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Impact of COVID-19 on the thyroid gland in Iraqi females

Kajeen Hassan Jasim [1], Ronak Haj Ersan [1,2*], Noor Adnan Naeem [1]

Lana Ziyad Sulayman [1], Rayan Sadiq [1] Nechervan Waheed [1]

Jihan Hasan Jasim [3] and Azheen Qasem [1]

[1]*Department of Medical Laboratory, College of Health Science, Cihan University-Duhok, Duhok, Iraq*
[2]*Department of Pharmaceutical Chemistry , College of Pharmacy, Cihan University-Duhok, Duhok, Iraq*
[3]*Department of Medical Laboratory, College of Health Science, Duhok University, Duhok, Iraq*

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Abstract: Thyroid dysfunction has been observed in COVID-19 patients, prompting investigations by endocrinologists. The management of thyroid disease may be affected by pandemic-related restrictions and healthcare reorganization. In this study, we explored the association between COVID-19 and thyroid problems in Iraqi patients, with a particular focus on potential gender-specific effects and the impact of COVID-19 treatment on thyroid function. Our results revealed that SARS-CoV-2 can lead to reversible thyroid dysfunction, including subclinical and atypical thyroiditis. Significantly, our study demonstrated that COVID-19 patients had lower levels of triiodothyronine (T3) and tetraiodothyronine (T4) compared to a healthy control group. Additionally, we found that TSH levels in COVID-19 patients were higher than in non-COVID-19 patient group. whereas the CRP and Il-6 levels were increased in COVID-19 patients in comparison to the control group ($p<0.05$). These findings highlight the heightened susceptibility of Iraqi women to develop thyroid-related conditions and associated issues in the context of COVID-19. Our study aimed to investigate the correlation of TSH, T4, T3 among COVID-19 survivors (150 Individuals; 75 Healthy and 75 who had COVID-19 virus). Our results suggest that COVID-19 virus may have an important impact on thyroid health and the hypothalamus-pituitary-thyroid (HPT) axis in women which might be aggravated by the severity and chronicity of the disease.

Keywords: COVID-19; SARS-CoV-2; thyroiditis chronic lymphocytic; hypothyroidism; hyperthyroidism.

1. Introduction

In late December 2019, a pandemic of mysterious pneumonia characterized by fever, dry cough, fatigue, and gastrointestinal symptoms emerged, originating from a seafood wholesale market in China. This novel disease was attributed to the Coronavirus (COVID-19), primarily caused by the SARS-CoV-2 virus, leading to severe acute respiratory illness.[1] SARS-CoV-2 shares structural similarities with related coronaviruses and can persist on surfaces, with UV light exposure being a rapid inactivation method.[2] The transmission of SARS-CoV-2 occurs primarily through respiratory droplets and aerosols, released when infected individuals cough, sneeze, talk, or breathe.[3] While most experience mild to moderate respiratory symptoms and recover without specific treatment, some develop severe illness, particularly those with underlying health conditions.[4] Interestingly, gender differences in COVID-19 susceptibility have been observed, with females showing a lower infection rate.[5] Furthermore, this study explores the potential impact of COVID-19 on thyroid function in Iraqi female patients. Thyroid hormones play crucial roles in immune responses and have been linked to COVID-19 outcomes.[6]

* Corresponding author: E-Mail: ronak.arsan@duhokcihan.edu.krd, Phone: + 9647502206580

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Additionally, certain medications used to treat COVID-19 can affect thyroid function directly or indirectly.[7]

This investigation aims to illuminate the association between COVID-19 and thyroid dysfunction in Iraqi females, considering the potential effects of COVID-19 treatment on thyroid function. We also examine the role of thyroid diseases in COVID-19 susceptibility and progression. By depend understanding of these interactions, we can better address the unique health considerations that women face concerning thyroid disorders and COVID-19.[8] Furthermore, females appear to have a lower susceptibility to COVID-19 infection compared to males.[9] Where the TSH and FT3 levels were significantly lower in deceased COVID-19 patients compared to those who recovered from severe or critical cases.[8, 9]

