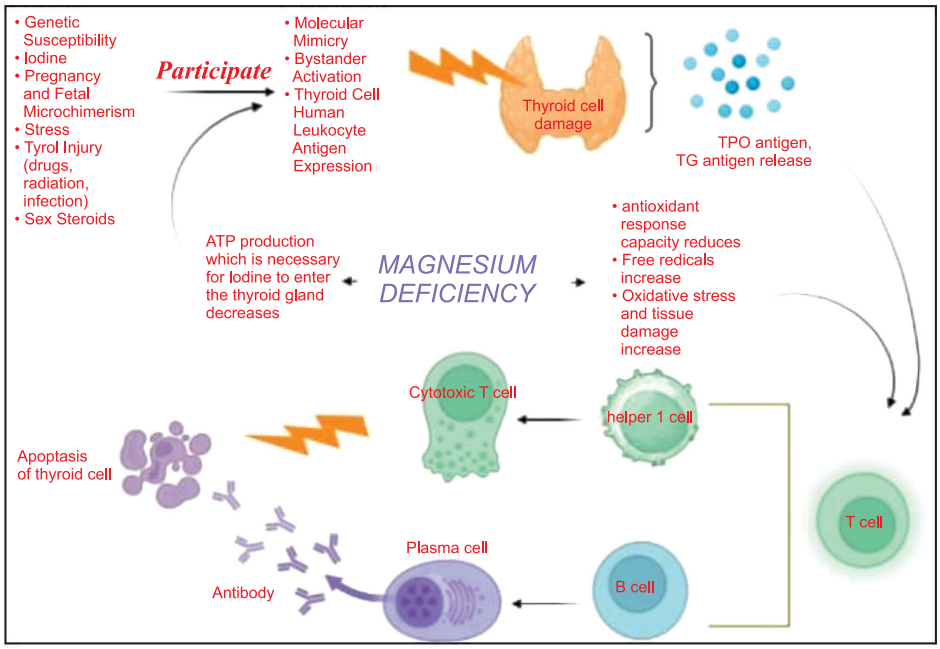


Fig. 1. Magnesium deficiency and Hashimoto's thyroiditis

hormone levels, TPOAb and TGAb levels in the patients with Hashimoto's thyroiditis disorder.

MATERIALS AND METHODS

Study patients

The present study included 52 patients with normal and 52 patients with low magnesium levels who consulted to Trakya University Faculty of Medicine Endocrinology and Metabolism Diseases outpatient clinic due to Diabetes Mellitus, hypertension or obesity between January 2014 and June 2023.

Exclusion criteria were as follows:

1) smokers;
2) those under the age of 18 years;
3) those with a previous history of thyroid surgery;
3) those with missing data;
4) those with parathyroid disorder;
5) those with renal disorder;
6) those with acute myocardial infarction, history of any malignancy,

Addison's disease, liver cirrhosis, history of gastrointestinal malabsorption disease;

7) patients receiving medications that affect serum magnesium levels;

8) and those with hypo/hyperthyroidism.

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Trakya University Faculty of Medicine (No.TUTF-GOBAEK 2023/299).

Clinical evaluation and laboratory data

Demographic data and history of relevant diseases were obtained from patients' self-reports or from electronic recording system (The e-Nabız) – Birinci (2023). The spectrophotometric method was performed in a Beckman Coulter AU5800 (Beckman Coulter, Brea, CA, USA) with its original kits for the determination of Mg level. The determinations were carried out in the Trakya University Biochemistry laboratory. The reference range for normal Mg level was 0.74-1.07 mmol L^{-1}. Blood samples were obtained and analyzed in the laboratory on the same day. Serum thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) levels were determined by immunochemiluminescent testing using anti-TPO and anti-Tg kits (Roche Diagnostics, Germany), in which TPOAb >34 IU mL^{-1} and TGAb > 40 IU mL^{-1} were considered as positive. All laboratory tests were performed in the same center and in the central laboratory of the hospital.

Ultrasonographic evaluation

Thyroid ultrasonographic examination was performed by the same experienced physician, using commercially available ultrasound equipment, LOGIQ P5 US with a 6-10 MHz multi-frequency convex probe (General Electric ® Medical System, Solingen, Germany) equipped with a 7.5Hz ultrasonography device. In ultrasonographic evaluation, the presence of markedly decreased echogenicity, diffuse pseudonodular appearance, heterogeneous parenchyma and fibrous septation were considered to be an indicator of Hashimoto's thyroiditis (HT).

