DOI: https://doi.org/10.53350/pjmhs202317591

ORIGINAL ARTICLE

Association of Hypothyroidism and Subclinical Hypothyroidism with Covid-19 infection: A cross sectional study

SYED ANEES AHMED GARDEZI, SYED HAIDER TIRMIZI, ELLEYYEEN AVAIS, MUHAMMAD UZAIR, MUNEEB UR REHMAN, HAMMAD
Department of Medicine, Pakistan Emirates Military Hospital, Rawalpindi- Pakistan
Correspondence to Dr. Syed Haider Tirmizi, Email:syedhaidertirmizi@gmail.com, Tel:+92-310-5783707

ABSTRACT

Background: A complex relationship of viral infections and the functionality of thyroid gland mainly due to a complex role of immunomodulatory signaling molecules, receptors and hormones.
Aim: To check the Association of Hypothyroidism and Subclinical Hypothyroidism with Covid 19 infection.
Study Design: Cross sectional study.
Methodology: 100 patients presenting to emergency and medical OPDs or already admitted with Covid 19 infections were enrolled into the study. Only those admitted patients whose previous reports of thyroid profile were available and showed no anomaly, were included in the study. Presence of SARS-Cov-2 was confirmed using nasal or throat swab using reverse transcriptase polymerase chain reaction. 3ml blood sample was taken from the anticubital fossa of the patients under sterile conditions in Gel tube containing clot activator. Thyroid function tests of patients were carried out in automated analyzer by chemiluminescence method. Data was analyzed using SPSS version 25.0.
Results: Out of total 100 patients 60 (60%) were male and 40 (40%) were females. Mean age of the patients was 40.6 ± 10.5 years. 54 (54%) of the patients had normal T3 levels where as 46 (46%) of the patients had below normal T3 levels. 47(47%) of the patients had lower T4 levels. TSH levels were normal in 50 (50%) patients whereas 35 (35%) had reduced levels and 15(15%) had raised levels. Mean T3 levels of study population was 2.04 ±1.1 pg/ml (0.1-4.1), T4 levels were 0.93 ±0.50 ng/dl (0.1-1.7) and TSH levels were 2.5 ±2.1 mIU/L (0.1-8.1). Prevalence of hypothyroidism was greater in our Covid population under study. 2 (2%) patients were diagnosed as having subclinical hypothyroidism.
Conclusion: Presence and development of Hypothyroidism is significantly associated with SARs-Cov-2 viral infection. It has prognostic and diagnostic significant.
Practical Implication: Due to the emerging nature of the COVID-19 crisis, this study helped researchers to investigate the functionality of thyroid gland due to Covid-19 infection.
Keywords: Covid 19, endocrine disorder, hypothyroidism, Serum T3, T4, Thyroid gland, thyroid stimulating hormone.

INTRODUCTION

An infectious disease caused by a novel single stranded RNA virus came into existence at the end of year 2019 in China which caused around 2857866 deaths till April 2021. After this it has rapidly spread throughout the world with varying degree and spectrum of clinical manifestations[1]. It is hypothesized to spread from animal species which were infected to humans in turn causing person to person spread. This virus is highly contagious causing increased mortality and morbidity around the world[2]. Prognosis is worst in elderly patients especially those having other comorbid conditions such as diabetes mellitus, obesity, respiratory and cardiac illnesses.

Cytokine storm and exaggerated immune response leads to sepsis which is thought to be major cause of death in patients with Covid 19 infection[3]. SARS-Cov-2 virus leads to production of various spike proteins which are important for reception, recognition and fusion of cell membrane. It is composed of two subunits. These S proteins usually target the ACE-2 angiotensin converting enzyme receptors present on the human cells epithelial surfaces. These then alter the renin angiotensin system[4]. ACE receptors are expressed on various organs including intestine, testis, heart, thyroid gland, kidneys and lungs. This leads to increased vulnerability of these organs to SARS-Cov-2 infection. Susceptibility pattern is directly affected by the amount of expression of these receptors on specific organs[5].

