International Journal of Research in Medical Sciences
*Bhattacharya J et al. Int J Res Med Sci. 2026 Sep;14(9):3849-3856*
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20262807

**Original Research Article**

# Investigating the correlation of ferritin and uric acid levels in hypothyroidism: a case-control study

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**Received:** 25 July 2026
**Revised:** 08 August 2026
**Accepted:** 10 August 2026

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## ABSTRACT

**Background:** Hypothyroidism is one of the most prevalent endocrinological disorder in our country as well as other parts of the world. Uric acid is a known antioxidant while ferritin, besides its role in iron storage is an acute-phase reactant. The present study is an endeavour to study the metabolic changes in uric acid and ferritin levels in relation to subclinical and overt hypothyroidism.
**Methods:** The 34 subclinical, 27 overt hypothyroid and 35 age and sex matched control individuals in the age group of 18-60 years were included. Serum thyroid stimulating hormone (TSH), Free thyroxine (fT4) and ferritin were measured using electrochemiluminescence immunoassay techniques; while uric acid was measured using Uricase, Trinder-End Point spectrophotometric method.
**Results:** The serum uric acid levels were found to be significantly higher in overt hypothyroidism as compared to subclinical hypothyroidism. No significant difference was found in the serum ferritin levels of the individuals with subclinical and overt hypothyroidism.
**Conclusions:** Hence, the present study suggests that hypothyroidism results in an increased serum uric acid level most probably caused by decreased renal clearance of uric acid due to compromised fT4 function. However, no such effect was found in serum ferritin levels.

**Keywords:** Subclinical hypothyroidism, Overt hypothyroidism, Serum uric acid, Serum ferritin

## INTRODUCTION

Hypothyroidism is known to be the most common form of thyroid disorders in India with a prevalence of about 11%.[1] The clinical presentations of hypothyroidism include a myriad of signs and symptoms from nothing at all to fatigue, weight gain, constipation, cold intolerance and change in voice.[2] The cardinal defect in hypothyroidism is the inadequate production of thyroid hormones by the thyroid gland. Hypothyroidism is further classified into primary (abnormality of the thyroid gland), secondary (pituitary cause) and tertiary (hypothalamic cause).[3] Decreased blood levels of fT4, with an elevated thyrotropin (i.e., TSH) level is diagnostic in primary causes (thyroid source) while TSH level may be normal to low in secondary or tertiary causes.[4] Subclinical primary hypothyroidism (SH) is characterized by elevated TSH levels with normal fT4 levels. Subclinical hypothyroidism may progress to overt hypothyroidism (OH) in approximately 2-5% cases annually when fT4 values also become below normal values with elevated TSH levels.[5]

Uric acid, an end product of purine catabolism, is also an effective antioxidant. Apart from its predictive value in diagnosis of gout, serum uric acid levels have also been associated with metabolic syndrome, hypertension, cardiovascular diseases, diabetes mellitus, and dyslipidemia.[6-9] Hypothyroidism has been found to be associated with increased serum uric acid level in various studies.[10] However, some studies have found no such correlation.[11]

Ferritin, the major iron storage protein, also acts as an acute phase reactant.[12] Elevated serum ferritin levels have been linked with various diseases like sideroblastic anemias, neurodegenerative disorders, malignancies and coronary artery disease.[13] On the other hand, low serum ferritin levels have been found to be correlated to hypothyroidism in various studies.[14]

However, very few studies are available till now regarding the correlation of serum ferritin and uric acid levels in hypothyroidism. Keeping in mind this lacuna, the present study will be undertaken to explore any relationship between the changes in the uric acid and serum ferritin levels in the both SH and OH as it would significantly help in understanding the metabolic changes related to the uric acid and ferritin in this disease. Hence, it was hypothesized for the present study that hypothyroidism at its different clinical spectrum is linked to changes in serum ferritin and uric acid levels.

## METHODS

The present study is case-control study with 34 SH cases, 27 OH cases and 35 healthy controls (N) attending the OPD Clinical Biochemistry Laboratory of Jhargram Government Medical College and Hospital, Jhargram between May 2025 to November 2025.

### *Study design*

The study was conducted as a case-control study for a period of six months. Cases were selected using the method of convenience following specific inclusion and exclusion criteria, irrespective of any gender. Appropriate age and sex matched controls were selected.

### *Procedures*

The study was initiated after obtaining the permission from the institutional scientific review committee and the institutional ethics committee (IEC). Informed consent was obtained from all participants according to the IEC guidelines.

