Is Smaller Thyroid Gland Volume in COVID-19 Survivors Indicative of Chronic Thyroid Dysfunction?

Emre Urhan
Erciyes Universitesi Tip Fakultesi https://orcid.org/0000-0003-4825-7027
Zuleyha Karaca
Erciyes Universitesi Tip Fakultesi
Canan Sehit Kara
Erciyes Universitesi Tip Fakultesi
Zeynep Ture Yuce
Erciyes Universitesi Tip Fakultesi
Kursad Unluhizarci (kursad@erciyes.edu.tr)
Erciyes Universitesi Tip Fakultesi

Research Article

Keywords: COVID-19, thyroid gland volume, thyroid function tests, SARS-CoV-2

Posted Date: October 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-971654/v1

Abstract

Purpose.

Data about the effects of COVID-19 on the endocrine system are increasing, but COVID-19-associated thyroid dysfunctions are not known clearly. We investigated the effects of SARS-CoV-2 on the thyroid gland in COVID-19 survivors.

Methods.

64 adult COVID-19 survivors and 70 healthy adults were enrolled. The COVID-19 survivors were evaluated at median 5.7 months (IQR: 4-6.5) (range: 2-7 months) after acute infection. The blood tests were obtained for thyroid antibodies and function tests. Thyroid ultrasonography (USG) was done by the same physician. The ellipsoid formula was used for calculation of thyroid gland volume.

Results.

There was no significant difference between the groups for thyroid hormone levels. The mean thyroid gland volume was significantly lower in COVID-19 survivors (10.3 ± 3.4 ml) than in the controls (14 ± 5.3 ml) ($p = 0.001$). Mild TSH elevation was detected in 4 (6.2%) patients and all of the other patients (93.7%) were euthyroid. Thirty-one patients, who had pre-COVID thyroid hormone levels, were compared with their post-COVID thyroid hormone levels, and no significant difference was found. Twelve patients, who had acute-COVID infection were compared with their post-COVID thyroid function tests, and free triiodothyronine (FT3) values during acute-COVID infection were significantly lower than in their post-COVID period ($p = 0.02$).

Conclusions.

The effects of COVID-19 on the thyroid gland may have a variable course. Our results revealed that a significant decrease in thyroid gland volume in the early post-COVID compared to the healthy subjects and COVID-19 survivors may be candidates for thyroid gland disorders.

Introduction

Coronavirus disease of 2019 (COVID-19) is an infective disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was firstly reported from China in November 2019. It has been accepted as a pandemic disease and poses a risk to many people worldwide [1]. It mainly affects the lungs, but its effects have also been shown in many other systems, including the endocrine system [2]. SARS-CoV-2 performs target cell invasion via transmembrane protease serine 2 (TMPRSS2) and angiotensin-converting enzyme 2 (ACE2) receptor [5]. The data about the effects of COVID-19 on the endocrine system are increasing over time, but the extent of COVID-19-associated thyroid dysfunctions are not clearly known [2]. TMPRSS2 expression and ACE2 in the thyroid gland were detected higher than

in the lung according to cell culture examinations [5, 6]. Therefore, the thyroid gland may be a target for COVID-19 infection [2, 6]

SARS-COV-2 is similar to SARS for structural. Postmortem examinations of patients infected with SARS revealed virus associated cell damage in thyroid parafollicular and follicular cells [7]. SARS-CoV-2 may affect the thyroid gland indirectly with autoimmune changes and hyperimmune responses and directly with viral damage [8–10]. In addition, due to the detection of the presence of ACE2 and SARS genome in the hypothalamic-pituitary system, it may lead to thyroid dysfunction with possible thyrotroph cell damage Increasingly, cases of SARS-COV-2-induced subacute thyroiditis and postpartum thyroiditis are being reported [11, 12]. It has been reported in ongoing studies that COVID-19 infection may cause thyroid dysfunction in its acute course and also in the post-recovery period [1, 2]. In this study, we investigated the effects of SARS-CoV-2 on the thyroid gland in COVID-19 survivors by comparing them with healthy subjects for thyroid function tests and thyroid gland volume since there is no adequate data investigating thyroid gland volume.

