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Original Article

Serum Ferritin–TSH Ratio as a Novel Biomarker for Symptom Severity in Hypothyroidism

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ABSTRACT

Background Hypothyroidism can be biochemically identified as the state of thyroid gland dysfunction that exhibits an, often less-than-ideal correlation between its degree and TSH levels along with symptomatic burden. In thyroidal hormone production and metabolism, the iron status may be used in order to determine variations between them. Objectives To correlate the iron store, which may be measured as serum ferritin, TSH, and the Ferritin/TSH ratio with disease symptoms experienced by primary hypothyroid patients. Methods Cross-sectionally, from the outpatient clinics of endocrine and internal medicine,72 patients with proven primary hypothyroidism were selected over 4 months, within a teaching hospital at an urban city located in the province of Sindh of Pakistan. Severity was assessed with the Hypothyroid symptom Scale(HSS),TSH/FT4 was quantified using chemiluminescent immunoassay while ferritin usedELISA. Results Pearsons correlation coefficient and studentt-test were conducted. Mean age of participants were 39.6 ± 10.8 yrs; 52 (72.2%) were women. Ferritin positively correlated to symptom Burden of HSS (r=−0.41;95%CI −0.59 to −0.20; P<0.001),and TSH showed a directly proportional correlation (r=0.46,95%CI 0.26 to0.63; P<0.001) with HSS. The ratio of Ferritin:TSH yielded the strongest correlations with HSS (r=0.58, 95%CI 0.40 to 0.72;P<0.001) . Those scoring more than 18 in HSS had the lower Fer:TSH value when compared to those scoring18 orbelow(3.5±1.6 versus 6.1 ± 2.4; P<0.001). Conclusion A low Ferritin:TSH value correlates with a significant increase in symptom intensity in primary hypothyroidism, and showed a higher association than either TSH or ferritin individually with HSS scores, prior to adjusted and cross-sectional studies and longitudinal validity; it's value can not be recommended bedside use. Keywords Marker, Ferritin, Hypothyroidism, Iron, Symptom, TSH

EDITORIAL INFORMATION

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INTRODUCTION

Hypothyroidism is a common endocrine disorder resulting from insufficient thyroid hormone availability And produces a wide spectrum ofclinical manifestations from mild constitutional symptoms to severe metabolic, neurocognitive, cardiovascular, and reproductive phenomena.1The prevalence depends on age, sex, iodine intake, population characteristics and definition. There is a particular greater prevalence in women and older individuals. Primary hypothyroidism is biochemically a disease characterized most appropriately by a subnormal concentration of free thyroxine (fT4) and elevations of the level of thyroid-stimulating hormone (1). Typical signs and symptoms included fatigue, lethargy, weight gain, heat intolerance, constipation, cognitive impairment, mood disturbances and disturbances in menstrual function (2). Most individuals with primary hypothyroidism develop these signs and symptoms at some point but symptoms by themselves are non-specific and even more common among euthyroid people than biochemical hypothyroidism so they fail to characterize the existence and severity of thyroid deficiency so assessment of primary hypothyroidism today involves biochemical measurement and assessment of

patient perceived health state instead of assuming one thyroid hormones measurement sufficiently represents the patient's experience(1-3).

The connection between biochemistry and signs and symptoms is most complicated in treatment. Levothyroxine may be utilized to restore serum TSH to the normal range in many treated hypothyroid individuals but not infrequently some patients complain continued Fatigue, cognitive symptoms, poor mood, mental and physical wellbeing, and low quality of life even after biochemical restoration to Normal TSH (3-5) . Evidence from recent system Review studies indicate that persistent signs and symptoms occur in treating hypothyroidism remain relevant clinically and existing Treatments are not equally reliable symptomatic improvement (4). A systematic survey of quality life in individuals with overt hyperthyroidism suggest that a reduction in physical and emotional well-being occur in individuals with symptoms even if the patient has received treatment (6). These findings again suggest that symptomatology may correlate to many complex factors and do not depend solely on serum TSH level (2-6).

One biologically plausible source of variations in the expression of symptoms and altered thyroid function is iron metabolism. The thyroid axis involves multiple metabolic pathways that are influenced by iron. Limited iron status (deficiency) is known to impair thyroid hormone production and processing.

