Subclinical Hypothyroidism Progressing to Clinical Overt Hypothyroidism Following Moderate COVID-19 Pneumonia: A Prospective Case-Control Study on Post-COVID Sequelae

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Abstract

Among the various post-COVID sequelae, thyroid function impairment stands as a significant concern. COVID-19-related primary hypothyroidism has been documented in the literature. This study aimed to determine the number of cases with subclinical hypothyroidism and a history of moderate COVID-19 pneumonia who progressed to clinically overt hypothyroidism at six months. A prospective case-control study enrolled adult patients with known subclinical hypothyroidism and a history of moderate COVID-19 pneumonia as cases. Detailed medical history and physical examinations were conducted for all participants. Thyroid profiles, including free T4 and TSH, were measured at baseline and again at six months for all cases. The results revealed that 20% of cases with a history of moderate COVID-19 exhibited low free T4 levels at six months following infection, indicating progression from subclinical to clinical hypothyroidism. The mean TSH level at baseline was 7.29 mU/L, which increased to 8.76 mU/L at six months. New-onset symptoms were more prevalent in these cases compared to the controls. Furthermore, the mean baseline TSH level for cases progressing to clinical hypothyroidism was significantly higher (9.17 ± 0.63 mU/L) compared to those who did not progress (6.82 ± 1.16 mU/L; $p<0.001$). These findings suggest that patients with subclinical hypothyroidism and a history of moderate to severe COVID-19 pneumonia should undergo periodic monitoring to ensure timely treatment initiation if overt hypothyroidism develops.

Keywords: clinical overt hypothyroidism; COVID-19; post-COVID sequalae; subclinical hypothyroidism; thyroid dysfunction

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1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can manifest with various signs and symptoms beyond the respiratory system, affecting other systems like the endocrine system [1,2]. The mechanism of SARS-CoV-2's organ impact mirrors its affinity for organs expressing angiotensin-converting enzyme 2 (ACE2) receptors. Endocrine cells widely express both ACE2 receptors and transmembrane serine protease 2.

Furthermore, COVID-19 can trigger a robust immune response and systemic inflammation. This inflammatory response may impact the thyroid gland and its function, as cytokines released during the immune response could potentially influence thyroid hormone production and regulation. Therefore, SARS-CoV-2 can cause a spectrum of thyroid disorders, including thyrotoxicosis (Graves' disease or subacute thyroiditis) and hypothyroidism (primary autoimmune thyroiditis or secondary hypothyroidism due to pituitary dysfunction) [3].

Serum TSH measurement serves as the primary screening test for detecting thyroid dysfunction [4]. The American Association of Clinical Endocrinology recommends continuing regular levothyroxine treatment for patients with recently diagnosed hypothyroidism following COVID-19 infection [5].

COVID-19-related primary hypothyroidism has been documented in the literature. Lania et al. reported a 5.2% incidence of primary hypothyroidism, with subclinical presentations in 90% of cases and overt presentations in the remaining 10% [6]. Additionally, they found a higher in-hospital mortality rate among hypothyroid COVID-19 patients compared to euthyroid COVID-19 patients. Muller et al. reported two cases of primary hypothyroidism due to chronic autoimmune thyroiditis (CAT) among COVID-19 patients admitted to high-intensity care units [7]. Both cases developed primary hypothyroidism during COVID-19 and persisted

even after discharge. Tee et al. reported a case of overt primary hypothyroidism due to CAT one week after a mild COVID-19 resolution [8].

With growing evidence of primary hypothyroidism occurring during or after COVID-19, our understanding of the various COVID-19 sequelae continues to evolve, necessitating continuous development and adaptation of management approaches. Therefore, this study aimed to determine the number of cases where subclinical hypothyroidism with a history of moderate COVID-19 pneumonia progressed to clinically overt hypothyroidism after six months.

2. Methodology

2.1 Study Design and Ethics

A prospective case-control study was conducted for one year in eastern India. The study protocol received approval from the Clinical Research Ethics Committee (CREC-STM) of Calcutta School of Tropical Medicine, Chitta Ranjan Avenue, Kolkata (Reference Number: CREC-STM/2022-AS06). Written informed consent was obtained from all participants before they enrolled.