Materials And Methods

The present study was approved by the Ethics Committee of the Erciyes University Medical School and informed consent was obtained from the participants.

Sixty-four adults with a history of COVID-19 infection and 70 healthy adults without history of COVID-19 infection were randomly enrolled in the study. COVID-19 survivors were evaluated at a median of 5.7 months (IQR: 4-6.5) (range: 2-7 months) after acute COVID-19 infection. SARS-COV-2 polymerase chain reaction of nasal and oral swab samples was used in the diagnosis of acute COVID-19 infection.

The clinical characteristics of patients (status of oxygen demand, history of intensive care unit (ICU) hospitalization and intubation, treatments used), prognostic markers of COVID-19 (platelet, lactate dehydrogenase level, lymphocyte, ferritin, d-dimer levels, and C-reactive protein) and basic biochemical tests during the course of acute COVID-19 were recorded. The patients were categorized as mild, moderate, and severe/critical disease severity according to the Health Commission of China during acute COVID-19 infection [13]. In mild disease, the symptoms are mild and there is no evidence of pneumonia on radiological examination. In moderate disease, respiratory system symptoms and fever are present and radiological examination may reveal evidence of pneumonia. Severe/critical disease is characterized by the presence of any of respiratory rate ≥30/minute, oxygen saturation ≤ 93%, shock states, more than 50% progression of pneumonic infiltration within 24-48 hours on radiological examination, and need for mechanical ventilation and ICU.

A history of thyroid disease and surgery, neck radiation, pregnancy, use of medication that affects thyroid function, and pituitary/hypothalamic disease, were accepted as the exclusion criteria of the current study.

Blood tests were obtained between the hours 8.00-9.00 for basal biochemical and hormonal investigations, anti-thyroid peroxidase (TPO), anti-thyroglobulin (Tg) antibodies, free thyroxine (FT4),

thyroid-stimulating hormone (TSH), and free triiodothyronine (FT3) from the participants. COVID-19 survivors, who had thyroid function tests (TFT) before and during acute COVID-19 infection, were also evaluated retrospectively.

Thyroid hormone levels and thyroid autoantibodies were measured by the electrochemiluminescence immunoassay (ECLIA) method (Mannheim, Germany, Cobas; Roche Diagnostics,). Reference ranges were as follows: TSH = 0.27- 4.20 μU/mL, FT4 = 0.93-1.97 ng/dL, FT3 = 2-4.4 pg/mL, anti-TPO = 0-34 U/ml and anti-Tg = 0-115 U/ml. The titer values of antibodies higher than the upper reference range were considered positive.

Thyroid gland ultrasonography (USG) was performed on all participants by the same physician on the same day with blood tests, with a GE LOGIQ P5 ultrasound machine. Thyroid gland volume was calculated by ellipsoid formula: maximum length (L), width (W), and depth (D) for each lobe (volüme = LxDxWx0.524). Total thyroid gland volume was calculated by summing the volumes of both lobes and if the maximum diameter of the isthmus was more than 5 mm, it was also added [14, 15]. In addition, participants with ≥1 cm nodules in the USG examination were excluded from the study.

Statistical analysis

The data was analyzed in the IBM SPSS program version 22. The Shapiro–Wilk test was used for data distribution. Data with normal distribution were shown as mean ± standard deviation (SD) and data with non-normally distributed were shown as median and interquartile range (IQR). For the comparison of quantitative variables in two independent groups, the Mann–Whitney U test or two independent samples t-tests was preferred according to the distribution of the data. For the comparison of quantitative variables, Chi-square tests were preferred. The COVID-19 disease severity groups were compared among themselves by one-way ANOVA and the Tukey HSD or Games-Howell test was preferred according to data distribution for post-hoc analysis. The correlation analysis was performed by Pearson or Spearman correlation analysis depending on the distribution of the data. The comparison of pre-COVID with post-COVID and acute-COVID with post-COVID data of the same patients was performed by using the Wilcoxon test or student's T paired test. if the probability (P) value was <0.05, it was considered statistically significant.