More broadly, evidence for an association between iron deficiency and thyroid function parameters and autoimmune conditions of the thyroid came from an earlier meta-analysis, which reported overall associations but large between-study heterogeneity, particularly regarding different individual measures and populations (7).

Newer clinical research found lower iron and/or ferritin levels in individuals with hypothyroidism, and observed inverse relationships between some iron measures and TSH levels (8,9). The overlap in the symptomatic manifestations of hypothyroidism and iron deficiency (e.g., fatigue, poor concentration, low exercise tolerance, general poor wellbeing) provides a biological rationale for a shared impact on individuals' health (7-9). Recent observational evidence that directly addressed such possible interaction was reported. Thus, Sylus et al.

Provided evidence that subclinical and frank hypothyroidism are accompanied by significantly lower values of serum ferritin, iron and transferrin saturation in patients compared to euthyroid controls, and thatT SH showed an inverse association with various measurements of iron deficiency (10).

An additional study based on a large national database conducted on adult Jordanians (n=3,605) reported that individuals with iron deficiency/iron deficiency anemia had lower levels offT3andfT4and higherlevels ofTSH (11). A case control study based on matching participants concluded that the patients with hypoothyroidism had significantly lower ferritinin comparison with their healthy control cases and a strong inverse correlation was observed between ferritinin patients with hyperthyroidism (12). Some other reports on subjects with the same condition had similar findings and found lower ferritinin hypothyroid individuals, or found an inverse association between ferritin and TS H in different populations of hypothyroid individuals, although it has not been clear whether there was a unique ferritin threshold for disease expression and it is not fully proven it is a cause (13-14).

As with serum ferritin, the interpretation needs to be contextualized by other factors. While widely used to assess iron status, and being very useful in confirming absolute iron deficiency when low, ferritin is also influenced by inflammation and other systemic factors, and on its own it may not reflect the complete picture of iron available in the body (15). Literature reviews of iron deficiency in chronic and inflammatory conditions often stress the importance of using transferrin saturation and other indices alongside ferritin when there may be ambiguity in interpretation (16).

Research into circulating ferritin has similarly pointed out the need to consider it both an iron-stores marker and a marker for inflammation (17), and general overviews of iron deficiency testing advise using a combination of ferritin, transferrin saturation, hematological indices, inflammatory markers and if necessary soluble transferrin receptor or hepcidin measurements (18).

In the context of chronic inflammatory disease, combination of ferritin and transferrin saturation has also been proposed as a more accurate means of detecting iron deficiency (19). Although there has been growing interest in the links between iron status and thyroid function, much of the research has been conducted by assessing ferritin, iron status parameters, TSH, fT4 and fT3 separately or on a pair-wise basis (7,10-14). Far less is known about whether a summary statistic combining ferritin and TSH levels is associated with perceived illness severity. In theory, an index using ferritin divided by TSH relates the relative amount of iron stored to the pituitary drive of the thyroid axis.

However, the ratio, being calculated using two bio-logically inter-dependent parameters may not possess additional clinical value beyond the correlation between the two underlying variables without proper evaluation.

In this present study, the study objective was to investigate the associations of serum ferritin, TSH and a ratio of ferritin-and-TSH levels with perceived severity in hypothyroid adults. The null hypothesis was that there is no association between the ferritin-TSH ratio and hypothyroid symptom severity in adults with primary hypothyroidism.

MATERIALS AND METHODS

A 4 month cross-sectional observational study was carried out on adults attending general medicine and endocrinology clinics of tertiary-care hospital outpatient clinics in urban locality of Sindh, Pakistan due to the availability of a heterogeneous patient group having endocrine disorders as well as malnutrition. It was an observational study of patients diagnosed by non-probability consecutive sampling technique. Eighty eligible patients approached during the period of four months but seventy-two eligible patients signed the informed consent form and completed the clinical evaluation & laboratory investigations and were taken into the study.

A target sample of 72 participants was selected with reference to sample sizes used in comparable observational studies evaluating biochemical correlations in hypothyroid populations and the feasibility of recruitment during the defined four-month study period. Adult patients aged 18–60 years with a confirmed diagnosis of primary hypothyroidism were eligible. Primary hypothyroidism was operationally characterized by an elevated serum TSH concentration with or without a reduction in fT4, thereby encompassing biochemical patterns compatible with subclinical and overt primary hypothyroidism (1,2). Newly diagnosed patients and patients receiving a stable dose of thyroid hormone replacement therapy for at least three months were eligible for inclusion.