This finding suggests that low TSH or FT3 levels could predict worse outcomes in severe COVID-19 patients.[7] Thyroid hormones play a role in the immune response through genetic and non-genomic pathways. T4 and T3 hormones stimulate cytokine production, which is part of the cytokine storm seen in systemic viral infections.[10] Viral infections can also trigger subacute thyroiditis.[4] On the other hand, respiratory infections can worsen thyroid storms in individuals with decompensated hyperthyroidism.[9, 10] It's important to note that certain drugs used to treat COVID-19, Similar to low-molecular-weight heparin, corticosteroids, and hydroxychloroquine, certain drugs used in COVID-19 treatment have the potential to adversely affect the thyroid gland.[11]

COVID-19 has been associated with various thyroid-related issues, including thyrotoxicosis (an overactive thyroid), hypothyroidism (an underactive thyroid), and thyroiditis (inflammation of the thyroid gland).[6, 9] Some COVID-19 patients have shown abnormal thyroid hormone levels, and there is evidence of a link between the severity of the virus and thyroid dysfunction.[8] Additionally, cases of COVID-19 triggering or exacerbating thyroid conditions, such as Graves' disease, have been reported. However, the exact mechanisms and implication of these relationships are still being studied.[12, 13]

The relationship between thyroid cancer and COVID-19, there is limited direct evidence to suggest a significant connection.[14] COVID-19 primarily affects the respiratory system, and its impact on thyroid cancer remain less explored.[15] Ongoing research is vital to comprehensively understand potential links between COVID-19 and thyroid cancer.[14] the unprecedented nature of the COVID-19 pandemic, ongoing research endeavors hold the promise of unveiling additional insights regarding the intricate relationship between COVID-19 and diverse thyroid pathologies, including thyroid cancer.[16]

This study explores the correlation between COVID-19 and thyroid-related concerns in patients from Iraq, particularly in females, and investigates whether COVID-19 treatments affect thyroid function in Iraqi women. SARS-CoV-2 has the potential to induce transient thyroid dysfunction, encompassing subclinical and non-typical forms of thyroiditis. Pre-existing thyroid conditions do not elevate the susceptibility to COVID-19 infection or its transmission. Women are more prone to thyroid problems compared to men, and thyroid conditions can affect women differently.

2. Experimental

2.1. Materials

We included 150 participants and 75 of them with confirmed COVID-19 diagnosed through reverse-transcription polymerase chain reaction (RT-PCR) tests. Our participants were adult Iraqi woman patients aged 18- years or older who had laboratory-confirmed COVID-19 diagnoses and available information regarding thyroid disease. We chose to primarily investigate females in our study due to several factors aligned with our research goals. Firstly, prior research has indicated the existence of gender-related differences in the occurrence and clinical consequences of thyroid disorders and COVID-19.These disparities encompass variations in disease susceptibility, severity, and immune responses between males and females. Secondly, hormonal differences between males and females, such as those related to menstrual cycles, may influence the interactions between COVID-19 and thyroid function. Additionally, the thyroid gland has been shown to express gender-specific variations in key molecular components that may play a role in viral susceptibility. Given these factors, our study seeks to provide a thorough investigation into the connection between COVID-19 and thyroid diseases in female individuals.

Therefore, collected 5 mL venous blood samples from each patient and recorded demographic data, COVID-19 status, and thyroid function parameters. Subsequently, we employed COBAS e 411 analyzers and conducted statistical analyses using SPSS software (version 20, IBM, Chicago, USA). Our study comprised 75 patients with COVID-19 and thyroid dysfunction and 75 healthy woman and normal thyroid function. Data analyzed and compared all relevant parameters between the COVID-19 and control groups to shed light on the intricate relationship between COVID-19, thyroid disease, and gender-specific factors.