Statistical analysis

IBM SPSS Statistics (version 22.0, IBM, NY, USA) was used to analyze the data. The results were expressed as a mean (standard deviation) or median and range. Patients were divided into 2 groups according to serum magnesium concentrations: those with serum magnesium concentration <0.74 mmol L^{-1} were in the magnesium deficient group, and those with the level of ≥0.74 - ≤ 1.07 mmol L^{-1} were considered as the sufficient magnesium level group. The sufficient magnesium group (0.74-1.07 mmol L^{-1}) was treated as the control group. Demographic data (age, gender), the levels of serum TPOAb, TGAb, TSH and ultrasonographic HT findings were used in the statistical analysis, and their distributions are shown in Table 1. Data in each

Table 1

Characteristics of the patients in terms of serum magnesium levels

		All patients	Serum magnesium level (mmol L^{-1})		*P*
			low (<0.74 mmol L^{-1}) N:52	normal (0.74-1.07 mmol L^{-1}) N:52	
Sex (*n*, %)	male	22 (21.2%)	12(23.1%)	10(19.2%)	0.631
	female	82 (78.8%)	40(76.9%)	42(80.8%)	
Age (years)		48±17.1	51.3±17.8	44.9±16	0.064
Age group (*n*, %)	young (18–39 years)	39(37.5%)	16(30.8%)	23(44.2%)	0.249
	middle-aged (40–64 years)	41(39.4%)	21(40.4%)	20(38.5%)	
	elderly (≥65 years)	24(23.1%)	15(28.8%)	9(17.3%)	
serum magnesium level (mmol L^{-1})		0.74±0.12	0.64±0.06	0.84±0.05	<0.001
TSH (mIU L^{-1})		2.3±1.2	2.4±1.2	2.1±1.2	0.202
TPOAb (+) (IU mL^{-1})		42(40.4%)	29(55.8%)	13(25%)	0.001
TGAb (+), (IU mL^{-1})		35(33.7%)	24(46.2%)	11(21.2%)	0.007
Ultrasonographic HT findings		45(43.3%)	14(13.5%)	31(29.8%)	0.001

Abbreviations: TSH – serum thyroid-stimulating hormone, TPOAb – serum thyroid peroxidase antibody, TGAb – serum thyroglobulin antibody, HT – Hashimoto's thyroiditis. Data are expressed as number (percentage) or mean±standard deviation.

group were analyzed using single-factor analysis of variance, while Chi-square test was used for inter-group comparisons. A logistic regression model was utilized for confounding factors; TPOAb, TGAb and ultrasonographic HT findings were analyzed as dependent factors. In logistic regression analysis using the backward method, modeling was performed for 3 groups. Model 1a: adjusted for all covariates as TGAb, TPOAb and HT; Model 2b: additionally adjusted for TGAb and HT; Model 3c: adjusted for ultrasonographic HT findings. $P<0.05$ was considered as statistically significant. Additionally, Receiver Operating Characteristic (ROC) Curves were utilized to determine the predictive magnesium levels in terms of Hashimoto's thyroiditis in individuals with ultrasonographic HT findings. The Youden Index (J) was used to evaluate the ROC curve (Youden 1950). Using the Youden Index, the cut-off point indicating the magnesium level with the most appropriate sensitivity and specificity associated with ultrasonographic HT findings was determined on the ROC curve.