Individuals with known chronic inflammatory diseases, liver disorders, renal impairment, pregnancy, hematological conditions affecting iron metabolism, or current iron supplementation during the preceding three months were excluded. These criteria were applied to reduce major non-thyroid influences on serum ferritin and iron metabolism. Although a low ferritin concentration provides useful evidence of depleted iron stores, ferritin is influenced by inflammation and systemic illness, and interpretation of iron status may require additional biochemical indices when these conditions are present (15–19).

Laboratory and clinical evaluation Data were collected via structured manner composed of laboratory and clinical evaluation. A designed data collection questionnaire obtained patients' information regarding demographic profile, history such as age, sex, duration of hypothyroidism, history of presenting symptoms. Hypothyroid Symptom Scale (HSS), the questionnaire of assessing fatigue, gain of weight, decreased intellect and intolerance of cold symptoms was scored.

It assesses symptom level by summated score of Hypothyroid symptoms Scale.

Total score indicated more symptom burdened.

After obtaining venous blood samples in asepsis, samples were sent to a certified laboratory for examination. Serum TSH and fT4 levels were assessed with chemiluminescent immunoassay and serum ferritin with enzymelinked immunossorbent assay. The ratios of ferritin-TSH was calculated in each subject as serum ferritin/serum TSH (ng/mL / mIU/L).

The primary analytical outcome was the relationship between HSS score and the ferritin–TSH ratio. Associations of HSS score with serum ferritin and TSH were evaluated as component-marker analyses. For secondary descriptive comparison, participants were divided at the sample median HSS score into an HSS ≤18 group and an HSS >18 group. Ferritin–TSH ratio values were additionally summarized using the reported categories of <3.5, 3.5–6.0, and >6.0 to evaluate the pattern of symptom scores across increasing ratio levels. Because the symptom categories and ratio categories were sample-based secondary analyses, continuous HSS and continuous biochemical measurements remained the principal basis for assessment of association.

The Shapiro-Wilk test was used to assess the normality of the continuous variables, which were reported as meansSD. Categorical variables were reported as counts and percentages. The relationship between serum ferritin levels, TSH levels, ferritin:TSH ratio and HSS score was analyzed using the Pearson correlation coefficient.

The 95% confidence intervals for correlation coefficients were derived using Fisher's z-transformation.

An independent-samplest-test was used to compare the two HSS groups. Where mean SD and sample size was provided fully for both group means such that mathematically they were full imputers of required data mean differences, 95% CIs, t statistics and Cohen's ds to provide standardized mean difference for better estimating power and clinical use of estimates, were generated from these inputs. Analyses were all two-sided withp<0.05 being interpreted as statistically significant. All 72 patients had full clinical and laboratory data provided as reported so no values required imputation.

RESULTS

We approached a total of 80 patients during the study period. Of the 80 patients, 72 met eligibility, gave informed consent, completed the study procedures, and were eligible for analysis, while eight were excluded due to recent iron supplements intake or other co-existent health problems with altered iron metabolism. Therefore, 90.0% of contacted patients finally entered analysis.

The study population, which did not lose any observation among the 72 individuals selected for analysis, had a median age 39.6 ± 10.8 years (ranging between 21 and 55) and consisted of females (n = 52, 72.2%) and males (n = 20, 27.8%).

Mean duration of hypothyroidism was 3.8 ± 2.1 years, and the mean HSS was 18.6 ± 6.4. Averaged from group means of two equally-sized HSS groups, the participants showed a mean serum ferritin level around 38.9 ± 16.2 ng/mL, mean serum TSH was 8.8 ± 3.5 mIU/L, and mean ferritin/TSH ratio was 4.8 ± 2.4. Table 1 outlines participants' demographic, clinical and biochemical profile.