### *Inclusion criteria*

Hypothyroid patients diagnosed with TSH >4.2 µIU/ml in the age range of 18 to 60 years will be selected as the case group.

The case group was further sub-divided into two groups: SH with elevated TSH levels (normal reference value for TSH 0.27-4.2 µIU/ml) and but fT4 values within normal reference range (0.93-1.7 ng/dL), and OH with decreased fT4 values and increased TSH.

SH was TSH >4.2 µIU/ml and fT4 >0.93 ng/dl (12 pmol/l) and OH was TSH >4.2 µIU/ml and fT4 <0.93 ng/dl (12 pmol/l)

### *Exclusion criteria*

Pregnant patients, conditions where serum uric acid levels are raised like gout, chronic renal failure, etc and conditions where serum ferritin levels are raised like β-thalassemia, hemochromatosis etc were excluded.

### *Measurement of study parameters*

Serum TSH, fT4 and Ferritin was measured in the full autoanalyzer, Roche cobas e411 using electrochemiluminescence immunoassay techniques; while uric acid was measured in the full autoanalyzer, Erba EM200 Biochemistry analyser using Uricase, Trinder-End Point spectrophotometric method by the Dept of Biochemistry, JGMCH.

### *Statistical analysis*

For statistical analysis, the data obtained were analyzed by SPSS 26.0 version. Test parameter data were tested for normality using Kolmogorov-Smirnov Test. For comparison between two groups, Mean±SD and median/mean rank values were obtained for parameters following parametric and non-parametric distribution respectively. Multiple comparison between the study parameters were conducted using ANOVA for parametric data and Kruskal Wallis H test for non-parametric data. Multiple comparison post hoc ANOVA with Bonferroni correction was done for Uric acid, which followed parametric distribution, while the non-parametric Friedman's two-way analysis with Dunns pairwise tests were performed for TSH and fT4 as Kruskal Walis H-test showed a significant p value for these parameters. Relationship between the study parameters within a group was assessed using Spearman or Pearson's correlation analysis respectively for those following non-parametric and parametric distribution. For all analyses, p value was considered to be significant at the level of $p<0.05$ with 95% confidence interval.

### *Quality assurance and control*

Quality control of this study was ensured by: Thorough maintenance of aseptic uncontaminated procedure of blood collection followed by proper preservation and immediate dispatch of the blood sample to Central Laboratory for testing. Use of pre validated reagents and quality control materials for 2 levels. Monitoring of results obtained with daily follow-up of the patients. Monitoring the coefficient of variation (CV) value for assessing the accuracy of the test. A CV lower than 10% was achieved. Running of at least 2 levels of control materials for monitoring the biochemical assays. Evaluation and re-evaluation of the difficulties felt by the Principal Investigator during data collection and lab technician performing the tests

Data confidentiality will be maintained as per protocol.

## RESULTS

The present study is case-control study with 34 SH cases, 27 OH cases and 35 healthy controls (N) intended to assess the TSH, fT4, Uric Acid and Ferritin levels of each of these groups, and find any correlation between aforementioned parameters in Hypothyroidism by statistical tests.

The Kruskal-Wallis H-test results show no statistically significant difference in the age distribution of the study individuals in the three groups, as the p>0.05.

The gender distribution, too shows no statistically significant difference among the groups, as the p value of the Chi-square test is also>0.05 (Figure 1).

There is no statistically significant difference in the gender distribution across groups as shown in Table 1.

Table 2 shows the distribution of the test parameters. From this table it is evident that values of ferritin, TSH and fT4 have been represented by the median as they follow non parametric distribution while the uric acid value is represented by mean±SD as it follows a normal distribution pattern. Pattern of distribution of the data were analysed by Smirnov-Kolmogorov test (data not shown).

For TSH and FT4, as the Kruskal Walis test showed a significant p value, Friedman's two-way analysis with Dunns pairwise tests were performed as these values followed non parametric distribution (Table 4). No such test was done for the serum ferritin level because the p value was not significant in Kruskal Walis test.

As ANOVA showed significant group difference for the serum uric acid values, post hoc test with Bonferroni correction (Table 5) was performed to show the significance of difference between each group separately.

Each row tests the null hypothesis that the sample 1 and 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is 0.05.

Table 4 shows that there is statistically significant difference between all the 3 groups for TSH values as is evident from the p values of the Dunn's pairwise test.