2.1.1. Brief Summary of How COVID-19 Affects the Thyroid Gland

COVID-19 can lead to the diagnosis of pulmonary and systemic inflammation, along with multi-organ involvement.[7, 8] The most frequent critical complications of COVID-19 include acute respiratory distress syndrome (ARDS), respiratory failure, sepsis, acute cardiac injury, and heart failure.[15] SARS-CoV-2 has been reported to exhibit tissue tropism in the cardiovascular, coagulative, gastrointestinal, and nervous systems. Additionally, ACE2 expression has been detected in several endocrine organs, such as the pancreas, testes, ovaries, adrenal gland, thyroid, and pituitary gland, suggesting that these organs could be susceptible target tissues for SARS-CoV-2 infection.[14, 16] Infection with SARS-CoV-2 has the potential to worsen pre-existing endocrine conditions or induce new abnormalities.[3] As a result, such endocrine diseases may worsen the prognosis of COVID-19.[11] A complex interaction is believed to exist between thyroid gland issues and the disease infection, often involving their associated inflammatory-immune responses.[12, 15] SARS-CoV-2 utilizes the critical molecular complex consisting of ACE2 and transmembrane protease serine 2 (TMPRSS2) to infect host cells.[14] Significantly, the levels of ACE2 and TMPRSS2 expression are higher in the thyroid gland compared to the lungs.[8, 9]

Our study suggests that the thyroid gland and the entire hypothalamic-pituitary-thyroid (HPT) axis may be more susceptible to damage from SARS-CoV-2. Specifically, COVID-19-related thyroid issues encompass thyrotoxicosis, hypothyroidism, and nonthyroidal illness syndrome.

2.1.2. Spread of COVID-19 was Significant Among Iraqi Females

The spread of COVID-19 among Iraqi females has raised questions about why it appears to affect them differently.[12] Several factors contribute to this phenomenon. Firstly, gender-based disparities have been observed, with studies suggesting variations in disease susceptibility, severity, and immune responses between males and females in Iraqi sample areas.[11,13] Secondly, COVID-19 is known to disrupt the nervous system, leading to symptoms like loss of smell and taste. Moreover, the virus has been detected in the nervous system.[12, 13] Additionally, the cytokine storm triggered by COVID-19, characterized by elevated levels of pro-inflammatory cytokines like interleukin (IL)-6, IL-7, and tumor necrosis factor (TNF)-α, can have widespread effects, including on the endocrine system.[16] Evidently, COVID-19 can significantly affect thyroid function, impacting TSH-secreting cells and disrupting the pituitary endocrine axis feedback loops.[17] This disruption in thyroid function has been observed in COVID-19 patients.[18, 19] Furthermore, Viral infections, including COVID-19, can potentially trigger thyroid gland disorders through mechanisms such as antigen release, molecular mimicry, cytokine secretion, HLA-DR expression, and Toll-Like Receptor activation.[20] These factors collectively contribute to the complex connection between COVID-19 and the thyroid issues in Iraqi females.

2.2. Biological Infection

2.2.1. Thyroid Gland and COVID-19

SARS-CoV-2 and ACE2/TMPRSS2 Expression: Both SARS-CoV-2, responsible for COVID-19, and its predecessor, SARS-CoV-1, employ a key molecular complex involving angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) for cell entry and infection.[21] Notably, the thyroid gland exhibits abundant expression of ACE2 and TMPRSS2, surpassing their levels in the lungs.[9, 10] This unique expression pattern suggests a potential role of the thyroid gland in immune responses, as ACE2 expression inverse correlates with immune markers, substances like

interferon response and the presence of immune cells like CD8+ T lymphocytes and natural killer (NK) cells.[11, 12]

