Analysis of Thyroid Functional Status of the Covid-19 Survivors: A Single Center Study

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ABSTRACT

Background: Numerous researches had illustrated the long-term impact of COVID-19 on thyroid gland worldwide. The aim of this study is to observe similar consequences among Bangladeshi population since there is not much information available.

Materials and Methods: A total of 58 adult patients with a mean age of 29.53±9.005 years were studied to observe the long-term effect (> 6 months to 2 years) of COVID-19 infection, on their thyroid functions. Through convenience sampling, COVID-19 positive patients were selected, excluding any previously known thyroid illness or surgery, other endocrine complaints, pregnancy, COPD or bronchial asthma, hypertension, malignancy, or kidney disease. Thyroid functional status was assessed by quantitative determination of thyroid hormones and autoantibodies.

Results: Between a case group of 58 adult COVID-19 survivors and a control group of 27 healthy individuals, there was no significant difference in thyroid hormone levels (FT3, FT4, and TSH). However, two patients developed thyroid toxicity, with increased levels of FT3, FT4 and a decreased level of TSH. Concomitantly, increased levels of thyroid autoantibodies were also observed in two other patients.

Additionally, female participants showed significantly lower levels of FT3 and FT4 compared to the control group ($p = 0.02$ and $p = 0.008$, respectively). Among all of the COVID-19 survivors, a total of 10 patients (17%) showed deviations from the normal range of thyroid hormones and thyroid autoantibodies. The rest of the 48 patients (83%) revealed no abnormality.

Conclusion: Female survivors experienced a significant change in thyroid functional status that lasted longer. However, further research needs to be performed on a larger scale before reaching a conclusion.

Keywords: COVID-19, thyroid functionality, thyroid autoantibodies, hyperthyroidism.

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INTRODUCTION

In 2019, the people of the world became familiar with one of the most devastating pandemics, COVID-19. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (China-WHO Joint Mission, 2020). As it is a novel viral disease, there is a lot more to be discovered. In Bangladesh, the first case of COVID-19 was reported on March 8, 2020 (1). Still, people are being affected in this country, either knowingly or unknowingly. Like many other countries, Bangladesh was also hit by the five consecutive waves involving various variants of SARS-CoV-2, among which the second wave was the most destructive one (2). COVID-19 has caused 6.83 million deaths worldwide until now. In Bangladesh, around 2.04 million people are reported to be affected by the Corona virus, including about thirty thousand known cases of tragic deaths. Therefore, it has become urgently necessary to study the impact of this novel kind of virus on the population of Bangladesh (3).

Despite numerous studies, the effect of coronavirus on the human endocrine system, particularly the thyroid gland, remains unknown. The SARS-CoV-2 virus is reported to interact with the thyroid gland through a complicated association of hormones and immunomodulatory signal molecules (4, 5). Because SARS-Cov-2-related thyroid dysfunction has been found in various studies, it is still unclear how thyroid autoantibodies function against the increased viral load of Corona virus (5).The expression of angiotensin converting enzyme 2 (ACE-2) combined with transmembrane protease serine 2 (TMPRESS2) is the key cellular complex for the virus to infect human cells, and interestingly, both of these are expressed in the thyroid gland too, even more than the lungs (6). In addition, it is also known that antibodies against the SARS CoV2 react with cellular antigens, including those on the thyroid. Furthermore, the spike protein

shows molecular mimicry toward thyroid peroxidase. Thus, the induction of antibodies to COVID19 may interact with the thyroid surface receptors (7). As the peak period of COVID-19 severity has passed in this country, the long-term effect of the virus on the thyroid gland is the subject of this study. Many recent studies have shown that COVID-19 can cause thyroid dysfunction in both the acute and convalescent phases (8). According to the UK National Institute for Health and Care Excellence (NICE) (9) and other integrated classifications of post-COVID symptoms (10), a crucial part is "long COVID" (symptoms persisting >12 weeks) and "Phase 3" (persistent post-COVID symptoms that last for more than 24 weeks). Long COVID exhibits a slew of symptoms affecting various other organs of the human body in the absence of respiratory symptoms. However, it is unclear whether this type of action will last for a long time in the case of the thyroid gland interfering with the normal physiological balance of the human body.

PATIENTS AND METHODS

Case Selection

This cross-sectional study involved mainly the population of the Chattogram division of Bangladesh. The case population was patients who had been affected by COVID-19 previously (within the last 6 months to 2 years). Referred by specialist physicians, these patients with plausible symptoms of thyroid illness underwent a thyroid hormonal assay at the Institution of Nuclear Medicine and Allied Sciences (INMAS), Chattogram. Thus, through convenience sampling, adult COVID-19 survivors were selected. Healthy individuals who were neither affected by COVID-19 nor suspected cases were selected for the control group. Informed written consents were collected after proper explanation about the research.