As regards fT4 levels between the groups, there statistically significant differences between the fT4 values of the OH and SH groups as well as between the OH and N groups but the difference between the fT4 values of the SH and N groups is not statistically significant as shown by the p values.

There is statistically significant difference between TSH levels of all 3 group as shown in Table 4.

Table 5 shows that there is statistically significant difference between the uric acid values of the SH and OH groups as well as the OH and N groups (p<0.05). However, the present study finds no significant difference between the uric acid values of the SH and N groups, as shown by the p value for post hoc ANOVA.

This bar chart (Figure 4) diagrammatically represents the findings in Table 5. The post hoc ANOVA suggests significant differences between the uric acid levels of SH and OH groups as well as the OH and N groups (p<0.05).

Table 6 shows the results of Spearman's correlation for parameters in SH groups. However, none of the parameters show any statistically significant correlation among themselves as the p>0.05 for all of the studied pairs.

Table 7 shows the results of Spearman's correlation for the parameters in OH groups. From the p values, it is evident that there is statistically significant correlation between TSH and fT4 as well as between TSH and uric acid in the OH group. The correlation is also statistically significant between ferritin and uric acid. However, no significant correlation is suggested between TSH and ferritin or between fT4 and ferritin.

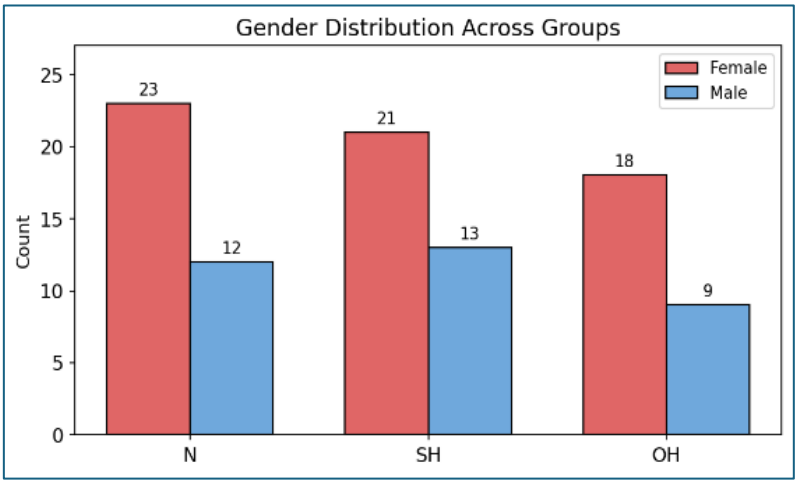


**Figure 1: Gender distribution of study individuals across groups.**

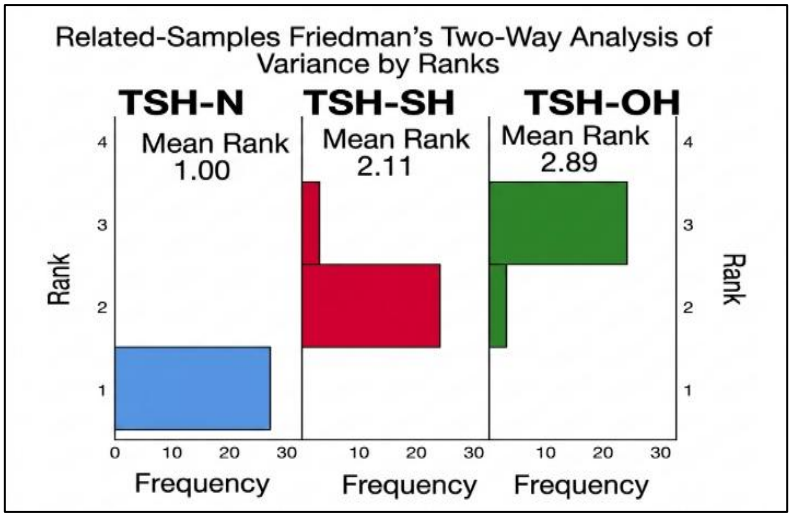


**Figure 2: Grouped frequency histogram of ranks showing mean ranks of TSH for the 3 groups (N, SH, OH) as calculated for Friedman's two-way analysis of variance by ranks.**