Various cell elements and proteases have been implicated in infection with SARS-CoV-2, including integrins, which contribute to cell invasion.[22] ACE2 has been shown to bind to integrins, modulating downstream signal transduction.[12, 17] This study suggests that thyroid hormones, specifically T4, regulate the expression of genes responsible for the creation.[16, 17] Therefore, thyroid hormones may influencethe integrin-related cellular process entry of SARS-CoV-2, impacting infected patients.[13,16]

Many study introduces the concept of olfactory receptors (ORs) within the thyroid gland and their potential involvement in COVID-19-related thyroid issues, as ORs are simultaneously expressed with key viral entry mediators.[18, 20] Impairment of OR signaling in patients with COVID-19-related anosmia (loss of smell) is linked to a molecular mechanism that underlies this condition.[19] Damage to these receptors could affect various peripheral organs, including the thyroid gland.[18, 20] Also , the role of the excessive activation of Th1/Th17 immune responses often referred to as a "cytokine storm." in targeting and potentially causing inflammation within the thyroid gland[21, 22]. These immune responses are associated with inflammation and could potentially affect the thyroid gland, contributing to thyroid-related issues.[18, 20] The interaction involving thyroid gland and COVID-19 is complex, involving factors such as ACE2, TMPRSS2, integrins, olfactory receptors, and immune responses. Further research is needed to fully elucidate the mechanisms and implications of this relationship.

2.2.2. Thyroid Abnormalities Among Individuals with COVID-19

The World Health Organization's clinical management guidelines do not currently advise evaluating thyroid function in COVID-19 patients.[23] However, in the past outbreak of the SARS-CoV virus, a few studies did report variations in thyroid function.[4, 19] These research studies identified a significant decrease in the serum levels of T3 and T4 among individuals with SARS-CoV when contrasted with those in the control group. [17, 21]. Furthermore, a positive correlation between the severity of SARS and TSH levels, indicating that as the disease became more severe, TSH levels tended to increase.[18, 22] Additionally, a substantial percentage about (7%) of SARS case, four or more months after recovery, exhibited low thyroid hormone levels, including hypothyroidism, primary hypothyroidism, and chronic lymphocytic thyroiditis.[19] It's worth noting that significant hypothyroidism typically resolves in many patients with primary hypothyroidism after three to nine months.[23, 24] This underscores the importance of monitoring thyroid function in COVID-19 survivors with understanding the potential effect of the virus on thyroid health.

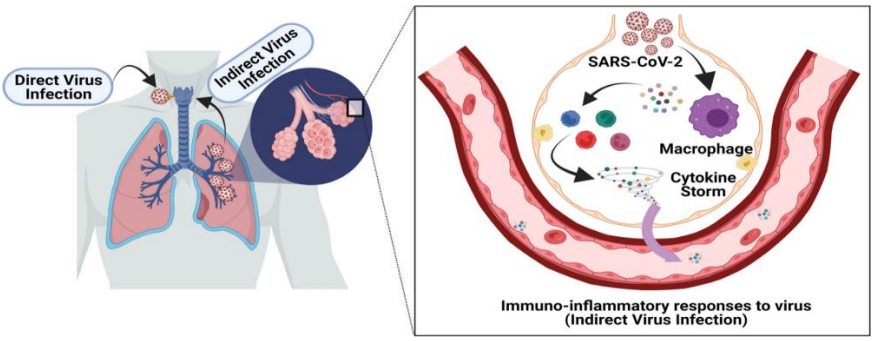

Figure 1. An illustration illustrating the possible pathways of COVID-19 infection within the thyroid gland.

