



Correlation of serum ferritin and thyroid hormone levels: A matched case–control study

Lejla Čano Dedić^{1,2}, Emsel Papić^{2*}, Arzija Pašalić³, Dalila Smajlović⁴, Sabina Šečić-Selimović³, Sabina Šegalo²

¹Department of Medical-Biochemical Diagnostics, Polyclinic Atrijum, Sarajevo, Bosnia and Herzegovina, ²Department of Laboratory Technology, Faculty of Health Studies, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, ³Department of Nutrition and Health Dietetics, Faculty of Health Studies, University of Sarajevo, Sarajevo, Bosnia and Herzegovina, ⁴Institute for Health Protection of Employees of the Ministry of Internal Affairs, Sarajevo Canton, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Introduction: Hypothyroidism is a common disorder of the endocrine system caused by insufficient biologically active hormones at the tissue level or the inability of the tissue to utilize thyroid hormones. Iron plays a crucial role in the synthesis and metabolism of thyroid hormones, and it is stored in the body as ferritin. We aimed to evaluate the correlation between serum ferritin (SF) levels and thyroid hormone panel levels in both hypothyroid and euthyroid subjects.

Methods: In 2022, a matched case–control study was conducted. The study involved participants with hypothyroidism and a control group ($n = 53$). The levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and SF were measured using the chemiluminescence immunoassay on a Mindray CI 900-i analyzer (Shenzhen Mindray Bio-Medical Electronics Co., China).

Results: The hypothyroid group had TSH levels that were significantly higher (10.76 [8.54-18.76] vs. 1.76 [1.26-2.58]; $p < 0.001$) and SF concentrations that were significantly lower (39.08 [21.15-45.70] vs. 54.09 [41.41-71.82]; $p < 0.001$) compared to the control group. In both male and female subjects of the hypothyroid group, a strong negative correlation was found between SF concentration and TSH levels ([$Rho = -0.855, p < 0.01$]; [$Rho = -0.747; p < 0.01$]). In female subjects of the hypothyroid group, a weak positive correlation was found between SF concentration and fT3 ($Rho = 0.488; p < 0.05$). In the euthyroid group, a correlation of the same strength and direction was found for fT4 ($Rho = 0.366; p < 0.05$).

Conclusion: Research results indicate a correlation between lower SF concentrations and hypothyroidism, which is of particular importance for understanding the etiopathogenesis, diagnosis, monitoring, and treatment modalities of patients with hypothyroidism.

Keywords: Hypothyroid; serum ferritin; thyroid stimulating hormone; triiodothyronine; thyroxine

INTRODUCTION

Functional disorders of the thyroid gland are a diverse and non-specific group of diseases that result from quantitative changes in hormone secretion or the structure of the gland. It is crucial to recognize the development of the disease in time, as the complexity of symptoms can vary (1,2). Therefore, highly sensitive and specific laboratory methods are imperative for a timely and reliable diagnosis (3). Hypothyroidism is one of the most common chronic diseases worldwide, characterized by high thyroid stimulating hormone (TSH) levels and triiodothyronine (T3) and thyroxine (T4) concentrations below the normal

reference range (4). A broad spectrum of clinical symptoms in this disorder includes changes in body weight, fatigue, weakness, depression, decreased cardiovascular contractility, infertility, reversible dementia, neurosensory, musculoskeletal, and gastrointestinal symptoms (3,5,6). The incidence and prevalence rates of hypothyroidism are challenging to interpret due to genetic factors, environmental influences, dietary habits, population selection, and diagnostic variability. However, the incidence is primarily age-dependent, with the highest incidence rate between 30 and 50 years of age (2,3,7). In Europe, the prevalence rates in the general population vary between 0.2% and 5.3%, with an estimated additional 5% of cases remaining undiagnosed. Recent studies emphasize that women and white people are at a higher risk of developing hypothyroidism (4). Trace elements play a key role in the normal functioning of the thyroid gland. Iodine, in particular, plays a crucial role in the synthesis of thyroid hormones, while the function of other trace elements, for example, iron,