Table 1. Baseline Demographic and Clinical Characteristics of Participants (N=72)

Variable	Category	n (%) or Mean ± SD
Age, years	—	39.6 ± 10.8
Sex	Male	20 (27.8)
	Female	52 (72.2)
Duration of hypothyroidism, years	—	3.8 ± 2.1
Serum ferritin, ng/mL	—	38.9 ± 16.2
Serum TSH, mIU/L	—	8.8 ± 3.5
Ferritin–TSH ratio	—	4.8 ± 2.4
HSS score	—	18.6 ± 6.4

HSS, Hypothyroid Symptom Scale; SD, standard deviation; TSH, thyroid-stimulating hormone.

The correlation of serum ferritin and HSS score was a moderate negative (r=0.41, 95%CI 0.59 to 0.20; P<0.001) with reduced levels of ferritin the more symptoms. The correlation of TSH with HSS score was moderate positive (r=0.46, 95%CI 0.26 to 0.63; P<0.001). The correlation of ferritin/TSH ratio and HSS was the highest absolute coefficient but was moderate to strong negative (r=0.58, 95%CI 0.72 to 0.40; P<0.001).

The correlations are shown in Table 2.

The larger absolute correlation for the ratio cannot, on its own, confirm an independent benefit to the measure; it is unadjusted.

Table 2. Associations of Ferritin, TSH, and Ferritin–TSH Ratio With HSS Score (N=72)

Variable	Pearson r	95% CI	p-value
Serum ferritin	−0.41	−0.59 to −0.20	<0.001
Serum TSH	0.46	0.26 to 0.63	<0.001
Ferritin–TSH ratio	−0.58	−0.72 to −0.40	<0.001

CI, confidence interval; HSS, Hypothyroid Symptom Scale; TSH, thyroid-stimulating hormone.

Table 3 Results of serum ferritin, TSH and ferritin-TSH ratio measurements in subjects with the 2 secondary criteria (primary comparison) Variable1 Secondary variable 190% confidence interval Cohen's d2 F (95% CI1 for lower bound and upper bound for upper bound) P value ferritin level HSS≤18 47.5±14.6 ng/ml ferritin level HSS>18 30.2±12.8 ng/ml difference17.3310.85 to23.75 1.26 5.355.350.001 TSH 1844.7±6.9 mIU/L TSH>1823.3±23.0 mIU/L3 difference17.43−60.8 to9.94 0.28 4.965.530.0324 TSH level186.9±2.8 mIU/L TSH>1810.7±3.2 mIU/L difference-3.835.21 to-2.39 1.26 5.365.360.001

Ferritin-TSH ratio186.1±2.4 Ferritin-TSH ratio>183.5±1.6 difference2.631.64 to3.56 1.27 5.415.410.001 NOTES:1In general t represents comparison of samples HSS 18 versus ferritin > 18 . When difference in calculated means it represented in first sample–second sample; otherwise the difference represented in first data.2Difference with standard value (the mean of two groups which is 38.9 ng/dl for Ferritin, etc) , is calculated as t. Cohen’s d statistic is difference in means divided by std . 3t-test with 20 participants.

Table 3. Biochemical Measures According to Hypothyroid Symptom Burden

Variable	HSS ≤18 (n=36)	HSS >18 (n=36)	Mean Difference (95% CI)*	t (df=70)	p-value	Cohen's d
Ferritin, ng/mL	47.5 ± 14.6	30.2 ± 12.8	17.3 (10.85 to 23.75)	5.35	<0.001	1.26
TSH, mIU/L	6.9 ± 2.8	10.7 ± 3.2	−3.8 (−5.21 to −2.39)	−5.36	<0.001	−1.26
Ferritin–TSH ratio	6.1 ± 2.4	3.5 ± 1.6	2.6 (1.64 to 3.56)	5.41	<0.001	1.27

Values are mean ± SD unless otherwise specified. Mean difference calculated as HSS ≤18 minus HSS >18. CI, confidence interval; HSS, Hypothyroid Symptom Scale; SD, standard deviation; TSH, thyroid-stimulating hormone.

A progressive descriptive reduction in symptom burden was additionally observed across increasing ferritin–TSH ratio categories. Participants with ratios <3.5 had a mean HSS score of 22.8 ± 5.7, those with ratios of 3.5–6.0 had a mean score of 18.7 ± 4.8, and those with ratios >6.0 had a mean HSS score of 14.2 ± 4.9. The difference in mean HSS between the lowest and highest ratio categories was 8.6 points. Because category-specific denominators and complete omnibus-analysis inputs were not available for these secondary categories, the category-level findings are presented descriptively, whereas the continuous correlation remains the principal inferential assessment of the ferritin–TSH ratio.