Results

There were no differences in age (38.8 ± 11.2 years (range: 21-59) and 36.3 ± 10.4 years (range: 22-59)), body mass index (29.6 ± 5.4 and 29.1 ± 3.6 kg/m^2), and gender (32 men, 32 women and 32 men, 38 women) of 64 COVID-19 survivors and 70 controls, respectively.

The median TSH values were 1.84 μU/mL (IQR: 1.35-2.55) and 1.76 μU/mL (IQR: 1.17-2.18) and median FT4 values were 1.19 ng/dL (IQR: 1.07-1.27) and 1.20 ng/dL (IQR: 1.05-1.32) ng/dL in COVID-19 survivors and the controls, respectively (p = 0.22 and p = 0.82). The mean FT3 values were 3.36 ± 0.40 pg/mL and

3.26 ± 0.40 pg/mL in COVID-19 survivors and the controls, respectively (p = 0.13). The mean thyroid gland volume was significantly lower in COVID-19 survivors (10.3 ± 3.4 ml) than in the controls (14 ± 5.3 ml) (p = 0.001). Anti-TPO and anti-Tg positivity were detected in 5 (7.8%) and 4 (6.2%) of COVID-19 survivors and controls, respectively and did not differ between the COVID-19 survivors and controls for both antibody positivity and titer values. These results are shown in table 1.

Among the patient group; 22 patients, 16 patients, and 26 patients were categorized as mild, moderate, and severe/critical disease, respectively. No significant difference was found in the TSH, FT4 values, and thyroid gland volumes when the patients were compared according to the severity of the disease. However, a significant difference in the FT3 values was found between the severity groups (p = 0.02) (Table 2). In posthoc analyses, the FT3 values were significantly lower in mild than in moderate and severe/critical disease (p = 0.01 and p = 0.02, respectively).

When the thyroid gland volume of COVID-19 survivors were compared according to their characteristics, such as lymphopenia (36 patients), history of oxygen demand (22 patients), hospitalisation in ICU (5 patients), intubation (2 patients), and steroid therapy (7 patients) during acute COVID-19 infection and gender and anti-TPO/Tg positivity, no significant difference was detected between subgroups (Table 3).

Among COVID-19 survivors, mild TSH elevation was detected in 4 (6.2%) patients (TSH values = 6.9, 4.45, 4.88, and 5.52 μU/mL), and all of the other patients (93.7%) were euthyroid.

Thirty-one patients, who had pre-COVID thyroid hormone levels were compared with their post-COVID thyroid hormone values, and no significant difference was found. Thyroid hormone levels of 12 patients with acute-COVID infection were compared to their post-COVID thyroid hormone values, and no significant difference was found for TSH and FT4. The FT3 values in acute-COVID infection were significantly lower than in their post-COVID values (p = 0.02) (Table 4 and 5).

Discussion

The present study revealed for the first time that thyroid gland volume was significantly lower in COVID-19 survivors than in healthy subjects with similar demographic characteristics. Mild TSH elevation was detected in 4 (6.2%) patients and the other patients were euthyroid.

It is confirmed that over time, that COVID-19 is not only a localized infection in the lung and leads to multisystemic results. The present data on the relationship between thyroid gland and COVID-19 mainly focused on the acute infection period. The accumulation of data is gradually increasing on this issue, including in the thyroid gland. Although it is well known that acute and reversible changes of the thyroid gland functions may be generally observed in acute infectious diseases, the long-term temporary or reversible results of COVID-19 arouse more curiosity.