*Corresponding author: Emsel Papić, Department of Laboratory Technology, Faculty of Health Studies, University of Sarajevo, Sarajevo, Bosnia and Herzegovina.
E-mail: emsel.papic@fzs.unsa.ba

Submitted: 19 October 2023/Accepted: 08 December 2023

DOI: <https://doi.org/10.17532/jhsci.2023.2611>



selenium, zinc, magnesium, and others have gained attention in recent years. Although the precise mechanism of the synergistic effect of iodine and iron is still not entirely understood, empirical evidence has shown that individuals with iodine deficiency exhibit decreased synthesis and secretion of thyroid hormones (8). In hypothyroidism, ferritin values are also impaired as an indicator of the level of iron stores, which can consequently lead to reduced conversion of the inactive form of T₄ into the active form of T₃, as well as reduced inhibition of the synthesis of thyroid peroxidase (9,10). T₃ is a key hormone of body homeostasis that in addition governs the activation of the gene for ferritin production in the liver. When the free fraction of the hormone T₃ (fT₃) is low, the production of ferritin in the liver is slowed down, also it has been reported that ferritin production in the liver was significantly reduced in patients treated with thyreostatics. Recent studies suggest that the determination of serum ferritin (SF) levels may be useful for the assessment of thyroid function and hormone effects on peripheral tissues (8-12). The aim of this study is to evaluate the relationship between SF and thyroid hormone panel levels in hypothyroid and euthyroid patients.

METHODS

The matched case-control study was conducted in 2022 at the Department of Medical-Biochemistry of the Polyclinic Atrijum, after obtaining ethical approval from the institution. Subjects of both genders older than 18 years, with medical documentation and laboratory analysis of thyroid hormone and ferritin concentrations performed in the Polyclinics laboratory, were included in the study. Defined exclusion criteria for the study were: Age under 18 years, pregnancy, confirmed other endocrinopathies, diseases of the cardiovascular system, kidney and liver dysfunction as well as acute and chronic infections. Subjects with a sub-clinical form of hypothyroidism (TSH >5.10 μIU/mL and normal free thyroxine [fT₄] and fT₃ levels) were also excluded from the study. Based on the above criteria, 53 newly diagnosed subjects were included in a hypothyroid group (n = 53). Sex and age-matched apparently healthy subjects with euthyroid status were included in a control group (n = 53). Included participants signed an informed consent form and the principles of the Declaration of Helsinki were followed. Venous blood samples were collected by venipuncture in tubes with separating gel under aseptic conditions and centrifuged. TSH, fT₃, fT₄, and SF were determined from transparent serum samples using the Chemiluminescent immunoassay on a Mindray Cl 900-i analyzer (Shenzhen Mindray Bio-Medical Electronics Co., China). Hypothyroidism was diagnosed in subjects with serum concentrations TSH >5.10 μIU/mL (reference range 0.35-5.10 μIU/mL), fT₄ concentration <6.43 pmol/L (reference range 6.43-18.02 pmol/L), and fT₃ concentration <2.76 pmol/L (reference range 2.76-6.45 pmol/L). The reference interval for SF was 12.0-135.0 ng/mL for women and 27-350 ng/mL for men. Commercial control samples at two concentration levels were used to verify accuracy and precision, and the coefficient of variation for the parameters tested ranged from 2.86% to 4.72%.

The statistical analysis was performed using IBM SPSS software (version 26.0, Statistical Package for the Social

Sciences, Chicago, Illinois, USA) for Windows. The normality of the distribution for the observed variables was tested using the Kolmogorov-Smirnov test. If deviations from the normal distribution were found, non-parametric tests were used. The data are presented as median and interquartile range as well as mean and standard deviation. The Chi-square test was used to examine significant differences in categorical variables. The correlation coefficients were calculated using the Pearson test and the Spearman test. Statistical significance was set at a $p \leq 0.05$.