There is a complex relationship of viral infections and the functionality of thyroid gland mainly due to a complex role of immunomodulatory signalling molecules, receptors and hormones[6]. The massive inflammatory immunological response associated with viral infections is the main reason of alteration of lifelong thyroid gland functionality due to its inflammation[7]. Assessment of thyroid function tests (TSH, T3, T4) is not a routine practice or recommended by patients with Covid 19 infection[8]. Due to the emerging nature of the COVID-19 crisis and lack of local data regarding effect on thyroid function, present study was planned. This study helped researchers to investigate the functionality of thyroid gland due to Covid-19 infection.

Thus aim of this present study was to check association of development of hypothyroidism and subclinical hypothyroidism with Covid 19 infections.

Received on 19-11-2022
Accepted on 22-04-2023

METHODOLOGY

It was a descriptive cross-sectional study. The total duration for which the study was carried out in one year. Open epi sample size calculator version 3 was used to calculate the sample size. A sample size of 79 was calculated to meet the objectives of our study i.e., power of test 80% with a confidence interval of 90% and alpha of 0.05 using 5.4% prevalence of hypothyroidism in admitted patients suffering from SARS-COV-2 infection. Non probability and purposive sampling technique was used. Sample size was inflated to 100. 100 patients presenting to emergency and medical OPDs or already admitted with Covid 19 infections were enrolled into the study. Only those admitted patients whose previous reports of thyroid profile were available and showed no anomaly, were included in the study. Those patients with previously diagnosed thyroid disease, endocrine disorder, cardiac or renal problems, taking any medications previously (such as ACE inhibitors, corticosteroids) were excluded from the study. Thyroid function tests were carried out on the day of admission (to exclude cases with preexisting thyroid dysfunction) and after 5th day with COVID 19 infection. Prior Approval was taken from the ethical review committee board (reference number of ethical review committee form). Prior to enrolling the patients into the study written informed consent was taken from the patients or guardians. Demographic details and detailed medical history of patients was recorded.

Presence of SARS-Cov-2 was confirmed using nasal or throat swab using reverse transcriptase polymerase chain reaction. Patients were divided into three categories based on clinical symptoms. Mild cases (minimal symptoms, no indications of pneumonia found on imaging), Moderate cases (symptoms such as fever, respiratory tract problems and pneumonia on imaging),

Severe cases (presence of any of the following feature: respiratory rate ≥ 30 breaths/min, O2 saturation ≤ 93% at rest, partial pressure of oxygen PaO2 ≤300mmHg) and Critical cases (any of the following features: respiratory failure requiring mechanical ventilation, signs of shock/organ failure requiring treatment in Intensive care units).3 ml blood sample was taken from the anticubital fossa of the patients under sterile conditions in Gel tube containing clot activator. Thyroid function tests of patients were carried out in automated analyser by chemiluminescence method. Serum total thyroxine T3, total triiodothyronine T4 and thyroid stimulating hormone TSH levels were evaluated. Subclinical hypothyroidism is labeled when thyroid hormone levels were within normal laboratory ranges but mildly elevated TSH. TSH levels were classified into three categories: below normal (<0.4mIU/L), normal range (0.4-4.0 mIU/L) and increased levels (>4mIU/L). T3 Below normal (<2.1pg/ml), normal range (2.1-4.4 pg/ml) and increased levels (>4.4 pg/ml). T4 below normal (<0.89ng/dl), normal range (0.89-1.76ng/dl) and increased levels (>1.76ng/ml).

Statistical analysis: Statistical Package for Social Sciences version 25.0 was utilized for Data analysis. Mean and SD was calculated for variable such as Age. Percentage and Frequency was calculated for variables (categorical) such as gender and grouping of patients based on Covid 19 severity, T3, T4 and TSH levels. Mean and SD was calculated for quantitative variables such as age and mean levels of thyroid profile (T3, T4 and TSH). Data Normality was assessed using Shapiro wilk test, which showed a parametric distribution of data. Comparison of thyroid function test among various grades of Covid 19 disease was assessed by using One Way ANOVA. Chi square test was used to assess the levels of thyroid hormones among various age groups and genders among Covid 19 patients. p value of ≤0.05 was considered to be significant.