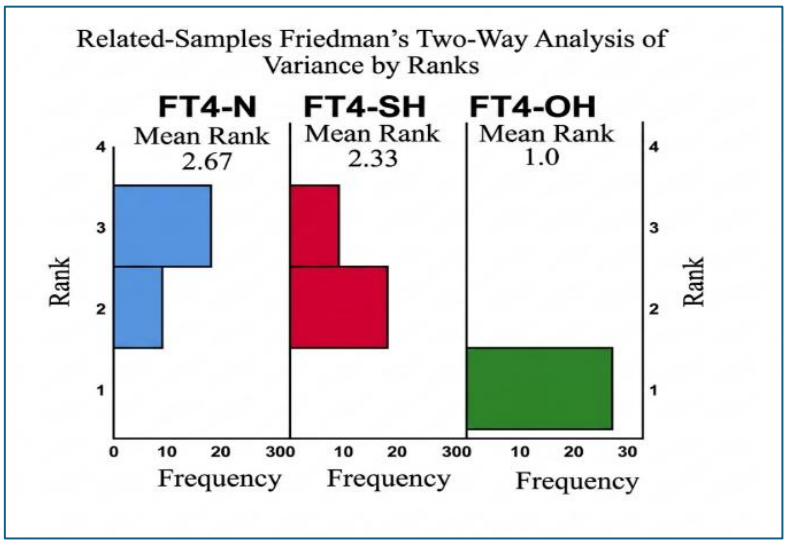


**Figure 3: Grouped frequency histogram of ranks showing mean ranks of fT4 for the 3 groups (N, SH, OH) as calculated for Friedman's two-way analysis of variance by ranks.**

*This figure reinforces diagrammatically our finding in Table 4, in which we found no significant statistical difference between the SH and N groups while the p values are significant for the other 2 pairings, i.e. between the SH and OH groups and OH and N groups.

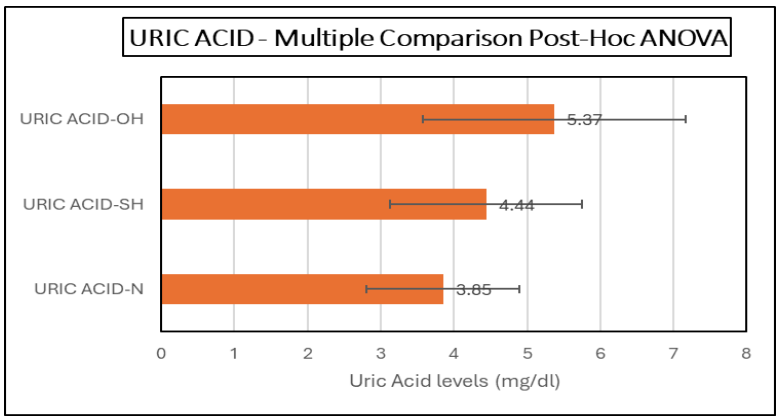


**Figure 4: Mean with standard deviation of uric acid for the 3 groups (N, SH and OH), further analysed by post-Hoc ANOVA with Bon Ferroni correction.**

**Table 1: The age and sex distribution in the 3 groups-N, SH and OH.**

| Variables | N | SH | OH | Test statistic | P value |
|---|---|---|---|---|---|
| **Age (Median) (in years)** | 38.0 | 37.5 | 39.0 | H value=0.352* | 0.84 |
| **Sex (Female:Male)** | 23:12 | 21:13 | 18:9 | Chi-square value=0.189** | 0.91 |

*Statistical Test applied is Kruskal-Wallis H test; **Statistical Test applied is Chi-square test

**Table 2: The frequency values of test parameters, both parametric (Uric acid) and non parametric data (Others).**

| Study parameters | N | Mean±SD | Median |
|---|---|---|---|
| **TSH (N)** | 35 | - | 1.9 |
| **FT4 (N)** | 35 | - | 1.28 |
| **Ferritin (N)** | 35 | - | 55.7 |
| **Uric acid (N)** | 35 | 3.85±1.05 | - |
| **TSH SH** | 34 | - | 10.125 |
| **TSH OH** | 27 | - | 25.45 |
| **FT4 SH** | 34 | - | 1.16 |
| **FT4 OH** | 27 | - | 0.74 |
| **FERRITIN SH** | 34 | - | 82.735 |
| **FERRITIN OH** | 27 | - | 69.53 |
| **URICACID SH** | 34 | 4.44±1.31 | - |
| **URICACID OH** | 27 | 5.37±1.80 | - |

*N: normal, SH:subclinical hypothyroidism, OH: overt hypothyroidism.