RESULTS

The average age of the subjects with hypothyroidism was 38.22 ± 8.58 years, compared with 37.45 ± 9.74 years in the control group. The proportion of men (n = 18; 34%) and women (n = 35; 66%) was equal in both groups. Statistically significant differences in the age and gender distribution were not found ($p = 0.665$, $p = 1.0$).

Table 1 shows the average concentrations of the parameters examined in the groups studied. The ferritin concentration was significantly higher in the control group ($p < 0.001$) than in the group of subjects with hypothyroidism (54.09 [41.41-71.82] vs. 39.08 [21.15-45.70]). Subjects with hypothyroidism had significantly higher TSH levels compared to the control group ($p < 0.001$) (10.76 [8.54-18.76] vs. 1.76 [1.26-2.58]), while in the control group, the levels of fT₃ (4.44 ± 0.88 vs. 2.67 ± 0.57 ; $p < 0.001$) and fT₄ (11.05 [9.53-13.76] vs. 5.74 [5.01-6.11]; $p < 0.001$) were about twice as high.

The control group showed significantly higher SF concentrations in both male (83.99 ± 25.10) and female (45.78 [34.96-54.85]) subjects compared to those with hypothyroidism (male: 52.41 ± 16.04 , female: 28.76 [13.65-39.76]). A similar pattern was observed for fT₃ levels, with males in the control group having higher levels (4.31 ± 0.97) than those with hypothyroidism (2.66 ± 0.60), and women in the control group showing higher levels (4.47 ± 0.84) than those with hypothyroidism (2.68 ± 0.56). The TSH concentration in male subjects with hypothyroidism was twice as high as in female subjects with hypothyroidism (18.65 [13.22-21.23] vs. 9.76 [8.14-13.54]). Compared to the control group, there was a fourfold increase in TSH values in males with hypothyroidism (18.65 [13.22-21.23] vs. 4.25 [3.79-5.16]) and a fivefold increase in females with hypothyroidism (9.76 [8.14-13.54] vs. 1.76 [1.29-2.54]). Both male and female subjects with hypothyroidism had lower fT₄ concentrations than those in the control group (male: 5.43 [4.98-6.22] vs. 10.38 [8.57-14.92]; female: 5.76 [5.29-6.11] vs. 11.53 [9.76-13.76]). All the variables

TABLE 1. Average serum ferritin and thyroid parameters in the groups studied

Variable	Case group	Control group	p
SF (ng/mL)	39.08 (21.15-45.70)	54.09 (41.41-71.82)	<0.001
TSH (μIU/mL)	10.76 (8.54-18.76)	1.76 (1.26-2.58)	<0.001
fT ₃ (pmol/L)	2.67 ± 0.57	4.44 ± 0.88	<0.001
fT ₄ (pmol/L)	5.74 (5.01-6.11)	11.05 (9.53-13.76)	<0.001

*Data are presented as the median and interquartile range (25th and 75th percentiles) and as mean and standard deviation. SF: Serum ferritin; TSH: Thyroid stimulating hormone; fT₃: Free triiodothyronine; fT₄: Free thyroxine (fT₄)

TABLE 2. Differences in mean serum levels of ferritin and thyroid parameters concerning sex differences of subjects

Variable	Case group		Control group		<i>p</i>
	Male	Female	Male	Female	
SF (ng/mL)	52.41±16.04	28.76 (13.65-39.76)	83.99±25.10	45.78 (34.96-54.85)	<0.001
TSH (μIU/mL)	18.65 (13.22-21.23)	9.76 (8.14-13.54)	4.25 (3.79-5.16)	1.76 (1.29-2.54)	<0.001
fT3 (pmol/L)	2.66±0.60	2.68±0.56*	4.31±0.97	4.47±0.84	<0.001
fT4 (pmol/L)	5.43 (4.98-6.22)	5.76 (5.29-6.11)	10.38 (8.57-14.92)	11.53 (9.76-13.76)	<0.001

*Data are presented as the median and interquartile range (25th and 75th percentiles) and as mean and standard deviation. SF: serum ferritin; TSH: thyroid stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine (fT4)

examined showed statistically significant differences at the level of $p < 0.001$ (Table 2).