Patients with a previous history of thyroid illness or surgery, any other endocrine complaints, pregnancy, COPD or asthma, hypertension, diabetes, cancer, kidney disease, or those taking drugs like amiodarone, interferon, etc. that may interact with thyroid function were excluded from the study. For sorting COVID-19 positives, both RT-PCR confirmed and suspected cases were included. Because of the lack of knowledge and asymptomatic nature of this disease, many of the cases were unaware of testing by RT-PCR.

Sample collection

In this study, three principal hormones were measured and compared: FT3 (free triiodothyronine), FT4 (free thyroxine), Thyroid Stimulating Hormone (TSH), and the two most important anti-thyroid antibodies: anti-thyroglobulin antibody (TgAb) and anti-thyroid peroxidase antibody (TPOAb). For this, the blood serum sample was used. 8 cc of blood were collected from each patient, and serum was isolated.

Estimation of thyroid hormones and anti-thyroid antibodies were done by the chemiluminescent immunoassay (CLIA) technique with the most advanced technology of ADVIA Centaur@XPT. Reference ranges for this tests were as follows: FT3: 3.50-6.50 pmol/L, FT4: 11.5-22.7 pmol/L, TSH: 0.35-5.50 μIU/mL, Anti-Tg: <4.5 IU/mL and Anti TPO: <60.0 IU/mL.

Statistical Analysis

The statistical analysis was performed on MS Excel and IBM SPSS (Statistical Package for Social Sciences, for windows 20) software. Data with normal distribution were shown by mean ± SD (standard deviation). For quantitative variables, comparison was done by independent two-sample T test. To study the association between categorical variables, Chi-square tests were performed. The correlation analysis was performed by the Pearson or Spearman correlation analysis.

RESULTS

A total of 58 adult COVID-19 survivors and 27 healthy control individuals were enrolled for this study. There were no significant differences between age (29.539.05 and 32.2610.19 years), gender (female: 72% and 67% and male: 28% and 33%), height (1.58 meter and 1.58 meter), weight (60.63 kg and 60.29 kg), and body mass index (BMI) (24.16 and 24.04) of the case and control populations, respectively.

Two patients were found to be hyperthyroid, showing higher levels of FT3 and FT4 as well as a lower level of TSH compared with the reference values (Patient 01: FT3: 19.46 pmol/L, FT4: 57.88 pmol/L, and TSH: 0.008

IU/mL; Patient 02: FT3: 3.89 pmol/L, FT4: 23.88 pmol/L, and TSH: 0.279 IU/mL). Similarly, two more patients were observed with high levels of serum TSH and were positive for both TgAb and TPOAb (Patient 01: FT3: 5.23 pmol/L, FT4: 13.33 pmol/L, TSH: 16.615 IU/mL, TgAb positive, TPOAb positive; Patient 02: FT3: 5.99 pmol/L, FT4: 17.04 pmol/L, TSH: 16.675 IU/mL and TgAb positive, TPOAb positive). A comparison was made with the normal range of thyroid hormone levels (FT3: 3.50–6.50 pmol/L, FT4: 11.5-22.7 pmol/L, and TSH: 0.35–5.50 IU/mL).

Table 1. Comparison between Covid-19 survivors and control participants

	Covid-19 survivors (Case population)	Control population	*P* value
Gender	72% female, 28% male	67% female, 33% male	-
Age (years)	29.53±9.005 (range: 18-54)	32.26±10.19 (Range: 20-55)	0.22
Height (meter)	1.58±0.084	1.58±0.087	0.89
Weight (kg)	60.29±13.110	60.63±11.396	0.91
BMI (kg/m^2)	24.04±4.913	24.16±3.392	0.89
FT3 (pmol/L)	5.31±2.005	5.54±0.992	0.59
FT4 (pmol/L)	15.81±6.036	16.50±2.940	0.58
TSH (µIU/mL)	2.96±3.01	5.13±11.7	0.35
Anti-Tg	7(12%)	1(4%)	0.43
Anti-TPO	4 (7%)	1(4%)	0.69
Both antibody positives	4 (7%)	0 (0%)	-

BMI: body mass index, *FT_3:* free triiodothyronine, *FT_4:* Free Thyroxine, *TSH:* thyroid-stimulating hormone, *TgAb:* Anti thyroglobulin antibody, *TPOAb:* Anti thyroid peroxidase

Thyroid hormone levels were also compared between case and control participants depending on their gender. For the female participants the FT3 and FT4 values was significantly lower than that of control group (p=0.02, p=0.008 respectively).

Table 2. Comparison of thyroid hormone (FT3, FT4) levels in female and male group between sample and control participants.