RESULTS

Out of total 100 patients 60(60%) were male and 40(40%) were females. Mean age of the patients was 40.6±10.5 years. Age range of the patients included in the study fell between 23–71 years. 47(47%) patients were in age group <40 years and 53(53%) in >40 years. 34(34%) patients had moderate Covid disease, 36(36%) had severe and 30(30%) were in critical phase.

Fifty four (54%) of the patients had normal T3 levels where as 46(46%) of the patients had below normal T3 levels. 47(47%) of the patients had lower T4 levels. TSH levels were normal in 50(50%) patients where as 35(35%) had reduced levels and 15(15%) had raised levels. Mean T3 levels of study population was 2.04 ±1.1pg/ml (0.1-4.1), T4 levels were 0.93±0.50ng/dl (0.1-1.7) and TSH levels were 2.5±2.1mIU/L (0.1-8.1). Prevalence of hypothyroidism was greater in our Covid population under study. 2 (2%) patients were diagnosed as having subclinical hypothyroidism. Comparison of thyroid profile among patients with Covid 19 revealed no significant difference in serum T4 and TSH levels based on the severity of disease. However T3 levels were significantly lower among patients having severe and critical disease condition (Table 1 and 2).

Table 1: Comparison of thyroid hormones levels among patients with varying degree of Covid 19 infection.

Thyroid profile	Covid 19 disease severity			p value
	Moderate (n=34)	Severe (n=36)	Critical (n=30)	
Serum T3 (pg/ml)	2.2 ±0.9	1.2 ± 0.8	1.2±1.0	0.01
Serum T4 (ng/dl)	1.0 ± 0.4	0.8 ± 0.5	0.9± 0.4	0.4
Serum TSH(mIU/L)	0.2 ± 0.09	0.2± 0.09	0.2 ±0.08	0.9

Table 2 shows that moderate Covid 19 disease does not affect the levels of serum T3 levels significantly however as the disease severity increases the serum levels of T4 decreases and increased TSH levels are seen.

Comparison of thyroid profile among groups based on gender and age of Covid patients showed no significant differences and is shown in table 3 and 4.

Table 2: Comparison of thyroid hormones levels group among patients with varying degree of Covid 19 infection.

Thyroid profile		Covid 19 disease severity			p value
		Moderate (n=34)	Severe (n=36)	Critical (n=30)	
Serum T3 (pg/ml)	Below normal	16	17	13	0.9
	Normal	18	19	17	
Serum T4 (ng/dl)	Below normal	6	23	18	0.001
	Normal	28	13	12	
Serum TSH (mIU/L)	Below normal	16	13	6	0.9
	Normal	18	23	9	
	Increased	6	9	15	

Table 3: Comparison of thyroid profile among male and female Covid 19 patients

Thyroid profile		Gender		p value
		Male	Female	
Serum T3 (pg/ml)	Below normal	24	22	0.1
	Normal	36	18	
Serum T4 (ng/dl)	Below normal	28	19	0.5
	Normal	32	21	
Serum TSH (mIU/L)	Below normal	23	12	0.6
	Normal	28	22	
	Increased	9	6	

Table 4: Comparison of thyroid profile among various age groups of Covid 19 patients

Thyroid profile		Age group		p value
		<40 years	>40 years	
Serum T3 (pg/ml)	Below normal	22	24	0.5
	Normal	25	29	
Serum T4 (ng/dl)	Below normal	22	25	0.5
	Normal	25	28	
Serum TSH (mIU/L)	Below normal	17	18	0.7
	Normal	22	28	
	Increased	8	7	

DISCUSSION

Chronic thyroid dysfunction (hypothyroidism) may require life time hormonal replacement to compensate for decreases levels of serum T3 and T4. Primary hypothyroidism is the condition which occurs due to localized changes in the gland either due to autoimmune disease or any other local pathology. Secondary hypothyroidism is also known as central hypothyroidism which occurs due to disorders of pituitary gland or hypothalamus[10]. Covid 19 associated endocrine complications may include autoimmune thyroiditis, atypical thyroiditis and subacute thyroiditis[11].

