Original Article

Risk of Progression of Subclinical to Overt Hypothyroidism: A Cohort Study

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Abstract

Background: Subclinical hypothyroidism is defined by elevated serum thyroid stimulating hormone levels in the setting of normal levels of the thyroxine (T4) and triiodothyronine (T3). Iron acts as a cofactor in Thyroid peroxidase, which catalyses the initial two reactions of T3 and T4 biosynthesis. The chief clinical marker of iron deficiency is serum ferritin, which reflects the body iron stores. Whether hypoferritinemia affects the development of overt hypothyroidism from subclinical hypothyroidism is a question of concern.
Methods: Aim: To determine the predictive significance of serum ferritin in subclinical hypothyroidism. Material and method: A cohort observational study was carried out at Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda, India from June 2023 to December 2024 in Biochemistry department in collaboration with Medicine department, among 95 subjects of subclinical hypothyroidism attending the medicine outpatient department.
Results: A total of 29 (30.53%) patients of subclinical hypothyroidism were converted to overt hypothyroidism by the end of 6 months. While in subjects with normal ferritin levels (>30 ug/L) and low ferritin levels (15-30 ug/L), the conversion of subclinical hypothyroidism (TSH=7.09±1.33 μIU/mL in normal ferritin subgroup, TSH=7.23±1.74 μIU/mL in low ferritin subgroup) to overt hypothyroidism (TSH=8.73±4.31 μIU/mL in normal ferritin subgroup, TSH= 13.02±8.26 μIU/mL in low ferritin subgroup) was non-significant with p values (p=0.51 and p=0.06) respectively. The conversion of subclinical hypothyroidism (TSH= 8.02±1.34 μIU/mL) to overt hypothyroidism (TSH = 13.86±8.49 μIU/mL) was significant (p=0.005) in subclinical hypothyroid patients with very low ferritin levels (<15 ug/L).
Conclusion: Monitoring and correcting ferritin levels could be important in managing subclinical hypothyroidism to prevent progression.

Keywords: Ferritin; Thyroid stimulating hormone; subclinical hypothyroidism; overt hypothyroidism; euthyroidism.

Introduction

Thyroid dysfunction includes a range of conditions, from normal thyroid function (euthyroidism) to overt hypothyroidism (OTH), with subclinical hypothyroidism (SCH) representing a transitional stage. Euthyroidism is defined by TSH levels between 0.3 and 4.5 μIU/mL, T3 levels between 80 and 220 ng/dL, and T4 levels from 5 to 12 μg/dL. OTH is diagnosed when TSH levels exceed 10 μIU/mL and free thyroxine (fT4) is below the normal range, whereas SCH is marked by mildly elevated TSH levels (4.5–10 μIU/mL) with normal thyroid hormone levels. [1, 2, 3] Although SCH is often without symptoms, it is viewed as an early form of thyroid failure that can progress to OTH, particularly in individuals with additional risk factors. [4] Clinical signs of OTH—such as tiredness, cold sensitivity, and constipation—usually appear at more advanced stages, underscoring the importance of early recognition. [1]

Iron also plays a critical role in thyroid hormone production, acting as a cofactor for thyroid peroxidase (TPO), the enzyme that facilitates the initial steps of T3 and T4 synthesis. Serum ferritin (SF), which indicates the body's iron reserves, is a key marker of iron deficiency. [5] Low SF levels have been linked to both SCH and OTH, and iron supplementation has been shown to help restore normal thyroid function in iron-deficient females. [6, 7] Despite this connection, the role of hypoferritinemia in predicting the progression from SCH to OTH is still not well understood. [8, 9]

Considering the interplay between iron status and thyroid function, this study seeks to investigate whether serum ferritin levels can serve as a predictor for the advancement of SCH to overt hypothyroidism. Identifying such predictive factors early on could help facilitate timely treatment and better clinical outcomes.

Primary hypothesis: Among adults with subclinical hypothyroidism at baseline, low serum ferritin is independently associated with a higher risk of progression to overt hypothyroidism during follow-up compared with normal ferritin, after adjusting for age, sex, baseline TSH and iron/thyroid medication use.

Null hypothesis: Progression risk does not differ by ferritin status.

Aims and Objectives

To determine the incidence of progression from SCH to OTH during follow-up.