		COVID-19 Survivors	Control Group	P value
Female	FT_3 (pmol/L)	5.00±0.62	5.55±1.20	0.02*
	FT_4 (pmol/L)	14.74±1.89	16.63±3.38	0.008*
Male	FT_3 (pmol/L)	6.14±3.63	5.53±0.35	0.62
	FT_4 (pmol/L)	18.64±10.8	16.23±1.92	0.51

A bivariate correlation analysis was done to interpret the impact of age and BMI on thyroid function in the case population. One significant positive correlation was found between the weight and TSH level (Pearson's correlation coefficient of 0.378*; correlation is significant at the 0.01 level; two tailed test). Furthermore, the BMI of the female sample showed a weakly positive correlation with their TSH level (Pearson's correlation coefficient of 0.31).

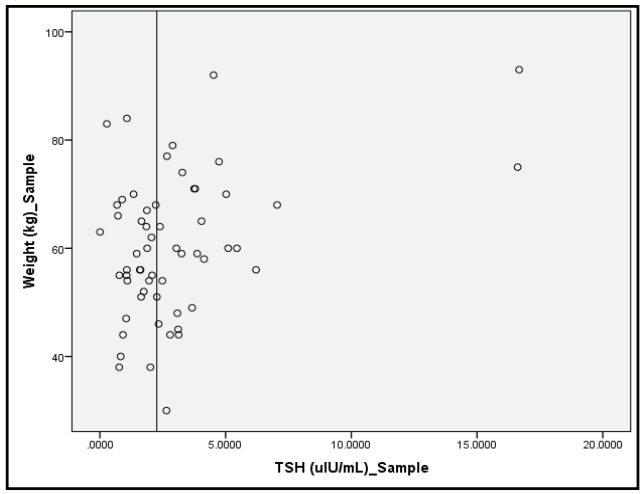

Figure 1: Correlation between weight and TSH level of COVID-19 survivors

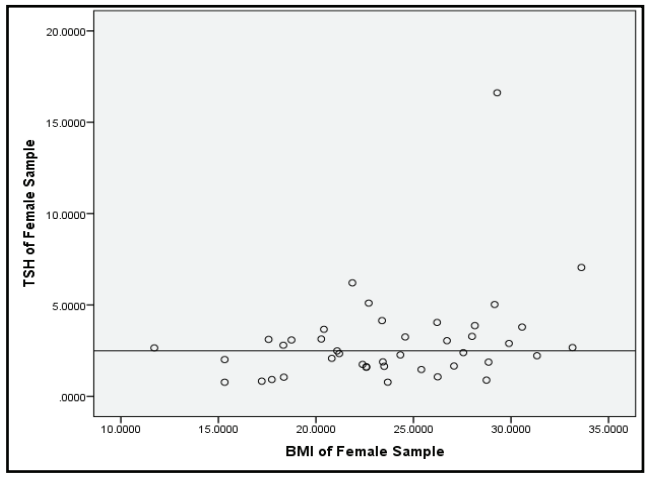

Figure 2 : Correlation between BMI and TSH level of female COVID-19 survivors

DISCUSSION

COVID-19 is being studied as a systemic infection that can easily affect multiple human body systems.This highly contagious infectious disease is caused by the SARS-CoV-2 virus, which is a positive-stranded (+ssRNA) virus. Following the entry of this virus inside

the host, many proteins are produced for the replication, transcription, and translation of the viral RNA. These proteins are involved in the pathogenesis of the COVID-19 disease. Many nonstructural and other structural proteins can block innate immune responses (11). Sometimes, chronic complications were also observed in various cases (12). Research in different disciplines has been performed to analyze the prolonged effect of COVID-19, but until now, no integrated explanation has been delivered regarding the diverse impact of long-term COVID-19 (13). However, most doctors and researchers agree that the long COVID symptoms persist because SARS CoV-2 can cause a massive inflammatory response (14).The higher level of ACE2 expression in the thyroid gland is the main reason for SARS-CoV-2 targeting the hypothalamic- pituitary -thyroid axis (4, 15). COVID-19-related subacute thyroiditis has been linked to painless thyrotoxicity, followed by hypothyroidism in some cases (16). With acute and reversible changes in thyroid gland functions, the thyroid volume was found significantly lower in COVID-19 survivors as well (8). COVID-19 has the potential to impair thyroid function through direct virus interaction with the gland, sick euthyroid syndromes, and autoimmune responses (17). Without the risk of developing thyroid disorder after COVID-19 infection, researchers have recently been concerned about the possibility of hyper- or hypothyroidism after receiving SARS-CoV-2 vaccination (18).Vaccines for COVID-19 consisting of mRNA are widely used. This kind of vaccine is capable of inducing a similar type of autoimmune response as COVID-19, which is concerning for developing subacute thyroiditis in the vaccinated patients (18, 19).