Table 4. HSS Scores Across Ferritin–TSH Ratio Categories

Ferritin–TSH Ratio Category	Ratio Range	HSS Score, Mean ± SD
Lower	<3.5	22.8 ± 5.7
Intermediate	3.5–6.0	18.7 ± 4.8
Higher	>6.0	14.2 ± 4.9

HSS, Hypothyroid Symptom Scale; SD, standard deviation.

Overall, the findings showed concordant patterns across continuous and group-based analyses: lower ferritin concentrations, higher TSH concentrations, and lower ferritin–TSH ratios were associated with greater hypothyroid symptom burden. Among the three continuous biochemical measurements, the ferritin–TSH ratio produced the largest absolute unadjusted correlation with HSS.

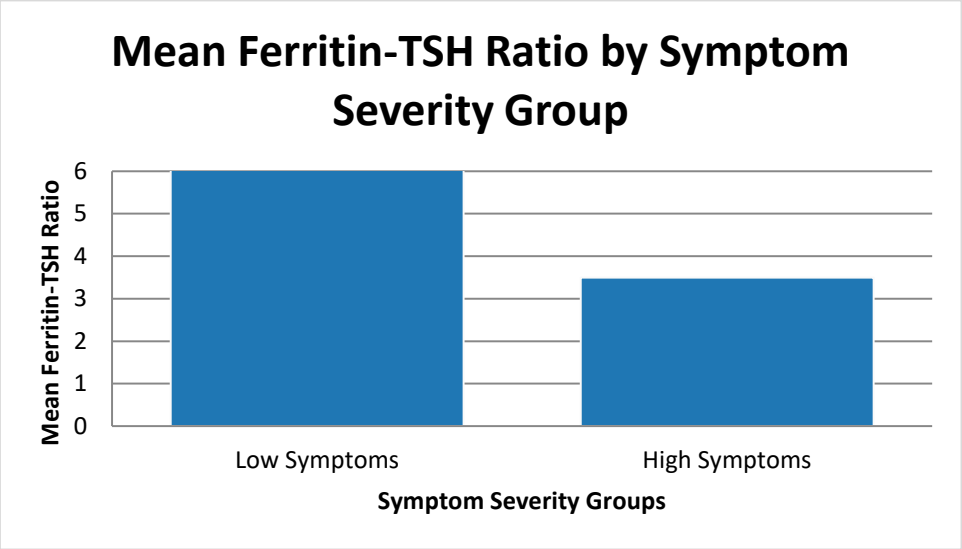

Figure 1 Distribution of ferritin-TSH ratio across symptom severity groups

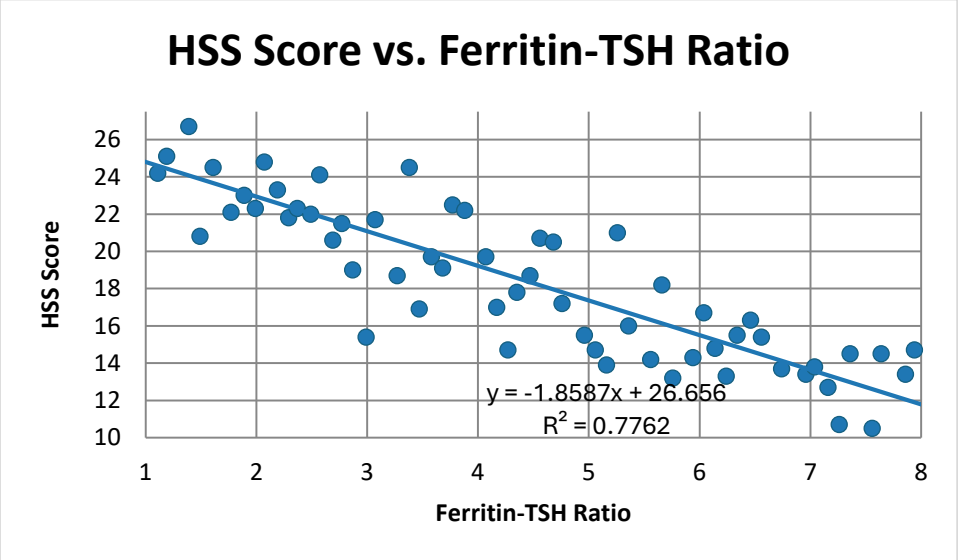

Figure 2 Correlation between ferritin-TSH ratio and HSS score

DISCUSSION

The present study evaluated the relationships of serum ferritin, TSH, and their derived ratio with symptom severity in adults with primary hypothyroidism. Three principal findings emerged. First, lower ferritin concentration was associated with greater symptom burden, whereas higher TSH was associated with greater symptom burden. Second, the ferritin–TSH ratio demonstrated the largest absolute correlation with HSS among the three unadjusted biochemical measures. Third, participants with HSS scores above the sample median had substantially lower serum ferritin and ferritin–TSH ratios and higher TSH concentrations than participants with lower HSS scores. The gradient in mean HSS across increasing ratio categories was directionally consistent with these continuous and group-based findings. Collectively, the results indicate an association between iron status, thyroid biochemical status, and clinical symptom expression, but they do not establish causal direction, diagnostic accuracy, or independent predictive superiority.

The inverse association between serum ferritin and HSS is broadly compatible with a growing body of literature connecting iron status and thyroid dysfunction. The systematic review and meta-analysis by Garofalo et al. found relationships between iron deficiency and thyroid-function abnormalities and thyroid autoimmunity, although substantial heterogeneity existed across studies and populations (7). Sylus et al. similarly demonstrated reduced serum ferritin, iron, and transferrin saturation in both subclinical and overt hypothyroidism and reported inverse relationships between TSH and several iron-status measures (10).