According to the results shown in Table 3, the correlation analysis revealed no significant relationship between ferritin and TSH levels or between ferritin and thyroid hormones in the groups studied ($p > 0.05$).

Based on the findings presented in Table 4, it was observed that there is a very strong negative correlation between the levels of SF and TSH in the group of subjects with hypothyroidism, regardless of gender. This correlation was found to be significant in male (Rho = -0.855 , $p < 0.01$) and female (Rho = -0.747 ; $p < 0.01$) subjects. In addition, a weak positive association between the concentration of ferritin and fT3 was observed in female subjects in the case group (Rho = 0.488 ; $p < 0.05$). In the control group, a similar association was observed between the concentration of ferritin and fT4 (Rho = 0.366 ; $p < 0.05$).

DISCUSSION

Ferritin is known to indicate the level of stored iron in the body. In recent years, its role in assessing disease activity in patients with hypothyroidism has gained attention. Thyroid hormones not only play a crucial role in iron metabolism but also in regulating ferritin expression in the body. However, hypothyroidism disrupts this relationship and the regulation of hematopoiesis, which causes iron deficiency anemia (13,14). Our study showed a significant correlation between thyroid hormone levels and ferritin levels in subjects with hypothyroidism, regardless of gender.

The research design did not show any statistically significant differences in the distribution of subjects by group. However, there was a higher incidence of hypothyroidism in female subjects. Research has shown that women of reproductive age and pregnant women have a greater risk of developing hypothyroidism due to the antithyroid function of estrogen, which reduces the concentration of active thyroid hormones. Hypothyroidism can also cause a decrease in thyroid hormones and disturbances in iron metabolism, leading to increased production of free radicals. These free radicals contribute to the development of oxidative stress and damage to blood cells (15-17).

In this study, subjects were divided into two groups based on their thyroid hormone values - hypothyroid and euthyroid. The hypothyroid group had significantly higher levels of TSH compared to the euthyroid group, which is consistent with previously published results (13,18,19). The study also found that men had higher TSH levels than women. High TSH levels were found to contribute to increased inflammation and decreased antioxidant potential of ferritin which is associated with iron in hypothyroid patients (18).

TABLE 3. Correlation analysis of serum ferritin levels and thyroid parameters in the groups studied

Variable	SF (ng/mL)	
	Case group	Control group
TSH (μIU/mL)		
Rho	-0.226	0.002
<i>p</i>	>0.05	>0.05
fT3 (pmol/L)		
R	0.234	-0.137
<i>p</i>	>0.05	>0.05
fT4 (pmol/L)		
Rho	0.117	0.040
<i>p</i>	>0.05	>0.05

SF: Serum ferritin; TSH: Thyroid stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine (fT4)

TABLE 4. Correlation analysis of serum ferritin levels and thyroid parameters concerning sex differences of subjects

Variable	SF (ng/mL)			
	Case group		Control group	
	Male	Female	Male	Female
TSH (μIU/mL)				
Rho	-0.855**	-0.747**	0.184	-0.188
<i>p</i>	<0.01	<0.01	>0.05	>0.05
fT3 (pmol/L)				
R	0.260	0.488*	-0.049	-0.074
<i>p</i>	>0.05	<0.05	>0.05	>0.05
fT4 (pmol/L)				
Rho	0.395	0.284	-0.290	0.366*
<i>p</i>	>0.05	>0.05	>0.05	<0.05

*:Correlation is significant at the 0.05 level; **: Correlation is significant at the 0.01 level. SF: Serum ferritin; TSH: Thyroid stimulating hormone; fT3: Free triiodothyronine; fT4: Free thyroxine (fT4)

Our research has uncovered a strong negative correlation between TSH and SF levels among both male and female individuals with hypothyroidism. These findings are consistent with a study conducted by Kumar et al. (19) in 2022. Furthermore, our investigation also revealed that the hypothyroid group had significantly lower ferritin levels compared to the control group. This result is in line with several comparative studies, including those conducted by Akhter et al. (10), Mishra et al. (11), Chatterjee et al. (13), and Sahana and Kruthi (20). These findings suggest that SF levels can potentially serve as an indicator of disease severity in hypothyroidism. However, it is important to note that SF levels decrease with age, which should be taken into consideration when interpreting the results (14).