Materials and Methods

A cohort study was carried out at Adesh Institute of Medical Sciences and Research (AIMSR), Bathinda, India from June 2023 to December 2024 in Biochemistry department in collaboration with Medicine department, among subjects of SCH attending the medicine outpatient department. Ethical clearance from the institutional ethical committee was obtained. (AU/EC_BHR/2K24/636)

Inclusion Criteria

- Participants between 18 and 50 years of age.
- Both males and females will be included.
- Individuals diagnosed with SCH, defined by TSH levels between 4.5 and 10 μIU/mL, with normal T3 and T4 values.
- Participants who voluntarily agree and sign the informed consent form.
- Individuals able and willing to undergo regular follow-up for a period of 6 to 12 months.

Exclusion Criteria

- Subjects currently receiving thyroid hormone replacement or antithyroid medications.
- Patients with baseline TSH levels above 10 μIU/mL or reduced free T4.
- Pregnant or Lactating Women.
- Subjects with pre-existing conditions such as chronic kidney or liver disease, cancer, or chronic inflammatory disorders.
- Those with anemia due to causes other than iron deficiency (e.g., thalassemia, vitamin B12 or folate deficiency).
- Individuals who have received iron therapy or blood transfusions in the last 3 months.
- Those who have had an acute infection or hospital admission within 4 weeks prior to study entry, as this may influence ferritin levels.
- Use of drugs such as corticosteroids, lithium, or antiepileptics that can interfere with thyroid or iron metabolism.

Sample size

The actual sample size is calculated based on the average prevalence rate of SCH (9%) by using Cochran's formula. [10]

$$Z^2pq/e^2$$

Where Z is Z score (1.96), p is prevalence of SCH, q was (1-p), e^2 was precision value. 79, but it is increased to 95 to have adequate number and to draw significant conclusion.

Data collection

The data regarding detailed history and medical assessment was collected from subjects of SCH, showing subclinical picture in biochemistry reports, attending the outpatient department of AIMSR hospital. Investigations such as T3, T4, TSH were observed, and SF was done on day one and after six months serum TSH was done on cases and controls, in laboratory attached to the hospital. SF and TSH were analysed on SNIBE analyser of Maglumi company. The analyzer works on the principle of chemiluminescence. The WHO defines low ferritin as levels <15 μg/L for adults. [11] However, in clinical practice, when SF levels dip below 30 μg/L, ID can be ascertained. [12]

Statistical Analysis

Descriptive statistics such as mean and standard deviation for continuous variables, frequency, and percentage for categorical variables were determined. ANOVA was used to find association between ferritin, SCH and TSH from day 1 and at the end of 6th month.

Results

Table 1 shows the various parameters in cases and controls. p values were calculated by Mann-Whitney U test. TSH values on day 1, ferritin levels and TSH levels at 6 months showed a significant difference in cases as compared to controls. In the present study majority 64 (67.37%) of the SCH patients were in the age group 40-60 years. The proportion of females 60 (63.16%) were high as compared to males 35(36.84%). Out of 95 patients of SCH (Table 2), 29 (30.53%) patients were converted to OTH by the end of 6 months. Out of total patients, 21(22.11%), 31(32.63%) and 43(45.26%) had ferritin levels <15, 15-30 and >30 ug/L respectively. The conversion of SCH to OTH was significant (p=0.005) in SCH patients with ferritin levels <15 ug/L. Both age and gender were found to be non-significant in SCH to OTH conversion (p=0.347, and p=0.066 respectively) in the three ferritin subgroups.

Table 1: Various parameters in cases and controls

	Cases	Controls	p value
TSH Day 1 (μIU/mL)	7.31±1.41	2.1±1.1	0.01*
Ferritin (μg/L)	53.93 ± 37.5	101 ±5.6	0.01*
TSH 6 month (μIU/mL)	15.3± 8.5	2.4±1.2	0.001*

* significant difference (p values were calculated by Mann-Whitney U test)

Table 2: Various parameters of the SCH patients.

Ferritin (μg/L)	**Number of patients (%)**	
<15	21(22.11%)	
15-30	31(32.63%)	
>30	43(45.26%)	
TSH (μIU/mL)	**1st Day**	**At end of 6th month**
<10	95 (100%)	66 (69.47%)
>10	0 (0.00%)	29 (30.53%)

Discussion

In the present study, we investigated the corelation between serum ferritin levels and the progression risk of SCH to OTH. Our findings support the hypothesis that low serum ferritin levels may serve as a predictive marker for thyroid dysfunction progression. In this study, SCH with SF below 15 ug/L showed a significant conversion to OTH as compared to those >15ug/L. (Table 3)

For the enzyme TPO, which is necessary for the synthesis of thyroid hormones, to operate properly, iron is a vital micronutrient. As an indicator of iron storage, ferritin shows how much iron is available for physiological functions. Numerous studies have shown that iron shortage can worsen pre-existing thyroid dysfunction and affect the production of thyroid hormones. [2]

Table 3: Association between SF, TSH value and outcome of SCH.