RESULTS

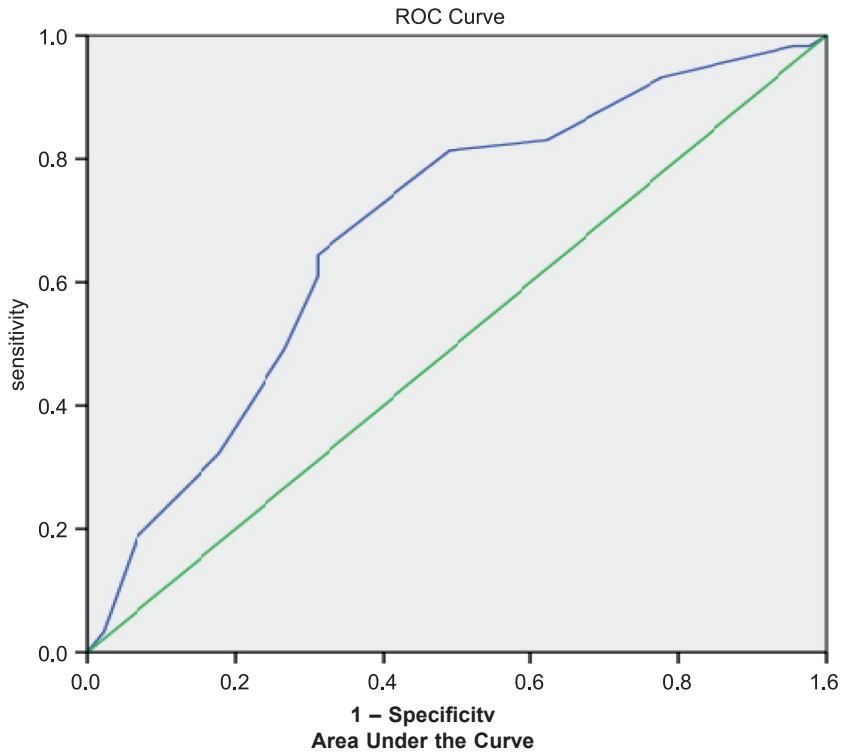
52 patients with low and 52 control subjects with normal serum magnesium levels were evaluated in the study. The mean age of the overall population was 48±17.1 years and 78.8% were female. There was no significant difference between the groups with low and normal magnesium levels in terms of age, gender and thyroid functions. Compared to patients with normal magnesium levels, statistically higher TPOAb and TGAb positivity rates were detected in the patients with low magnesium levels ($P = 0.001$, $P = 0.007$, respectively). Thyroid ultrasonographic evaluation revealed that radiological findings of HT were significantly more common in the group with low serum magnesium levels ($P = 0.001$) – Table 1. In the logistic regression analysis, when considering three independent variables (TPOAb and TGAb positivity, HT findings on ultrasonography), no significant independent predictive effect on magnesium deficiency was observed compared to the initial model. However, upon introducing only HT findings on ultrasonography as an independent variable in the third model, it was discovered that the likelihood of HT findings on ultrasonography was 4.007 times higher (95% CI: 1.754;9.152) in individuals classified as magnesium deficient (Table 2). A ROC curve analysis was performed to determine the most appropriate cut-off point for the serum magnesium level in terms of radiological HT findings. The Youden Index (J) revealed that the serum magnesium level of 0.72 mmol L^{-1} was an appropriate cut-off point with 68.9% sensitivity and 64.4% specificity for the presence of positive ultrasonographic HT findings (Figure 2).

Table 2

The relative risk of TPOAb positivity, TGAb positivity and ultrasonographic HT findings according to the levels of serum magnesium as determined by using multiple logistic regression analyses

Serum magnesium level (mmol L^{-1})		B	S.E.	Wald	df	P	OR	95% CI	
								Lower	Upper
Model 1[a]	positive TPOAb	-0.095	1.283	0.006	1	0.941	0.909	0.074	11.233
	positive TGAb	-0.059	0.788	0.006	1	0.941	0.943	0.201	4.422
	HT findings on ultrasonography	1.345	1.482	0.824	1	0.364	3.838	0.210	70.051
	constant	-0.498	1.311	0.144	1	0.704	0.608		
Model 2[a]	positive TGAb	-0.067	0.780	0.007	1	0.931	0.935	0.203	4.315
	HT findings on ultrasonography	1.440	0.742	3.771	1	0.052	4.222	0.987	18.067
	constant	-0.593	0.272	4.757	1	0.029	0.553		
Model 3[a]	HT findings on ultrasonography	1.388	0.421	10.846	1	0.001	4.007	1.754	9.152
	constant	-0.593	0.272	4.757	1	0.029	0.553		

Abbreviations: TSH – serum thyroid-stimulating hormone, TPOAb – serum thyroid peroxidase antibody, TGAb – serum thyroglobulin antibody, HT – Hashimoto's thyroiditis, OR – odds ratio, CI – confidence interval, S.E. – Standard error, B – Beta Regression coefficient. Relative risks of TPOAb positivity, TGAb positivity and ultrasonographic HT findings according to serum magnesium levels as determined by multiple logistic regression analyses. OR – odds ratio, CI – confidence interval. Model 1 [a] – adjusted for all covariates in model 1[a] as well as TGAb, TPOAb and HT; Model 2[b] – additionally adjusted for TGAb and HT; Model 3[c] – adjusted for ultrasonographic HT findings; Regression analyses were performed by using the backward method.



Test result variable(s): magnesium

Area	Std. Error	Asymptotic Sig.	Asymptotic 95% confidence interval	
			lower bound	upper bound
.685	.054	.001	.580	.789

Fig. 2. Receiver Operating Characteristic (ROC) Curves for predictive magnesium levels in terms of Hashimoto's thyroiditis. The Youden Index (J) was used to evaluate the ROC curve