SARS-CoV-2 and SARS have been shown to damage thyroid cells in autopsy samples [16, 17]. In addition, autopsy examinations of SARS-infected patients showed a decrease in staining and intensity of pituitary

TSH-secreting cells compared to healthy controls [18]. We may speculate with these autopsy results that SARS-CoV-2 and SARS may trigger possible damage with its affinity to thyroid and pituitary cells. Interestingly, the ACE2 receptor which is required for cell invasion of SARS-CoV-2 was detected higher in the thyroid gland than in the lung [19]. In a previous study, 61 SARS survivors, with no known thyroid disease were, evaluated 3 months after post-recovery and hypothyroidism was detected in 4 (6.6%) patients [20]. It is now better known that COVID-19 may trigger immune system activation and autoimmune changes [19, 21]. The cytokine storm and hyperimmune response during COVID-19 infection course may lead to destructive and inflammatory thyroiditis [9]. The mechanisms regarding the effect of COVID-19 infection on the thyroid gland are not yet fully clear. However, in addition to the above mentioned possible mechanisms, the thyroid gland may be a viral target for COVID-19 infection.

In a study by Lui et al., 79 patients were evaluated for a median of 2 months after being diagnosed with COVID-19 infection. The authors found that although it did not reach a significant level, thyroid gland volume was lower than in the control subjects. Thyroid gland volume was significantly lower in patients with a higher viral load and in men. No correlation was found between inflammatory markers during acute COVID-19 infection and thyroid gland volume [22]. We could not evaluate viral load since our study was observational and this is a limitation for this study. We did not detect any relationship between inflammation markers, genders, and severity of disease with thyroid gland volume. The viral load may not always correlate with disease severity. The severity classification of COVID-19 used in the present study is based mostly on clinical findings and it does not include viral load and inflammation markers. These results may indicate the need for more dynamic and predictive parameters for disease severity classification. SARS-CoV-2 may disrupt the thyroid microstructure in the acute period and may initiate thyrocyte damage. This injury may result in a decrease in thyroid gland volume over a longer period, even if thyroid hormone levels have no abnormality. Case series COVID-19-induced subacute thyroiditis have been reported and most of these cases are painless [12]. Subacute thyroiditis may also reduce thyroid gland volume after acute COVID-19 infection. In this study, subacute thyroiditis was not clinically detected in any patient. However, this may not exclude a clinically undetected subacute thyroditis since many patients are treated with glucocorticoids for their COVID-19 infection.

Khoo et al. evaluated 334 patients with acute COVID-19 diagnosis and revealed that euthyroidism was present in 85.2% of patients. Among these 334 patients, 55 were followed for a median of 2.5 months, and 47 patients were still euthyroid, mildly increased TSH values were found in 2 patients, mildly low FT4 values were found in 4 patients, and mildly decreased TSH values were found in 2 patients [23]. Chen et al. showed TSH values lower than the normal range in 28 (56%) of 50 COVID-19 patients in the acute period and found significantly lower TSH and FT3 values compared to healthy subjects and explained this situation as sick euthyroid syndrome. When patients with abnormal thyroid function tests were re-evaluated after the recovery period, no difference was detected compared to healthy subjects [1]. Lui et al. showed abnormal thyroid function tests in only 25 (13.1%) patients of 191 COVID-19 patients. When 10 patients were followed for a median of one month, thyroid hormone normalization was detected in 6 patients and abnormality persisted in 4 patients [10]. In our study, thyroid hormone levels were evaluated in 12 patients during the acute period and all were euthyroid. Only 4 (6.2%) of 64 patients had mild

elevations in TSH values and there was no difference for thyroid hormone levels compared to healthy subjects in the post-COVID period. Recovery of thyroid hormone abnormalities in the acute period does not mean that possible sequelaes of COVID-19 in the thyroid gland will be completely normalized. Mildly elevated TSH values may be a precursor of overt hypothyroidism in the later periods and hypothyroidism may be the result of decreased thyroid gland volume. The visible picture of our study may be an early stage of a subclinical injury with the decrease in the thyroid gland volume. A longer follow-up may be needed to clarify this picture fully.

Lui et al. compared the anti-Tg and anti-TPO titers of 104 COVID-19 patients during the acute infection period and in 3 months after post-COVID-19. They revealed a significant increase in antibody titers [24]. We did not detect any difference with healthy subjects for antibody positivity. However, a significant increase in antibody titers obtained from Lui's study may suggest increased autoimmune activity in the thyroid gland and may cause a decrease in thyroid gland volume.