**Table 3: Multiple comparison between the study parameter using ANOVA (for parametric data) and Kruskal Wallis (for non parametric data) tests.**

| ANOVA (for serum uric acid) | F | Sig (P value) |
|---|---|---|
| **Between groups** | 9.07 | <0.001* |
| **Kruskal-Wallis H (for others)** | | |
| Between groups | **H** | |
| TSH | 73.066 | <0.001* |
| FT4 | 60.962 | <0.001* |
| Ferritin | 1.543 | 0.462 |

*P value is significant for p<0.05 at 95% confidence interval.

**Table 4: Friedman's two-way analysis with Dunn's pairwise tests for TSH and fT4.**

| Sample 1-sample 2 | Test statistic | Std. error | Sig (P) |
|---|---|---|---|
| **TSHN-TSHSH** | -1.111 | 0.272 | <0.001 |
| **TSHN-TSHOH** | -1.889 | 0.272 | <0.001 |
| **TSHSH-TSHOH** | -0.778 | 0.272 | 0.004 |
| **FT4OH-FT4SH** | 1.333 | 0.272 | <0.001 |
| **FT4OH-FT4N** | 1.667 | 0.272 | <0.001 |
| **FT4SH-FT4N** | 0.333 | 0.272 | 0.221 |

**Table 5: Multiple comparison post hoc ANOVA with Bonferroni correction for uric acid.**

| (I) Grouping | (J) Grouping | Mean difference (I-J) | Std. error | Sig. | 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| **Uric acid SH** | OH | -0.92919* | 0.35819 | 0.033* | -1.8025 | -0.0559 |
| | N | 0.58403 | 0.33460 | 0.253 | -0.2317 | 1.3998 |
| **Uric acid OH** | SH | 0.92919* | 0.35819 | 0.033* | 0.0559 | 1.8025 |
| | N | 1.51323* | 0.35592 | <0.001* | 0.6455 | 2.3810 |
| **Uric acid N** | SH | -0.58403 | 0.33460 | 0.253 | -1.3998 | 0.2317 |
| | OH | -1.51323* | 0.35592 | <0.001* | -2.3810 | -0.6455 |

*The mean difference is significant at the 0.05 level.

**Table 6: Correlation between the study parameters of SH.**

| Spearman's rho | | TSH-SH | FT4-SH | Ferritin-SH | Uric acid-SH |
|---|---|---|---|---|---|
| **TSH-SH** | Correlation coefficient | 1.000 | 0.006 | -0.123 | -0.036 |
| | Sig. (2-tailed) | - | 0.975 | 0.488 | 0.839 |
| | N | 34 | 34 | 34 | 34 |
| **FT4-SH** | Correlation Coefficient | 0.006 | 1.000 | 0.209 | 0.098 |
| | Sig. (2-tailed) | 0.975 | - | 0.237 | 0.580 |
| | N | 34 | 34 | 34 | 34 |
| **Ferritin-SH** | Correlation Coefficient | -0.123 | 0.209 | 1.000 | -0.153 |
| | Sig. (2-tailed) | 0.488 | 0.237 | - | 0.387 |
| | N | 34 | 34 | 34 | 34 |
| **Uric acid-SH** | Correlation Coefficient | -0.036 | 0.098 | -0.153 | 1.000 |
| | Sig. (2-tailed) | 0.839 | 0.580 | 0.387 | - |
| | N | 34 | 34 | 34 | 34 |

**Table 7: Correlation between the study parameters of OH.**

| Spearman's rho | | TSH-OH | FT4-OH | Ferritin-OH | Uric acid-OH |
|---|---|---|---|---|---|
| **TSH-OH** | Correlation Coefficient | 1.000 | -0.704** | 0.194 | 0.407* |
| | Sig. (2-tailed) | - | 0.0001 | 0.332 | 0.035 |
| | N | 27 | 27 | 27 | 27 |
| **FT4-OH** | Correlation Coefficient | -0.704** | 1.000 | -0.225 | -0.374 |
| | Sig. (2-tailed) | 0.0001 | - | 0.259 | 0.055 |
| | N | 27 | 27 | 27 | 27 |
| **Ferritin-OH** | Correlation Coefficient | 0.194 | -0.225 | 1.000 | 0.582** |
| | Sig. (2-tailed) | 0.332 | 0.259 | - | 0.001 |
| | N | 27 | 27 | 27 | 27 |
| **Uric acid-OH** | Correlation Coefficient | 0.407* | -0.374 | 0.582** | 1.000 |
| | Sig. (2-tailed) | 0.035 | 0.055 | 0.001 | - |
| | N | 27 | 27 | 27 | 27 |

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

## DISCUSSION

The present study evaluates the serum levels of uric acid and ferritin in hypothyroid cases. While the clinical signs and symptoms of overt hypothyroidism are often obvious, subclinical hypothyroidism often remains undetected due to its relative lack of clinical features. The present study has focused on comparing the effects that these two spectrums of hypothyroidism may have on uric acid as well as ferritin metabolism.