This study revealed some important insights about COVID-19 survivors in the Bangladeshi population, such as the fact that two patients were found to be hyperthyroid and two to have subclinical conditions even after a year of infection. Female patients showed lower levels of FT3 and FT4 compared with controls, which is noticeable and indicates further investigation. Moreover, patients with obesity (BMI 25–30), especially female participants, showed higher serum levels of TSH, which also indicates that, female COVID-19 survivors with obesity (BMI>30) are more vulnerable to hypothyroidism. Therefore, female individuals who suffer from COVID-19 need early thyroid functional tests and to take good care of themselves to be protected from any kind of thyroid related consequences.

There are some limitations to this study, such as the fact that not all COVID-19 patients could provide information for RT-PCR confirmation. So the patients with suspected cases needed to be considered. Because healthy individuals without even suspicion are difficult to find, the number of control patients is lower than that of cases.

CONCLUSION

Since the onset of the COVID-19 pandemic, the impact of COVID-19 on thyroid function has been studied in a variety of ways around the world. However, the research clearly shows that COVID-19 is more than just a pulmonary infection; it has a broader impact on human health. For this reason, some kind of prospective study could be done, especially focusing on the female survivors of Bangladesh.

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REFERENCES

1. Saha S, Tanmoy AM, Hooda Y, Tanni AA, Goswami S, Sium SM, et al. Covid-19 rise in Bangladesh correlates with increasing detection of B.1.351 variant. BMJ Global Health. 2021;6(5).
2. Amin R, Sohrabi M-R, Zali A-R, Hannani K. Five consecutive epidemiological waves of covid-19: A population-based cross-sectional study on characteristics, policies, and health outcome. BMC Infectious Diseases. 2022;22(1).
3. WHO coronavirus (COVID-19) dashboard [Internet]. World Health Organization. World Health Organization; [cited 2023Feb5]. Available from: https://covid19.who.int/
4. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of covid-19 on the thyroid gland: An update. Reviews in Endocrine and Metabolic Disorders. 2020;22(4):803–15.
5. Lui DT, Lee CH, Chow WS, Lee AC, Tam AR, Fong CH, et al. Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with covid-19. The Journal of Clinical Endocrinology & Metabolism. 2020;106(2).
6. Malik J, Malik A, Javaid M, Zahid T, Ishaq U, Shoaib M. Thyroid function analysis in COVID-19: A retrospective study from a single center. PLOS

ONE. 2021;16(3).

7. Ratnayake GM, Dworakowska D, Grossman AB. Can Covid-19 immunisation cause subacute thyroiditis? Clinical Endocrinology. 2021;97(1):140–1.
8. Urhan E, Karaca Z, Kara CS, Yuce ZT, Unluhizarci K. The potential impact of covid-19 on thyroid gland volumes among covid-19 survivors. Endocrine. 2022;76(3):635–41.
9. Kappelmann N, Dantzer R, Khandaker GM. Interleukin-6 as potential mediator of long-term neuropsychiatric symptoms of COVID-19. Psychoneuroendocrinology. 2021;131:105295.
10. Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining post-covid symptoms (post-acute COVID, Long COVID, persistent Post-COVID): An integrative classification. International Journal of Environmental Research and Public Health. 2021;18(5):2621.
11. Lei J, Kusov Y, Hilgenfeld R. NSP3 of Coronaviruses: Structures and functions of a large multi-domain protein. Antiviral Research. 2018;149:58–74.
12. Boaventura P, Macedo S, Ribeiro F, Jaconiano S, Soares P. Post-covid-19 condition: Where are we now? Life. 2022;12(4):517.
13. Marshall M. The four most urgent questions about long covid. Nature. 2021;594(7862):168–70.
14. Salamanna F, Veronesi F, Martini L, Landini MP, Fini M. Post-covid-19 syndrome: The persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Frontiers in Medicine. 2021;8.
15. Campi I, Bulgarelli I, Dubini A, Perego GB, Tortorici E, Torlasco C, et al. The spectrum of thyroid function tests during hospitalization for SARS COV-2 infection. European Journal of Endocrinology. 2021;184(5):699–709.
16. Puig-Domingo M, Marazuela M, Yildiz BO, Giustina A. Covid-19 and endocrine and metabolic diseases. an updated statement from the European Society of Endocrinology. Endocrine. 2021;72(2):301–16.
17. Puig-Domingo M, Marazuela M, Giustina A. Covid-19 and endocrine diseases. A statement from the European Society of Endocrinology. Endocrine. 2020;68(1):2–5.
18. Mehta A, Andrew Awuah W, Yarlagadda R, Kalmanovich J, Huang H, Kundu M, et al. Investigating thyroid dysfunction in the context of covid-19 infection. Annals of Medicine and Surgery. 2022;84:104806.
19. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-COV-2 proteins with tissue antigens: Implications for autoimmune diseases. Frontiers in Immunology. 2021;11.