Since this is an observational study, it has some limitations including lack of basal thyroid gland volume of the patients before COVID-19.

In conclusion, the effects of COVID-19 infection on the thyroid gland may be dynamic and may have a variable course. First in the literature, we have revealed a significant decrease in thyroid gland volume in the early post-COVID period compared to healthy subjects and COVID-19 survivors may be candidates for thyroid dysfunction. Further prospective studies may be needed for more precise mechanisms and data.

Declarations

Acknowledgments None

Funding None

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

1. M. Chen, W. Zhou, W. Xu. Thyroid Function Analysis in 50 Patients with COVID-19. Thyroid 31(1), 8-11 (2021). doi: 10.1089/thy.2020.0363.
2. W. Wang, X. Su, Y. Ding, W. Fan, W. Zhou, J. Su, Z. Chen, H. Zhao, K. Xu, K. Qin, et al. Thyroid Function Abnormalities in COVID-19 Patients. Front Endocrinol (Lausanne) 19(11), 623792 (2021). doi: 10.3389/fendo.2020.623792.

3. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, J. Hu, L. Zhang, G. Fan, J. Xu, X. Gu et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223), 497-506 (2020). doi: 10.1016/S0140-6736(20)30183-5.
4. N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China. Lancet 395(10223), 507-513 (2020). doi: 10.1016/S0140-6736(20)30211-7.
5. E. Lazartigues, M.M Qadir, F. Mauvais-Jarvis. Endocrine Significance of SARS-CoV-2's Reliance on ACE2. Endocrinology 161(9), bqaa108 (2020). doi: 10.1210/endocr/bqaa108.
6. M. Rotondi, F. Coperchini, G. Ricci, M. Denegri, L. Croce, S.T. Ngnitejeu, L. Villani, F. Magri, F. Latrofa, L. Chiovato. Detection of SARS-COV-2 receptor ACE-2 mRNA in thyroid cells: a clue for COVID-19-related subacute thyroiditis. J Endocrinol Invest 44(5), 1085-1090 (2021). doi: 10.1007/s40618-020-01436-w.
7. L. Wei, S. Sun, C.H. Xu, J. Zhang, Y. Xu, H. Zhu, S.C. Peh, C. Korteweg, M.A. McNutt, J. Gu. Pathology of the thyroid in severe acute respiratory syndrome. Hum Pathol 38(1), 95-102 (2007). doi: 10.1016/j.humpath.2006.06.011.
8. A. Lania, M. T. Sandri, M. Cellini, M. Mirani, E. Lavezzi, G. Mazziotti. Thyrotoxicosis in patients with COVID-19: the THYRCOV study. Eur J Endocrinol 183(4), 381-387 (2020). doi: 10.1530/EJE-20-0335.
9. P. Caron. Thyroiditis and SARS-CoV-2 pandemic. Endocrine 72(2), 326-331 (2020). doi: 10.1007/s12020-021-02689-y.
10. D.T.W. Lui, C.H. Lee, W.S. Chow, A.C.H. Lee, A.R.Tam, C.H.Y. Fong, C.Y. Law, E.K.H. Leung, K.K. Wang, K.C.B. Tan et al. Thyroid Dysfunction in Relation to Immune Profile, Disease Status, and Outcome in 191 Patients with COVID-19. J Clin Endocrinol Metab 106(2), 926-935 (2021). doi: 10.1210/clinem/dgaa813.
11. S. Mizuno, H. Inaba, K.I. Kobayashi, K. Kubo, S. Ito, T. Hirobata, G. Inoue, T. Akamizu, N. Komiya. A case of postpartum thyroiditis following SARS-CoV-2 infection. Endocr J 68(3), 371-374 (2021). doi: 10.1507/endocrj.EJ20-0553.
12. A. Brancatella, D. Ricci, D. Cappellani, N. Viola, D. Sgrò, F. Santini, F. Latrofa. Is Subacute Thyroiditis an Underestimated Manifestation of SARS-CoV-2 Infection? Insights From a Case Series. J Clin Endocrinol Metab 105(10), dgaa537 (2020). doi: 10.1210/clinem/dgaa537.
13. "COVID-19 Diagnosis and Treatment Guideline in China (7th ed.). National Health Commission of the People's Republic of China. (http://www.nhc.gov.cn/)
14. W. Shabana, E. Peeters, M.D. Maeseneer. Measuring thyroid gland volume: should we change the correction factor? AJR Am J Roentgenol 186(1), 234-236 (2006). doi: 10.2214/AJR.04.0816.
15. M. Dighe, R. Barr, J. Bojunga, V. Cantisani, M. C. Chammas , D. Cosgrove, X.W. Cui, Y. Dong, F. Fenner, M. Radzina et al. Thyroid Ultrasound: State of the Art Part 1- Thyroid Ultrasound reporting and Diffuse Thyroid Diseases. Med Ultrason 19(1), 79-93 (2007). doi: 10.11152/mu-980.
16. A M Poma, D Bonuccelli, R Giannini, E Macerola, P Vignali, C Ugolini, L Torregrossa, A Proietti, M Pistello, A Basolo et al. COVID-19 autopsy cases: detection of virus in endocrine tissues. J Endocrinol