Wang et al in his study during previous outbreak suggested that there is a significant decrease in serum levels of T3, T4 and TSH in patients with Covid 19 infection as compared to the control group[12]. Muller et al in his study gave a prevalence of subacute thyroiditis to be 10 % in patients admitted to ICU with COVID 19 infection[13]. Bernard et al in his observational study concluded that most COVID patients at the time of admission were euthyroid, however there was a small decline in levels of TSH and T4 during the course of disease as compared to non-Covid 19 cases[14]. Wei et al studied the effect of SARS-COV-2 infections effect on TSH producing cells in the pituitary gland and revealed that staining intensity decreased with increasing intensity of the disease[15].

Mateu Salat et al documented two cases of Graves disease related to Covid 19. One of the patients had graves disease which was in remission for 30 years the other one had no history of thyroid dysfunction[16]. Louis et al reported a case of Covid induced primary hypothyroidism and suggested that hyper inflammatory state precipitated by Covid 19 infection can be a major causative factor[17]. Chen et al analysed the thyroid function in 50 patients with Covid 19. He revealed that 56% of the patients had lower TSH levels. Levels of serum T3 and TSh were significantly lower in the

Covid 19 group as compared to healthy controls. Severity of Covid 19 infection was also indirectly related to the levels of thyroid hormones[18].

Kamil et al studied the effects of Covid 19 on thyroid gland function in children age (0-18 years) and concluded that in paediatric patients the pituitary gland and thyroid axis is not greatly affected by SARS-Cov-2 virus, especially in those with asymptomatic or mild disease. He also did not find any significant correlation between disease severity and thyroid hormone levels[19]. A study conducted in Nigerian population revealed that serum T3 and TSH concentrations were significantly higher in COVID 19 patients as compared to controls. 15.6% population had sick euthyroid and 6.7% had subclinical hypothyroidism[20]. A single centre retrospective study from Pakistan provided solid evidence of altered thyroid function due to pneumonia associated with Covid 19. They also suggested that TSH and T3 levels were significantly raised in Covid as compared to non-Covid patients. T4 levels were unaltered in Covid patients[21].

Bukhari et al studied the impact of thyroid dysfunction on clinical severity of Covid 19. He concluded that T3 levels at the time of admission may serve as an important prognostic factor in disease progression[22]. Ehtisham et al that apparent thyroid abnormalities were more prevalent in critically ill Covid 19 patients. Presence of thyroid nodules is also an indication of severe Covid 19 disease[23]. Rakhshinda et al found that Covid 19 patients had a higher proportion of thyroid abnormalities which vary clinically over time ad may recover gradually and spontaneous[24].

Limitations of study: This study was only done on a limited population, so in order to extrapolate the findings to wider populations, a larger study needs be done. Economical restrictions, a lack of genetic testing, and lengthy follow-ups are some of the constraints.

CONCLUSION

Presence and development of Hypothyroidism is significantly associated with SARs-Cov-2 viral infection. It has prognostic and diagnostic significant. Thus assessment of thyroid hormones should be made an essential part of initial examination of patients presenting to the Covid 19 subunits. In this way prompt and early diagnosis and further deteriorating effects on thyroid glands can be avoided. Prevalence of subclinical hypothyroidism was very low.

Authors' Contribution: **SAAG&SHT:** Conceptualized the study, analyzed the data, and formulated the initial draft. **EA&MU:** Contributed to the proof reading. **MUR&H:** Collected data.

