

# Post-COVID fatigue: a new era of complication by altered thyroid function

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## ABSTRACT

**Background:** Since late 2019, the development of severe acute respiratory distress syndrome (SARS) occurred, which began as a small cluster of cases in Wuhan, China and subsequently spread across the globe in the shape of a global pandemic. Coronavirus disease 2019 (COVID-19) initiates an immune response over-activity leading to release of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), which leads to overt thyroid dysfunction by disruption of thyroid transport proteins. Level of triiodothyronin ( $T_3$ ) is inversely proportional to IL-6 with a modest decrease of thyroid stimulating hormone (TSH) and thyrotropin ( $T_4$ ). Fatigue is usually expressed by lack of one or more of habits or routines, particularly a lack of exercise. It is also frequently associated with depression. Fatigue might be an indication of various underlying illnesses that necessitate medical attention. COVID-19-related thyroid disorders could biochemically manifest as thyrotoxicosis, hypothyroidism, as well as non-thyroidal illness syndrome. Post-COVID fatigue has become an alarming complication which remains undiagnosed causing more complication at later stage. There are very limited knowledge regarding altered thyroid function in patients who have recovered from COVID-19. Aims of this study were to know about the derangement of thyroid hormones.

**Methods:** This cross-sectional study was conducted in the Department of Biochemistry and Molecular Biology, BSMMU, Dhaka from July, 2020 to June, 2021. A total of 100 post-COVID patients (age 18 – 70 years) with fatigue were enrolled for this study. Among them, 50 were treated at home and 50 were treated in hospital. For this study, serum TSH and  $FT_4$  were measured by the automated analyser. The data were expressed as frequency and percentage, mean for normally distributed data.  $p$  value  $>0.05$  was considered statistically significant.

**Results:** The value of TSH and  $FT_4$  in home and hospital treated patients were 1.59, 2.96 mIU/L and 9.27, 17.28 pmol/L respectively. There was significant difference of level of serum TSH ( $p < 0.0001$ ) and  $FT_4$  ( $p < 0.0001$ ) between home and hospital treated post COVID-19 patients with fatigue.

**Conclusion:** Home treated post-COVID patients with fatigue expressed higher level of serum TSH and  $FT_4$  than that of hospital treated patients.

**Key words:** COVID-19, thyroid function, fatigue.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) began as a minor cluster of cases in Wuhan, China and then expanded across the globe.<sup>1</sup> The virus had infected over 243 million people worldwide, and the number of death had reached 4.9 million.<sup>2,3</sup> The World Health Organization reported around 1.3 million coronavirus disease 2019 (COVID-19) recovered since the epidemic began.<sup>4</sup> Many people from different age groups have reported persisting symptoms such as fatigue, loss of appetite, sensitivity to cough reflex, bacterial infection, gastric issues or other

health complications related to heart, lungs, limbs, intestine and brain.<sup>5</sup>

WHO is working enthusiastically for powerful immunizations and measures to prevent complications.<sup>6</sup> One study that looked at 143 people who had severe COVID-19 found that 87% of the participants still had ongoing fatigue for about 2 months after they were initially admitted to the hospital.<sup>7</sup> Weakness is associated with COVID-19 have also been described as post-COVID complication.<sup>8</sup> It is common in critically ill patients and it can be caused by a variety of pathophysiological causes. Its clinical implications are frequently significant, influencing the vital and functional prognosis in the short and medium term.<sup>9,10</sup> Most of the time, fatigue can be traced in lack of interest with one or more of habits or routines, particularly lack of exercise, depression.<sup>11</sup> Fatigue is feeling tired all the time and is not relieved by sleep and rest. When recovering from COVID-19, one may feel need to sleep more or feel exhausted after only taking a short walk. Even simple things, like washing and dressing, can be exhausting.<sup>12</sup> As the COVID-19 pandemic lingers, the possibility of 'pandemic fatigue' has raised worldwide concerns. Some studies examined whether there was a gradual reduction in protective behaviours against COVID-19 from March through December 2020. It was hypothesized in expectations of fatigue.<sup>13</sup>

Coronaviruses are known to have direct effects on several endocrine glands, including the thyroid gland.<sup>14</sup> After COVID-19, it was seemed largely responsible for the loss of ability to work or feeling fatigue.<sup>15</sup> Furthermore, SARS-CoV-2 enters cells using the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in the thyroid gland. Thus, the hypothalamic-pituitary-thyroid axis may be susceptible to disturbance in patients with COVID-19.<sup>16</sup> Many studies have shown the onset of subacute thyroiditis (SAT) after certain infections, including COVID-19. They have measured thyroid hormones and found derangement of TSH.<sup>17,18</sup> There are very limited knowledge of thyroid function in patients who have recovered from COVID-19 in Bangladesh. The aim of the study was to find out thyroid dysfunction as an important cause of fatigue in post COVID-19 individuals.