DISCUSSION

Thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) are markers of autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease. These antibodies are associated with thyroid dysfunction and are often measured in the diagnosis and during the management of thyroid disorders. Magnesium, an essential mineral, plays a crucial role in various biochemical reactions within the body, including thyroid function. TPOAb and TGAb are autoantibodies produced by the immune system that target specific components of the thyroid gland. TPOAb targets thyroid peroxidase, an enzyme involved in the production of thyroid hormones,

while TGAb targets thyroglobulin, a protein precursor of thyroid hormones. Elevated levels of these antibodies are indicative of autoimmune thyroid disorders, with TPOAb being more commonly associated with Hashimoto's thyroiditis. Magnesium is an essential cofactor in numerous enzymatic reactions involved in thyroid hormone synthesis and metabolism. It facilitates the conversion of thyroxine (T4) to triiodothyronine (T3), the biologically active form of thyroid hormone, by the enzyme 5'-deiodinase. Magnesium also influences the sensitivity of thyroid hormone receptors in target tissues. Consequently, alterations in magnesium levels can affect thyroid function and may contribute to the development or progression of thyroid disorders. Several studies have investigated the relationship between thyroid antibodies and serum magnesium levels. The precise mechanisms underlying the association between thyroid antibodies and serum magnesium levels remain unclear. It is hypothesized that magnesium deficiency may exacerbate autoimmune thyroid inflammation and dysfunction by influencing immune responses and inflammatory pathways (Wang et al. 2018).

The amount of magnesium found in the normal human body is 25 grams, of which 50-60% is present in the bones, while serum contains less than 1% of the total amount of magnesium, which is closely regulated. The range of normal serum magnesium concentrations is 0.74-1.07 mmol L^{-1}; the serum magnesium level of less than 0.74 mmol L^{-1} is referred to as hypomagnesemia (Barbagallo et al. 2009, Bergman et al. 2009, Mejia-Rodriguez et al. 2013). The kidney, which excretes about 120 mg of magnesium daily in the urine, is mostly responsible for maintaining magnesium homeostasis. Urinary excretion declines in the presence of reduced magnesium status (Bergman et al. 2009, Vermeulen et al. 2023).

In our study, serum magnesium levels below 0.72 mmol L^{-1} were found to be associated with TGAb and TPOAb positivity and also with the presence of ultrasonographic HT findings. This can be explained by two factors. Firstly, low serum magnesium levels can raise antibodies by triggering an autoimmune reaction. Low serum magnesium levels have been linked to lower immunological tolerance and aberrant immune cell activation, according to prior research (Wang et al. 2018). Another theory is that magnesium deficient patients are at higher risk in a number of pathways that are involved in the metabolism of antioxidants, including glutathione synthesis. As a result, low serum magnesium levels may reduce the ability of cells to respond to antioxidants and may permit the accumulation of free radicals, which can result in oxidative stress and tissue damage (Morabito et al. 2019, Liu et al. 2020). Epidemiological research has revealed a link between chronic inflammatory disorders, high blood C reactive protein levels and magnesium deficiency (Chacko et al. 2011, Shahi et al. 2019, Liu et al. 2020, Maier et al. 2021). In this study, euthyroid patients were included in the study because previous studies have shown that magnesium levels are affected in hypothyroidism and hyperthyroidism (Wang et al. 2018, Zhou

et al. 2022). Although TPOAb and TGAb positivity was associated with low serum magnesium levels in our study, logistic regression analysis revealed that this association was not statistically significant, while ultrasonographic HT findings were found to be significantly associated with magnesium deficiency. Considering this, it may be possible to suggest that the effect of magnesium deficiency can be more closely related to oxidative stress and inflammation than to autoimmune responses. Particularly in the patients without iodine insufficiency, magnesium deficiency is more substantially associated with ultrasonographic HT findings. Although a low serum magnesium level is not the cause of autoimmune thyroiditis, it may aggravate the condition by causing inflammation. In this situation, even if the autoantibody levels are not elevated, the thyroid gland may become inflamed, leading to early--stage HT findings on ultrasonography.

CONCLUSIONS

In the present study, ultrasonographic HT findings, TPOAb and TGAb positivity were all found to be associated with insufficient magnesium status; however, the logistic regression analysis showed that ultrasonographic HT findings were significantly correlated to magnesium deficiency, regardless of antibody levels. Magnesium supplementation may be helpful in the patients with ultrasonographically identified HT who have magnesium deficiency.

Author contributions

Conceptualization – EC, BYB, BA, MO, SYC¸ MC; Sample collection – EC, BYB, BA, MO, SYC¸ MC; Data analyses – EC, MC, ACY; Data Interpretation – EC, BYB, MC, ACY; Writing – original draft – EC, BYB, BA, MO, SYC¸ ACY, MC'; Critical review of the manuscript: all the authors; Validation: all the authors. All the authors have read and agreed to the published version of the manuscript.

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Ethics declarations: Ethical Approval The institutional Ethics Committee granted approval for the collection of the samples (No.TUTF-GOBAEK 2023/299).

Conflicts of interest

The authors have no relevant financial or nonfinancial interests to disclose.

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