Conflict of Interest: None to declare

Financial Disclosure: None

REFERENCES

1. Ciotti M, Ciccozzi M, Terrinoni A, Jiang WC, Wang CB, Bernardini S. The COVID-19 pandemic. Crit rev clin lab sci. 2020 Aug 17;57(6):365-88.
2. Hafner CM. The spread of the Covid-19 pandemic in time and space. Int j environ res pub health. 2020 Jun;17(11):3827.
3. Hu B, Huang S, Yin L. The cytokine storm and COVID- 19. J med virol. 2021 Jan;93(1):250-6.
4. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, Hirano T. How COVID-19 induces cytokine storm with high mortality. Inflamm regen. 2020 Dec;40(1):1-7.
5. Aksoy H, Karadag AS, Wollina U. Angiotensin II receptors: Impact for COVID- 19 severity. Dermatol Ther. 2020 Nov;33(6):e13989.
6. Baldelli R, Nicastri E, Petrosillo N, Marchioni L, Gubbiotti A, Sperduti I, Di Giacinto P, Rizza L, Rota F, Franco M, Lania A. Thyroid dysfunction in COVID-19 patients. J Endocrinol Inv. 2021 Dec;44(12):2735-9.
7. Lisco G, De Tullio A, Jirillo E, Giagulli VA, De Pergola G, Guastamacchia E, Triggiani V. Thyroid and COVID-19: a review on pathophysiological, clinical and organizational aspects. J Endocrinol Invest. 2021 Sep;44(9):1801-14.
8. Sen K, Sinha A, Sen S, Chakraborty S, Alam MS. Thyroid function test in COVID-19 patients: a cross-sectional study in a tertiary care hospital. Indian J Endocrinol Metabol. 2020 Nov;24(6):532.
9. Daraei M, Hasibi M, Abdollahi H, Mirabdolhagh Hazaveh M, Zebaradst J, Hajinoori M, Asadollahi- Amin A. Possible role of hypothyroidism in the prognosis of COVID- 19. Intern med j. 2020 Nov;50(11):1410-2.
10. Wiswell JG. The diagnosis and treatment of primary and secondary hypothyroidism. J Chronic Dis. 1961 Nov 1;14(5):544-57.
11. Speer G, Somogyi P. Thyroid complications of SARS and coronavirus disease 2019 (COVID-19). Endocrine j. 2021;68(2):129-36.
12. Wang W, Yao H. Evaluation and observation of serum thyroid hormone and parathyroid hormone in patients with severe acute respiratory syndrome. J Chin Antituberculous Assoc. 2003;25:232-4.
13. Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, Ferrante E, Orsi E, Resi V, Longari V, Cuzzocrea M. SARS-CoV-2-related atypical thyroiditis. The lancet Diabetes & endocrinology. 2020 Sep 1;8(9):739-41.
14. 14.Khoo B, Tan T, Clarke SA. Thyroid Function Before, During, and After COVID-19. J Clin Endocrinol Metab. 2021 Jan 23;106(2):e803-e811
15. Wei L, Sun S, Zhang J, Zhu H, Xu Y, Ma Q, McNutt MA, Korteweg C, Gu J. Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). Biochem Cell Biol. 2010 Aug;88(4):723-30.
16. Stasiak M, Tymoniuk B, Stasiak B, Lewiński A. The risk of recurrence of subacute thyroiditis is HLA-dependent. Intern j mol sci. 2019 Mar 3;20(5):1089.
17. Tee LY, Harjanto S, Rosario BH. COVID-19 complicated by Hashimoto's thyroiditis. Singapore Med J. 2020 Jul 16;62(5):265-.
18. Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. Thyroid. 2021 Jan 12;31(1):8-11.
19. YILMAZ K, Edip UN. Are thyroid functions affected in children diagnosed with COVID-19?. J Health Sci Med.;4(3):257-61.
20. Okwor CJ, Meka IA, Akinwande KS, Edem VF, Okwor VC. Assessment of thyroid function of newly diagnosed SARS-CoV-2 infected patients in Nigeria. Pan African Med J. 2021;40.
21. 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 Mar 30;16(3):e0249421.
22. Bukhari SA, Nabi AG, Farooqi MI. Clinical Severeity of Covid-19 Affected by Thyroid Disease. Paki J Med Health Sci. 2022 Jul 6;16(04):1177-.
23. Khaliq IU, Karim M, Irfan M, Tahreem B, Mudassar U, Ullah S, Amjad I, Javed I, Shujaat JM. Thyroid Diseases Have a Predictive Impact on the Clinical Severeity of Covid-19. Ann Romanian Soci Cell Biol. 2022 Feb 1;26(01):87-94.
24. Jabeen R, Sidhwani SK, Rehan M, Kuma R, Faraz A. Spectrum of Thyroid Illness in COVID-19. Pak J Med Health Sci. 2022 Jun 30;16(06):118-.