2.2 Study Population

The study recruited adult patients with known subclinical hypothyroidism who also reported a history of moderate COVID-19 pneumonia. These patients served as the cases. A control group comprised adult patients with known subclinical hypothyroidism but no documented evidence of prior COVID-19 infection. A positive COVID-19 Rapid Antigen Test (RAT) or Reverse Transcription Polymerase Chain Reaction (RTPCR) test confirmed the history of COVID-19 pneumonia for all cases.

Patients with TSH levels below 10 mU/L were excluded, as levothyroxine therapy is typically initiated only for levels above 10 mU/L [9]. Additionally, individuals with a history of thyroid treatment, symptomatic cases, goitre, female infertility, pregnancy, or lactation were excluded [10].

2.3 Study Sample

Given the literature-supported annual rate of 2-5% for progression from subclinical to overt hypothyroidism, with a 5% margin of error and 5% alpha level, the estimated sample size was 38 per group [10]. However, the study enrolled 55 cases and 50 controls, exceeding the initially determined sample size.

2.4 Case Definition

According to the American Thyroid Association and the Endocrine Society, subclinical hypothyroidism is biochemically defined by a normal serum free thyroxine (T4) concentration combined with an elevated serum TSH [9]. Similarly, the national COVID guideline characterizes moderate COVID-19 pneumonia by shortness of breath, difficulty in breathing, a respiratory rate of 25 to 29 breaths per minute, and an SpO_2 of 90-93% on room air [11].

2.5 Data Collection

A history of moderate COVID-19 pneumonia was documented from the patients' past medical records. Detailed history was taken and thorough physical examinations were performed. Symptoms and signs, particularly those related to thyroid dysfunction, were noted in detail. Baseline thyroid profiles, including free T4 and TSH levels, were obtained and recorded in all cases. At the end of six months, the thyroid profiles were repeated and assessed again.

2.6 Data Analysis

The obtained data were statistically analyzed. To ensure participant confidentiality, the data were anonymized. Descriptive data were represented as mean, standard deviation, frequency, and percentages, as applicable. The Shapiro-Wilk Test was used to assess the normality of the data. Student's t-test was employed to compare all continuous data, while categorical data were compared using either the chi-square test or Fisher's exact test. A p-value less than 0.05 was considered statistically significant. All statistical tests were conducted using standard statistical software, including GraphPad Prism (version 8.0.2, San Diego, CA, USA) and Microsoft Excel.

3. Results

The study enrolled 55 adult patients with known subclinical hypothyroidism who reported moderate COVID-19 pneumonia. Females comprised 70.9% (39/55) of the participants. Age ranged from 24 to 56 years, with a mean of 39.63 years. All cases were anti-thyroid peroxidase antibody (anti-TPO) negative and had normal free T4 at baseline with elevated TSH. Within six months after COVID-19 infection, 11 (20%) cases transitioned from subclinical to clinical hypothyroidism, exhibiting low free T4. Mean baseline TSH was 7.29 mU/L, increasing to 8.76 mU/L at six months. Notably, 22 (40%) cases reported new-onset lethargy, and 12 (21.81%) developed new-onset constipation at six months. The cases progressing to clinical hypothyroidism had significantly higher baseline TSH (9.17 ± 0.63 mU/L) compared to those who did not progress (6.82 ± 1.16 mU/L, $p < 0.001$). Thyroid dysfunction persisted throughout the year-long follow-up, confirming its non-transient nature (Tables 1-3).

Additionally, we observed 50 subclinical hypothyroidism patients with TSH levels below 10 mU/L, all of whom were anti-TPO negative. At six-month follow-up, only two (4%) progressed to overt hypothyroidism with TSH exceeding 10 mU/L, significantly less than the 20% observed in the COVID-19-infected subgroup.

4. Discussion

It has been reported that subclinical hypothyroidism can progress to overt hypothyroidism in about 2-5% of cases annually [10]. However, the rate of progression varies depending on several factors, including the underlying cause of thyroid dysfunction, initial TSH levels, and individual health characteristics. Notably, some individuals with subclinical hypothyroidism may remain stable or even revert to normal thyroid function without progressing further. Therefore, regular monitoring and appropriate management are crucial for individuals with subclinical hypothyroidism. Treatment decisions should be individualized based on a comprehensive assessment of their specific health factors and symptoms.