3. Results and Discussion

In our study, we investigated the impact of COVID-19 on thyroid function in female patients. We observed that a subset of COVID-19 patients (20.2%) in a healthcare center, primarily using non-intensive care equipment, presented with thyrotoxicosis, which was notable for its absence of neck and throat discomfort. This observation raised the possibility of COVID-19-related painless (silent) Thyroiditis or an advanced form of thyroid inflammation occurring without neck pain.[22, 23, 24] Among patients with thyrotoxicosis, 54% exhibited overt thyrotoxicosis, supporting the theory of inflammatory-mediated thyroid gland injuries, as evidenced by a direct correlation between serum TSH and IL-6 levels (Table 1).[17]

Table 1 and Figure 2 presents a comparison of various parameters between those diagnosed with COVID-19 (N=75) female patients and those who are healthy (N=75). Firstly, the average age of COVID-19 patients was slightly higher, with a statistically significant difference indicated by a P value of 0.002. Additionally, while the average BMI values were similar, a statistically significant difference (P=0.014) was observed. Notably, COVID-19 patients exhibited significant variations in thyroid-related parameters, including higher levels of TSH but lower levels of T4 and T3. Furthermore, markers of inflammation, such as serum CRP and Il-6 levels, were substantially elevated in COVID-19 patients compared to healthy individuals, with highly significant differences (both P<0.001). These findings provide valuable insights into the effect of COVID-19 on age, BMI, thyroid function, and inflammatory markers among female patients. our study highlights the clinical relevance of thyrotoxicosis in patients COVID-19. Specific scientific studies published related the severity of COVID-19 in patients with forerun thyroid conditions suggests that COVID-19 may exacerbate thyroid diseases.[1,3]

The apparent similarity in TSH, T4, and T3 levels can be attributed to several factors. Firstly, the thyroid function markers included in Table 1 represent a single in time and may not fully capture dynamic changes in thyroid hormones that can occur during the course of COVID-19 infection. Thyroid dysfunction, if present, may manifest at various phases of the disease, and the timing of blood sample collection can influence the results.[14,15] Secondly, the thyroid's performance can be affected by a range of factors, such as hormonal changes, inflammation, and immune system reactions. COVID-19 induces an inflammatory response, which can affect thyroid function. Moreover, our study cohort comprised individuals with a range of COVID-19 severity, introducing variability in thyroid hormone levels.[10,14] Therefore, while the initial data in Table 1 may suggest similar thyroid hormone levels in COVID-19 patients and healthy individuals, it is essential to delve deeper into the dynamics of thyroid function during COVID-19 infection, which our study aims to elucidate through further analyses and correlations with other parameters. Subsequent sections of this study provide a more comprehensive assessment of the connection between COVID-19 and thyroid performance, revealing nuanced patterns and associations.

Key distinguishing features of painless Thyroiditis, such as the absence of discomfort in the throat and the presence of TPOAb, differentiate it from subacute Thyroiditis.[19] However, it's important to note that not all thyrotoxic patients present with neck pain, although thyroid gland autoantibodies (TPOAb, TgAb, and TRAb) were detected in only few patients, raising concerns.[19,20] Patients with COVID-19 who exhibited clinical and radiological symptoms of pneumonia,[13] and throat pain associated with severe thyrotoxicosis were found to potentially experience leucopenia. [24] The reduced lymphocyte count observed in COVID-19 patients in the hospital could potentially impede the development of substantial tissue clusters within the thyroid gland, leading to a notable lack of thyroid gland capsule expansion and neck discomfort.[12, 15, 25] Furthermore, we identified cases of COVID-19 associated with Graves' disease, including individuals with a history of Graves' disease in remission for over three decades [22] as well as some with no prior history of thyroid gland disease. This suggests that COVID-19 may trigger or exacerbate Graves' disease.[23, 24]

In COVID-19 patients, a unique thyroid profile emerges, characterized by low TSH and FT3 levels, alongside elevated FT4 levels, referred to as "thyroxine thyrotoxicosis".[9,16] This thyroid pattern, distinct from typical thyroiditis, is often seen in patients without neck pain due to lymphopenia. Among those admitted to HICUs, 15% displayed this unusual thyroiditis, more common in males due to gender-