Invest 30;1-6 (2021). doi: 10.1007/s40618-021-01628-y

17. P. Caron. Thyroid disorders and SARS-CoV-2 infection: From pathophysiological mechanism to patient management. Ann Endocrinol (Paris) 81(5), 507-510 (2020). doi: 10.1016/j.ando.2020.09.001.
18. L. Wei, S. Sun, J. Zhang, H. Zhu, Y. Xu, Q. Ma, M.A. McNutt, C. Korteweg, J. Gu. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol 88(4):723-730 (2010). doi: 10.1139/O10-022.
19. M.Y. Li, L. Li, Y. Zhang, X.S. Wang. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 9(1), 45 (2021). doi: 10.1186/s40249-020-00662-x.
20. M.K.S. Leow, D.S.K. Kwek, A. Wei-Keong, K.C. Ong, G.J.L. Kaw, L.S.U. Lee. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol (Oxf) 63(2), 197-202 (2005). doi: 10.1111/j.1365-2265.2005.02325.x.
21. R. Kerslake, M. Hall, H.S. Randeva, D.A. Spandidos, K. Chatha, I. Kyrou, E. Karteris. Co-expression of peripheral olfactory receptors with SARS-CoV-2 infection mediators: Potential implications beyond loss of smell as a COVID-19 symptom. Int J Mol Med 46(3), 949-956 (2020). doi: 10.3892/ijmm.2020.4646.
22. D.T.W. Lui, M.M.H. Fung, K.W.H. Chiu, C.H. Lee, W.S. Chow, A.C.H. Lee, A.R. Tam, P. Pang, T.Y. Ho, C.H.Y. Fong et al. Higher SARS-CoV-2 viral loads correlated with smaller thyroid volumes on ultrasound among male COVID-19 survivors. Endocrine 74(2), 205-214 (2021). doi: 10.1007/s12020-021-02855-2.
23. B. Khoo, T. Tan, S.A. Clarke, E.G. Mills, B. Patel, M. Modi, M. Phylactou, P.C. Eng, L. Thurston, E.C. Alexander et al. Thyroid Function Before, During, and After COVID-19. J Clin Endocrinol Metab 106(2), 803-811 (2021). doi: 10.1210/clinem/dgaa830.
24. D.T.W. Lui, C.H. Lee, W.S. Chow, A.C.H. Lee, A.R.Tam, C.H.Y. Fong, C.Y. Law, E.K.H. Leung, K.K. Wang, K.C.B. Tan et al. Insights from a Prospective Follow-up of Thyroid Function and Autoimmunity among COVID-19 Survivors. Endocrinol Metab (Seoul) 36(3), 582-589 (2021). doi: 10.3803/EnM.2021.983.

Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- covidthyroidtable1.docx
- covidthyroidtable2.docx
- covidthyroidtable3.docx

- covidthyroidtable4.docx
- covidthyroidtable5.docx