Fatourechi et al. observed that the presence of anti-TPO antibodies influences the progression of subclinical hypothyroidism to overt hypothyroidism. Specifically, those without anti-TPO antibodies had a 2.6% annual progression rate, compared to 4.3% in those with positive antibodies [12]. This aligns with our own observation of a 4% progression rate at six months. These findings suggest a potential effect of COVID-19 infection on the progression

Table 1: Demographics of the sample.

Characteristics	Cases (N=55)	Controls (N=50)	P value
Male/female	16/39	14/36	0.901
Mean age [Mean ± SD (Range) (95% CI)]	39.63 ± 7.26 (24 – 56) (37.711, 41.549)	40.12 ± 5.15 (26 – 53) (38.693, 41.547)	0.693

Table 2: Symptoms at sixth month [n (%)].

Lethargy	22 (40.00%)	6 (12.00%)	0.001
Constipation	12 (21.81%)	2 (4.00%)	0.007
Dryness of skin	6 (10.91%)	2 (4.00%)	0.182
Feeling of cold	4 (7.27%)	2 (4.00%)	0.470
Decreased appetite	8 (14.55%)	2 (4.00%)	0.065
Hoarseness of voice	0 (0.00%)	0 (0.00%)	-
Menorrhagia	5 (9.09%)	2 (4.00%)	0.296
Weight gain	4 (7.27%)	2 (4.00%)	0.470
Paresthesia	0 (0.00%)	0 (0.00%)	-

Table 3: Thyroid profile (Mean ± SD) (95% CI).

Baseline free T4 (ng/dL)	1.35 ± 0.18 (1.302, 1.398)	1.38 ± 0.15 (1.338, 1.422)	0.358
Baseline TSH (mU/L)	7.29 ± 1.43 (6.912, 7.668)	6.98 ± 1.42 (6.586, 7.374)	0.268
Post-six-month free T4 (ng/dL)	1.24 ± 0.31 (1.158, 1.322)	1.32 ± 0.2 (1.265, 1.375)	0.123
Post-six-month TSH (mU/L)	8.76 ± 2.15 (8.192, 9.328)	8.15 ± 1.68 (7.684, 8.616)	0.111

of thyroid dysfunction. Further research is warranted to explore this possibility.

A study compared the frequency of patient visits for hypothyroidism before and after the COVID-19 pandemic, as well as investigating the incidence of hypothyroidism following COVID-19 infection [13]. They found a significant increase in newly diagnosed cases of both clinically overt and subclinical hypothyroidism in the post-pandemic years (2021–2022) compared to 2019. While 58 cases (55 hypothyroid and 3 subclinical) were diagnosed in 2019, this number leaped to 89 (77 hypothyroid and 12 subclinical) in 2020 and 101 (93 hypothyroid and 8 subclinical) in 2021. Additionally, the mean diagnosis time for hypothyroidism post-COVID-19 infection was reported to be three months for females and two months for males [13].

Chronic inflammation of the thyroid gland, leading to reduced hormone secretion, is a potential cause of hypothyroidism following COVID-19 infection. A descriptive cross-sectional study reported that 60.53% (23 of 38) of patients with COVID-19 pneumonia had subclinical hypothyroidism, suggesting a link between infection severity and the risk of developing hypothyroidism [14]. While the exact mechanisms of thyroid involvement in COVID-19 remain unclear, several possibilities exist. Firstly, ACE-2 and TMPRSS2, abundantly expressed in thyroid follicular cells, serve as viral entry points. Viral invasion could directly damage these cells. Secondly, the virus might trigger an immune response leading to autoimmune destruction of thyroid follicles. Finally, alterations in the hypothalamic-pituitary-thyroid axis could contribute. Additionally, medications used for treatment, such as anticoagulants and high-dose corticosteroids, may also affect thyroid function [15].

Unlike studies focusing on the association between COVID-19 and subclinical/overt hypothyroidism, our study specifically explored the progression of subclinical hypothyroidism to overt hypothyroidism following COVID-19 pneumonia. However, limitations due to small sample size, single-center design, and short follow-up period necessitate further multi-center studies with larger samples and longitudinal design.

5. Conclusion

Patients with subclinical hypothyroidism who also have a history of moderate to severe COVID-19 pneumonia should be followed up periodically at regular intervals. This regular monitoring will ensure early treatment initiation once they develop overt hypothyroidism and meet the necessary clinical criteria.

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Conflict of Interest Statement

The authors declare no conflict of interest.

Author Contributions

All authors have contributed equally. They have read and agreed to the published version of the manuscript.

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