Population-based data from Jordan subsequently showed lower fT3 and fT4 and higher TSH in adults with iron deficiency or iron-deficiency anemia (11), while matched case-control and more recent observational studies have also demonstrated inverse ferritin–TSH relationships in hypothyroid populations (12–14). An observational study examining anemia in primary hypothyroidism further demonstrated clinically relevant relationships between TSH, ferritin, and hematological abnormalities, emphasizing that altered iron status may coexist with thyroid dysfunction rather than representing an isolated laboratory observation (20). The present study extends these biochemical observations by showing that lower ferritin was also associated with greater patient-reported hypothyroid symptom severity.

There may be several potential biological pathways to account for this association. Iron availability is relevant to thyroid hormone synthesis and metabolism, including an involvement of iron-dependent enzymic reactions used in thyroid hormone formation (7-9), such that biochemical abnormalities of the thyroid may be linked with depleted iron status. Iron deficiency causes symptoms of fatigue, poor concentration and decreased exercise tolerance and 'overall sense of feeling unwell', which are almost identical to those found in hypothyroidism (15), thereby potentially allowing patients with reduced iron stocks to report increased burden of HSS when their thyroid biochemistry may only explain some of the clinical picture. However, cross sectional associations cannot elucidate if depleted iron stores lead to symptoms of thyroid disease, are related to both a nutritional or clinical common cause, or simply co-vary with a physiological process yet to be considered (7, 15, 20).

The observed positive relationship between TSH and symptom severity is also clinically plausible, although the strength of this relationship should not be overstated. Hypothyroid symptoms are nonspecific, and studies evaluating patient-reported outcomes repeatedly demonstrate imperfect correspondence between thyroid biochemistry and symptom experience (2–6). In a follow-up study using thyroid-specific patient-reported outcomes, several symptom domains showed associations with TSH or fT3, while others did not closely correspond to thyroid hormone measurements (21). More recent multivariable work in adequately treated hypothyroidism found that psychological factors, body mass index, and depression were more strongly related to thyroid-dependent quality of life than thyroid biomarkers themselves (22). Likewise, treated hypothyroid participants can report substantially poorer quality of life than euthyroid controls despite broadly comparable circulating thyroid hormone concentrations (23). These findings reinforce the likelihood that HSS represents a multidimensional clinical phenotype rather than a direct surrogate for TSH concentration alone.