In our study, we found that uric acid levels in the group with overt hypothyroidism is significantly higher (Mean 5.37±SD 1.80, Table 1) as compared to the group suffering from subclinical hypothyroidism (Mean 4.44±SD 1.32, Table 1), though the difference with that of the control group (Mean 3.85±SD 1.05) is not significant ($p>0.05$) (Table 5). Also, it was observed, that in the group with overt hypothyroidism, TSH levels have a significant positive correlation with uric acid levels and significant negative correlation with free T4 levels (Table 7). Torkian et al has concluded that individuals suffering from subclinical hypothyroidism had significantly higher uric acid levels as compared to euthyroid individuals due to impaired kidney function.[15] Xing et al in retrospective study among Chinese population, stated that subclinical hypothyroidism is significantly associated with higher uric acid levels and treatment of hypothyroidism in these individuals resulted in decrease in uric acid levels.[16] While Xie et al in a cross-sectional study among U. S. adults, quantitatively assessed and found higher serum uric acid levels among individuals with decreased sensitivity to thyroid hormones.[17] On the contrary, See et al in a decade-long study carried out in northern Taiwan found the association between hypothyroidism and hyperuricemia to be weak, though they suggested strong association between hypothyroidism and gout.[18]

The increase in serum uric acid levels in hypothyroidism has been attributed to impaired renal function by various studies.[19] Increased serum uric acid levels in hypothyroidism have been attributed to reduced renal blood flow and subsequent decreased glomerular filtration of uric acid proportional to decrease in fT4 levels.[20]

The fact that the serum uric acid levels of the two groups, i.e., the healthy controls and subclinical hypothyroid group show no significant difference may be explained by the fact that fT4 levels of these two groups show no significant differences (Table 5).

The present study finds the ferritin levels in overt hypothyroidism to be somewhat lower as compared to that in subclinical hypothyroidism, although the difference between the ferritin levels of the two groups was not significant (Table 3). In a study among hypothyroid individuals in Punjab, India, Saini et al found a significant negative correlation between TSH and serum ferritin, while, Swapnika et al found lower serum ferritin levels in subclinical hypothyroidism as compared to controls.[21,22] Contrarily, Tiwari et al noted that serum ferritin levels were raised in anti-TPO positive hypothyroidism, though low ferritin concentrations were detected in anti-TPO negative hypothyroidism.[23]

Various mechanisms have been suggested for low ferritin levels in hypothyroidism. Hypothyroidism may cause impaired absorption of iron due to hypochlorhydria and decreased intestinal motility.[24,25] Thyroid hormones have also been noted to have role in iron homeostasis and upregulation of ferritin gene expression through thyroid hormone binding elements located upstream of the ferritin gene.[26,27] Completing the other end of this vicious cycle is thyroid peroxidase, an iron containing enzyme required for synthesis of thyroid hormones, which requires iron for it normal functioning.[28]

However, ferritin cannot be deemed to be only a reflection of iron stores as it is also elevated in various inflammatory and immunological conditions.[29] The role of ferritin as an inflammatory marker may explain the insignificant relationship between ferritin and hypothyroidism in our present study as the immunological status has been found to be markedly altered in hypothyroid patients.[30]

### *Limitations*

Limitations of the present study include the limited sample size due to hospital-based study design. We suggest a larger community-based study to establish our findings more strongly. Another limitation of the study is that we did not measure the inflammatory markers in hypothyroid conditions which could have analysed the relationship of serum ferritin level with different inflammatory conditions sometimes found in hypothyroid disorders.

## CONCLUSION

In conclusion, the present study suggests that serum uric acid is significantly related to the fT4 levels as it is significantly increased in hypothyroid conditions due to renal insufficiency caused by lower fT4 levels. On the other hand, serum ferritin values did not show any significant changes in hypothyroid conditions as it is dependent on different inflammatory conditions which may be prevalent in hypothyroidism.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Bhattacharya J, Ghosh C, Dasgupta A, Sain BK. Investigating the correlation of ferritin and uric acid levels in hypothyroidism: a case-control study. Int J Res Med Sci 2026;14:3849-56.