Ferritin	SCH patients (n, %)	TSH at Day 1 (Mean±SD)	P value	Patient converted to OTH (n, %)	TSH at end of 6 months (Mean±SD)	P value
Normal ferritin levels >30 ug/dl	43(45.26%)	7.09±1.33	0.06	5(5.26%)	8.73±4.31	0.51
Low ferritin levels (30 ug/dl-15 ug/dl)	31(32.63%)	7.23±1.74	0.04	11 (11.58%)	13.02±8.26	0.06
Very low ferritin levels (<15ug/dl)	21(22.11%)	8.02±1.34	0.001*	13(13.8%)	13.86±8.49	0.005*

ANOVA was used to assess significance of data between ferritin, SCH and TSH from day 1 and at the end of 6th month
*Significant correlation

In our cohort, the rate of TSH increase and the development of OTH over time was considerably higher in those with lower baseline serum ferritin levels. This supports earlier studies showing a connection between iron deficiency and thyroid dysfunction, particularly in premenopausal women who are more likely to have both conditions. Further, low ferritin levels may indicate a "functional iron deficiency" that impacts iron-dependent metabolic pathways, such as thyroid hormone metabolism, even in the absence of anemia. Ferritin's importance as an early and sensitive marker in thyroid evaluation is further supported by this. [13]

Another study analysed iron salt, levothyroxine, and iron salt+levothyroxine in the treatment of subclinical hypothyroidism and iron-deficiency anemia. The outcome depicted that levothyroxine+iron salt was better to other treatment strategies. It is essential to consider subclinical hypothyroidism when iron salt is not helpful in iron-deficiency anemia, especially in endemic areas of iodine deficiency and goiter. Therefore, recommendation of levothyroxine+iron salt in patients with coincidental subclinical hypothyroidism and iron-deficiency anemia is suggested. [14]

A study conducted in Finland involved 25 women (with ferritin cut off of >30 ug/L) who continued to experience symptoms of hypothyroidism despite having normal thyroid hormone levels (euthyroid state). At the start of the study, none of the individuals were anemic, but all had serum ferritin levels below 60 μg/L. They received oral iron supplements for a duration of 6 to 12 months. Over time, their hypothyroid-related symptoms gradually subsided, with marked improvement observed once ferritin levels surpassed 100 μg/L. At this threshold, about two-thirds of the participants reported significant symptom relief [15]. Thus, ferritin supplementation in anaemic patients can reduce hypothyroid related symptoms, hence suggesting to play a role in preventing the conversion of subclinical to overt hypothyroidism which needs further evidence.

Iron supplementation in the management of hypothyroidism offers several benefits: it enhances the body's stress tolerance, boosts immune response, and reduces activity of the sympathetic nervous system. Furthermore, iron supports the binding of triiodothyronine (T3) to its nuclear receptors, facilitates iodine utilization in thyroid hormone production, and increases thyroid hormone availability by improving the function of deiodinases and thyroid peroxidase [16, 17].

Importantly, this study highlights the need for ferritin screening in patients with SCH, particularly those who are symptomatic or at risk for progression. Early detection and correction of iron deficiency may provide a cost-effective adjunct to monitoring SCH and possibly delay or prevent the onset of OTH.

Limitations

The study was limited by sample size and duration of follow-up, which may reduce statistical validity. This can be resolved by a larger, multicenter, and longitudinal studies for ferritin predictive of SCH progression and to determine whether iron supplementation in ferritin-deficient SCH patients alters disease trajectory. Other confounding factors like inflammation or chronic disease states were not fully excluded because ferritin is an acute-phase reactant, systemic inflammation (e.g., obesity, autoimmune disease) can elevate ferritin despite depleted bioavailable iron.

Conclusion

Low ferritin levels (<15ug/L) in SCH significantly (p=0.005) contribute to the pathophysiology and progression to OTH due to reduced thyroid hormone synthesis. If low ferritin truly increases the risk that SCH progresses to overt hypothyroidism, measuring and correcting iron deficiency could become a low-cost, high-value strategy to prevent thyroid failure.

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Availability of data and materials: Findable

Author contribution:

- Dr Premjeet Kaur - conceptualisation, data collection, manuscript writing, editing amd final approval
- Dr Rakendra Singh – conceptualisation

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