The ferritin–TSH ratio demonstrated the strongest unadjusted association with symptom severity in the present study. This result is potentially informative because the ratio mathematically combines two variables that showed opposite directional relationships with HSS: ferritin decreased as symptom burden increased, whereas TSH increased. Previous iron–thyroid studies have predominantly examined individual iron indices, individual thyroid hormones, or pairwise biochemical correlations rather than a ferritin–TSH composite linked to symptom burden (7,10–14). The present finding therefore provides a rationale for further evaluation of the ratio as an exploratory marker. Nevertheless, the larger absolute correlation coefficient cannot establish that the ratio contains independent information beyond its component variables. Because ferritin and TSH are mathematically embedded within the ratio and were individually associated with HSS, formal multivariable comparison is necessary before claiming incremental explanatory, diagnostic, or predictive performance.

The coexistence of newly diagnosed and thyroid-hormone-treated participants adds further clinical complexity. Levothyroxine is effective in restoring biochemical euthyroidism for most patients, but persistent symptoms remain a recognized clinical problem, and currently available interventions have not demonstrated consistent superiority for improving symptom burden in all affected patients (3–5). A recent systematic review specifically evaluating interventions for persistent symptoms found limited and heterogeneous evidence, with no single strategy supported by high-quality evidence across populations (4). Contemporary reviews of LT4/LT3 combination therapy similarly conclude that alternative thyroid-hormone strategies have not consistently produced superior symptomatic outcomes compared with levothyroxine monotherapy, despite patient preference in selected groups (24). Consequently, treatment

status may influence TSH, thyroid hormone concentrations, and symptom reporting independently, and future studies of a ferritin–TSH ratio should either stratify newly diagnosed and treated patients or incorporate treatment status into adjusted analyses (4,5,24).

Interpretation of the ferritin component must also consider the biological limitations of serum ferritin as a standalone marker. Ferritin is valuable for identifying depleted iron stores, particularly when concentrations are clearly low, but its concentration can increase with inflammation and systemic disease (15–17). Current diagnostic approaches therefore emphasize interpretation of ferritin alongside transferrin saturation and, where relevant, hematological or inflammatory markers (15,16,18,19). This is particularly important when evaluating a ratio that assigns ferritin a direct mathematical role, because inflammatory elevation of ferritin could increase the ferritin–TSH ratio without indicating greater physiologically available iron. Exclusion of participants with known inflammatory, hepatic, renal, and hematological conditions reduced some potential confounding in the present study, but the absence of a comprehensive reported iron profile and inflammatory markers limits the ability to distinguish absolute iron deficiency, functional iron restriction, and other determinants of ferritin concentration (15–19).

As for populations to reflect variability in the iron-thyroid linkage. Previous findings across various populations show that relationships can be variable based on context. A meta-analysis in 2025 that summarized data for 47 studies including >53 000 pregnant women indicates hemoglobin relationships to thyroid indices, although serum ferritin did not have a clear association with thyroid hormones in metaregression analyses (25) Iron deficiency prevalence throughout pregnancy has also established iron–thyroid relationships, suggesting intersection and variability between pregnancy iron and thyroid dynamics dependent upon population and pregnancy stage (26).

Other first-trimester pregnancy work has demonstrated that iron deficiency increase subclinical hypothyroidism as well as the prevalence of autoimmunity against thyroid gland and ferritin showed reverse relationships with anti-thyroid peroxidase activity and TSH hormone level (27).

The variations found in study outcomes and associations can be attributed to many factors: pregnancy and physiology , basal rates of iron-deficiency, presence of autoimmunity against the thyroid gland , definitions threshold levels used in clinical setting to diagnosed certain condition or use of thyroid, ratio of gender within the total sample. Inclusion/exclusion of specific types of iron-determinant (7,25-27)

The current findings may nevertheless have clinical relevance as a basis for hypothesis generation. Persistent hypothyroid-type symptoms should not automatically be attributed to TSH alone because thyroid-related and non-thyroid determinants frequently coexist (2–6,21–24). Similarly, assessment of possible iron deficiency should be based on an appropriate iron evaluation rather than the ferritin–TSH ratio itself (15–19). The ratio may ultimately prove useful as a compact research measure integrating two physiologically relevant domains, but clinical implementation would require evidence that it improves discrimination, calibration, risk stratification, or explanatory value beyond ferritin, TSH, fT4, and routinely available clinical variables. The present study therefore supports further investigation of the ratio rather than immediate use as a treatment threshold.