Our study found that both male and female subjects with hypothyroidism had significantly lower levels of fT3 and

fT₄, which is consistent with previous studies conducted by Sahana and Kruthi (20), and Sachdeva et al. (21).

We also observed a weak positive correlation between the concentration of SF and fT₃ in the hypothyroid group, regardless of gender ($p > 0.05$). However, our findings for male subjects different from those reported by Krishnamurthy et al. (14), where a positive correlation was found between SF and fT₄ ($r = 0.033$, $p = 0.0109$), and an inverse correlation with serum fT₃ ($r = -0.060$, $p < 0.0001$). In our female subjects with hypothyroidism, unlike the control group, we did not find any significant correlation between SF and fT₄ levels, which is consistent with the results obtained by Akhter et al. (10).

When interpreting test results, it is important to consider risk factors such as body weight, which can influence thyroid hormones, particularly fT₃, and the value of ferritin as an inflammatory marker. This is particularly important for female patients, where inflammation can remain hidden (22). In addition, most research suggests that changes in ferritin and thyroid hormone levels are due to changes in iron levels (11,13,18).

Therefore, monitoring thyroid hormone levels can be helpful in tracking patients with iron deficiency anemia and assessing the success of iron therapy, as emphasized in the study by El-Masry et al. (23). In line with this, determining ferritin and thyroid hormone levels is an important approach in evaluating patients with hypothyroidism.

CONCLUSION

Research results indicate a correlation between lower SF concentrations and hypothyroidism, which is of particular importance for understanding the etiopathogenesis, diagnosis, monitoring, and treatment modalities of patients with hypothyroidism.

Study limitation

The relatively small sample size in our study indicates the need of future large-scale studies to confirm the present finding.

Financial disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DECLARATION OF INTERESTS

Authors declare no conflict of interest.

REFERENCES

1. Stojanov M. Laboratorijska Endokrinologija. Beograd: Medicinska Knjiga; 2016.
2. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* 2018;14(5):301-16.

3. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet* 2017;390:1550-62. [https://doi.org/10.1016/S0140-6736\(17\)30703-1](https://doi.org/10.1016/S0140-6736(17)30703-1)
4. Chiovato L, Magri F, Carlé A. Hypothyroidism in context: Where we've been and where we're going. *Adv Ther* 2019;36(S2):47-58. <https://doi.org/10.1007/s12325-019-01080-8>
5. Guglielmi R, Grimaldi F, Negro R, Frasoldati A, Misischi I, Graziano F, et al. Shift from levothyroxine tablets to liquid formulation at breakfast improves quality of life of hypothyroid patients. *Endoc Metab Immune Disord Drug Targets* 2018;18(3):235-40. <https://doi.org/10.2174/1871530318666180125155348>
6. Ott J, Promberger R, Kober F, Neuhold N, Tea M, Huber JC, et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: A prospective case-control study in women undergoing thyroidectomy for benign goiter. *Thyroid* 2011;21(2):161-7. <https://doi.org/10.1089/thy.2010.0191>
7. Vanderpump MP. The epidemiology of thyroid disease. *Br Med Bull* 2011;99(1):39-51. <https://doi.org/10.1093/bmb/ldr030>
8. Zhou Q, Xue S, Zhang L, Chen G. Trace elements and the thyroid. *Front Endocrinol (Lausanne)* 2022;13:904889. <https://doi.org/10.3389/fendo.2022.904889>
9. Wopereis DM, Du Puy RS, van Heemst D, Walsh JP, Bremner A, Bakker SJ, et al. The relation between thyroid function and anemia: A pooled analysis of individual participant data. *J Clin Endocrinol Metab* 2018;103(10):3658-67. <https://doi.org/10.1210/je.2018-00481>
10. Akhter S, Nahar Z, Parvin S, Alam A, Sharmin S, Arslan M. Thyroid status in patients with low serum ferritin level. *Bangladesh J Med Biochem* 2013;5(1):5-11.
11. Mishra AK, Anand R, Verma SP, Gupta KK. Study of impact of subclinical hypothyroidism on iron status and hematological profile. *Int J Adv Med* 2018;5(2):446. <https://doi.org/10.18203/2349-3933.ijam20181087>
12. Zhang HY, Teng XC, Shan ZY, Wang ZJ, Li CY, Yu XH, et al. Association between iron deficiency and prevalence of thyroid autoimmunity in pregnant and non-pregnant women of childbearing age. *Chin Med J (Engl)* 2019;132(18):2143-9. <https://doi.org/10.1097/CM9.0000000000000409>
13. Chatterjee S, Chakrabarti P, Sinhamahapatra P. Relationship between iron metabolism and thyroid hormone profile in hypothyroidism. *Int J Res Med Sci* 2021;9(3):790-3. <https://doi.org/10.18203/2320-6012.ijrms20210879>
14. Krishnamurthy HK, Reddy S, Jayaraman V, Krishna K, Song Q, Rajasekaran KE, et al. Association of serum ferritin levels and thyroid hormones. *Open J Clin Diagn* 2023;13(03):68-79. <https://doi.org/10.4236/ojcd.2023.133007>
15. Bashboosh NN. Correlation between hypothyroidism and iron deficiency anemia in female patients. *World J Pharm Pharm Sci* 2017;6:80-9.
16. Vinayagamoorthi R, Dhiman P, Kollipaka R, Sabita P, Hemavarthy V. Association of hypothyroidism with low serum ferritin levels and iron-deficiency anemia during the first trimester of pregnancy. *Cureus* 2022;14(8):e28307. <https://doi.org/10.7759/cureus.28307>
17. Dahiya K, Verma M, Dhankhar R, Ghalaut VS, Ghalaut PS, Sachdeva A, et al. Thyroid profile and iron metabolism: Mutual relationship in hypothyroidism. *Biomed Res* 2016;27(4):1212-5.
18. Prabhu PS, Cheriyan S, Sulaiman L. A comparative study of serum ferritin and thyroid stimulating hormone (TSH) levels in hypothyroid and Euthyroid subjects. *Int J Clin Biochem Res* 2022;9(3):250-3.
19. Kumar S, Keshari JR, Kumari R, Prakash P, Kumar U, Prakash V. Relationship between iron profile and thyroid profile in hypothyroid patients. *Nat J Lab Med* 2022;11(1):BO01-3. <https://doi.org/10.7860/njlm/2022/48551.2556>
20. Sahana KR, Kruthi BN. Correlation of serum ferritin and thyroid hormone status among hypothyroidism. *Int J Biotechnol Biochem* 2020;16:51-7.
21. Sachdeva A, Singh V, Malik I, Roy P, Madaan H, Nair R. Association between serum ferritin and thyroid hormone profile in hypothyroidism. *Int J Med Sci Public Health* 2015;4(6):863.
22. Hendriantingtyas M, Wicaksono SA, Kuntjoro LP, Maharani, Utami SB. Correlation between ferritin and thyroid hormones in obesity. *Mal J Med Health Sci* 2020;16(Suppl 14):29-33.
23. El-Masry HM, Hamed AM, Hassan MH, Fayed HM, AbdElzaher M. Thyroid function among children with iron deficiency anaemia: Pre and post iron replacement therapy. *J Clin Diagn Res* 2018;12(1):BC01-5.