## METHODS

This cross-sectional observational study was conducted at Department of Biochemistry and Molecular Biology, BSMMU, Shahbag, Dhaka from July, 2020 to June, 2021. The total study subject was 100. All of them were recovered from SARS-CoV-2 infection. Fifty home-treated patients as group I and 50 hospital-treated patients as group II were taken. Reverse transcriptase-polymerase chain reaction (RT-PCR) / rapid antigen / antibody positive COVID-19 survivors of age between 18 to 70 years, with history of post COVID-19 fatigue, without any history of thyroid illness before COVID-19 were inclusion criteria for both group I and II. History was taken properly as the patients had taken any treatments of thyroid disorder. All possible investigation reports (specially if there were any reports of thyroid function tests) were checked to know if the patients had any thyroid disorders previously. Pregnancy, lactation, presence of any chronic illness like chronic liver and renal disease, history of heart failure, history of malignancy, any immunosuppressive disorders and radiation therapy were also excluded from the study. Prior to the commencement of this study, the research protocol was approved by the Ethical Institutional Review Board (IRB) of BSMMU, Dhaka.

The home and hospital treated post COVID-19 patients were contacted over telephone. The patients reported to the laboratory, informed written consent, demographic and personal details of the patients were recorded. Then sample were collected by maintaining all aseptic precautions. A prepared structured questionnaire, containing relevant history about presence of any thyroid disorders, history of fatigue after recovery from COVID-19 and clinical and laboratory findings were filled up by proper history taking. Clinical data were collected through interviews with patients. The serum was separated from individual sample and stored at -56°C. Estimation of serum TSH and FT<sub>4</sub> of post COVID-19 home and hospital treated patients were performed at the Department of Biochemistry and Molecular Biology, BSMMU. Collected data were entered, checked and edited (to remove the outliers) with the help of the Statistical Package for Social Sciences (SPSS) software, version 26 and analysed. The data were expressed as frequency and percentage, mean  $\pm$  SD for normally distributed data. p value  $\leq 0.05$  was considered statistically significant.

## RESULTS

A total of 100 study subjects with fatigue, aged 18-70 years were enrolled. Age distribution is presented in Table I.

**Table I.** Age distribution of the study population (N=100)

Age group (years)	Home Treated (n=50)	Hospital Treated (n=50)
20-29	3 (6.0%)	9 (18.0%)
30-39	15 (30.0%)	14 (28.0%)
40-49	6 (12.0%)	5 (10.0%)
50-59	19 (38.0%)	17 (34.0%)
60-70	7 (14.0%)	5 (10.0%)
Total	50 (100.0%)	50 (100.0%)
Mean $\pm$ SD	42.16 $\pm$ 14.14	50.0 $\pm$ 10.8

In this study, the mean value of serum TSH and FT<sub>4</sub> of home treated and hospital treated patients were different (Table II and III).

**Table II.** Mean value of TSH and FT<sub>4</sub> in home and hospital treated patients

	Home treated patient	Hospital treated patient	P value
TSH (mIU/L) (range) (Mean $\pm$ SD)	1.59 $\pm$ 1.21 (0.38-2.80)	2.96 $\pm$ 1.89 (1.07-4.85)	0.001
FT <sub>4</sub> (pmol/L) (range) (Mean $\pm$ SD)	9.27 $\pm$ 5.36 (3.88-14.63)	17.28 $\pm$ 2.07 (15.22-19.34)	0.0001

**Table III.** Comparison of deranged percentage of serum TSH and FT<sub>4</sub> in home treated patients

Home treated patient group	TSH (percentage)	FT <sub>4</sub> (percentage)
Below normal level	64	32
Normal level	12	52
Above normal level	24	16
Hospital treated patient group		
Below normal level	20	4
Normal level	72	92
Above normal level	8	4

## DISCUSSION

In this study 38% home treated and 34% hospital treated patients were within 50-59 years age group. Nikpouraghdam et al. reported that the majority SARS-CoV-2 infected patients were in the age group of 50 to 60 years old.<sup>19</sup> Another study observed that people with age more than 50 years had higher susceptibility to infection.<sup>20</sup> Derangement of thyroid hormones were noticed after recovery from COVID-19. It was observed that more home treated patients were found serum TSH level below normal after recovery from COVID-19. In this study, the difference of mean value of serum TSH was statistically significant between home and hospital treated patients. A recent study over 54 COVID-19 patients reported low serum TSH (<0.996 uIU/ml) which was in agreement with this study. It was statistically significant with disease severity (mean: 1.14  $\pm$  0.35,  $p < 0.001$ ).<sup>21</sup> Another study reported that TSH lower than the normal range was present in 56% (28/50) of the patients with COVID-19. The study reported that lower the TSH and FT<sub>3</sub> levels were noticed in more severe COVID-19 patients.<sup>22</sup> In this present study it was noticed that 32% home treated patients reported with reduced FT<sub>4</sub> level. The difference of mean FT<sub>4</sub> between group I and II was statistically significant. A recent study reported significantly lower levels of T<sub>4</sub> (121.98 nmol/L,  $P < 0.001$ ), and free T<sub>4</sub> (FT<sub>4</sub>) (16.08 pmol/L,  $P = 0.026$ ) after COVID-19 infection.<sup>23</sup> This study was in agreement with present study.

In conclusion, derangement of TSH and FT<sub>4</sub> was observed in of post COVID-19 patients with fatigue. Hospital treated post COVID-19 patients presented higher level of serum TSH and FT<sub>4</sub> with fatigue than that of home treated.

**Authors' contribution:** MMA: Conceptualization, collecting data, literature search and writing manuscript, editing and data analysis. MMR: Review and supervision. IC: collecting data, literature search and writing manuscript, editing and data analysis. FHM: Conceptualization, review, supervision.

**Conflict of interest:** Nothing to declare.

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