The study has several strengths. Consecutive recruitment reduced discretionary selection among patients presenting to the participating clinics, and all 72 included participants completed the reported clinical and laboratory assessments, eliminating missing observations in the reported analysis. Symptom burden was assessed systematically rather than inferred solely from thyroid-function tests, permitting direct evaluation of the relationship between biochemical measures and patient-reported clinical severity. Ferritin, TSH, and the derived ferritin–TSH ratio were evaluated within the same population, allowing their unadjusted associations with HSS to be compared. The consistency of direction across correlation analysis, median-based group comparisons, and ratio-category summaries also strengthens confidence that the observed association was not confined to a single presentation of the data.

Several limitations must be accounted for with similar rigor. Since this study's design was cross-sectional it is impossible to establish a timeline or causal mechanism. Also, a small and localized sample limits the

extent to which findings will be generalizable to other populations, treatment environments, Nutritional milieu, and thyroid disease phenotypes.

In a single group comprised of new hyper- or hypothyroidism with thyroid hormone treatment, the participants were treated as equivalent and the overt and subclinical biochemistry patterns were not segregated.

Several known important confounders; such as patient age, gender, disease duration, fT4, anemia, thyroid autoimmunity, body mass index, psychologically states, and inflammatory indices were not introduced into multivariable models despite strong evidence in current literature of their separate influence on PRRs regardless of TSH concentration (2,22,23). Only ferritin was used as the iron status marker and while current scientific assessment literature encourages a combined interpretation of Ferritin, Transferin saturation and various hematopoietic indicators as well as inflammatory indicators where possible (15-19), only Ferritin was presented and used. Also the division of HSS at the sample median was effective to portray descriptive comparisons but should not be read as a defined clinical severity criteria.

The ratio itself also introduces an important analytical limitation. Because ferritin appears in the numerator and TSH in the denominator, a participant with simultaneously lower ferritin and higher TSH will necessarily have a disproportionately lower ratio. The stronger observed correlation of the ratio with HSS may therefore reflect the combined directional behavior of two component variables rather than emergence of a biologically independent construct. Future analyses should compare appropriately specified models containing ferritin and TSH separately with models incorporating the ratio and relevant clinical covariates. Evaluation of multicollinearity, model fit, explained variance, calibration, discrimination, and internal validation would be necessary before describing the ratio as providing incremental predictive value.

Future research should consequently employ longitudinal and preferably multicenter designs with larger and more diverse populations. Studies should separately characterize overt and subclinical hypothyroidism and newly diagnosed versus treated disease, while recording levothyroxine dose and biochemical control. Comprehensive iron assessment should include hemoglobin, serum iron, transferrin saturation, total iron-binding capacity, ferritin, and inflammatory markers, with consideration of thyroid autoantibodies and relevant nutritional variables (7,15–20,25). Multivariable models should determine whether the ferritin–TSH ratio adds information beyond its individual components, fT4, demographic characteristics, treatment status, and relevant comorbidity. Prospective assessment of changes in the ratio alongside changes in symptom burden could then clarify temporal relationships, while independent validation cohorts would be necessary before proposing clinically actionable thresholds.

In conclusion the present work presents evidence for a clinically relevant association between the ferritin-TSH ratio and symptom severity in primary hypothyroidism which agrees with current understanding of multifactoriality of symptoms of thyroid disease and interplay between iron status and thyroid function, reinforcing that biochemic normalcy or a single test cannot fully describe the patients' experience (2-7,15,21-24). The ratio deserves further investigation as an exploratory integrative marker but should be treated with caution until its incremental contribution and its clinical consistency and validity are defined

CONCLUSION

The ratio was inversely related to hypothyroid symptom severity and had a closer unadjusted relationship with HSS score compared to serum ferritin or TSH.15 Decreased ferritin levels and increased TSH were also correlated with increased symptom burden, providing further evidence of interaction between iron-associated and thyroid associated biochemical parameters in the presentation of primary hypothyroidism. We conclude that the ratio ferritin/TSH should be interpreted as an exploratory compound measure, rather than as an established diagnostic or predictive biomarker. Prospective, larger scale studies assessing comprehensive iron profile, complete thyroid phenotype, medication use, confounding factors, multivariate analysis and external validation would be needed before application in clinical practice.

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