Table 1. The Impact of COVID-19 on the Thyroid Glands in Women

Characters	COVID-19 female patients N=75	healthy female N=75	P value
Age (yrs)	40.5 ± 14.1	35.0 ± 11.0	0.001
BMI (kg/m^2)	25.0 ± 5.5	24.0 ± 3.5	0.008
TSH (mU/L)	4.50 ± 0.45	3.80 ± 0.35	0.001
T4 (ng/dL)	4.70 ± 0.20	4.90 ± 0.20	0.000
T3 (ng/L)	0.65 ± 0.08	0.75 ± 0.06	0.000
*Serum CRP levels RV of the assay:<8 mg/L	3.0 (0.1, 17.6)	0.9 (0.1, 9.1)	<0.001
*Serum Il-6 levels RV of the assay:<3.13 pg/mL	1.8 (0.1, 30.9)	0.1 (0.1, 15.1)	<0.001

*Significantly different between groups COVID-19 female patients, and healthy female patients at $P < 0.05$

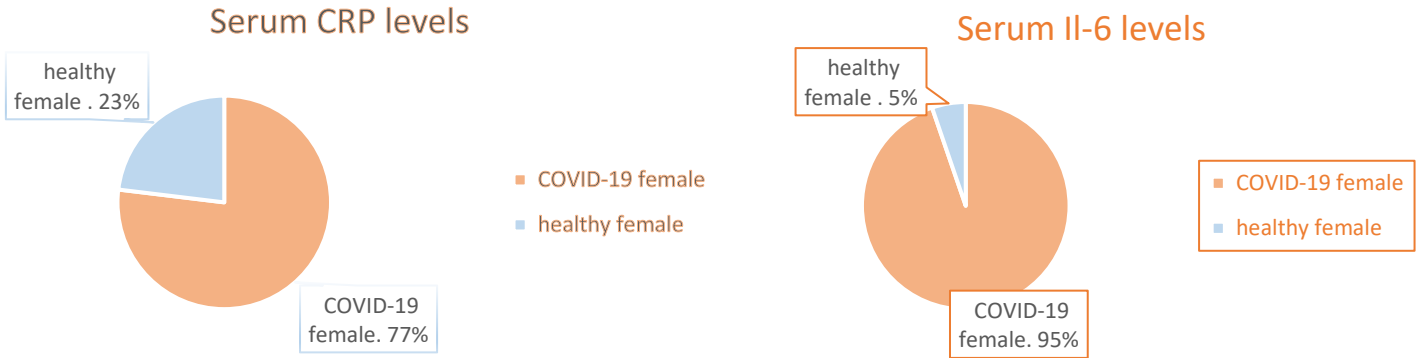

Figure 2. The levels of CRP and Il-6 on COVID-19 on the Thyroid Glands of females

specific immunological markers linked to ACE2. This highlights the intricate thyroid-COVID-19 relationship.[14,16]

The way outpatient thyroid problems are handled has been significantly affected by the COVID-19 pandemic. Telemedicine has become an essential tool to complement conventional thyroid care, given the current healthcare environment. Furthermore, it is worth noting that cancer has been identified as a common adverse outcome among COVID-19 patients hospitalized in Chinese healthcare facilities.[8]

4. Conclusion

Our study highlights the heightened susceptibility of Iraqi women to develop thyroid-related conditions and associated issues in the context of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has the potential to affect various organs during the viremic phase, including the thyroid and the hypothalamus-pituitary-thyroid (HPT) axis. This underscores the need for further clinical investigations to comprehensively understand and manage viral infections impacting the thyroid gland. Specifically, future research should prioritize assessing the influence of COVID-19 on thyroid autoimmunity and its potential effects on the pituitary gland. Continuous monitoring and follow-up measurements will be crucial to elucidate the long-term consequences of COVID-19 on thyroid health.

Ethic Commission Approval Statement

The study was approved by the Ethic Committee of University of Duhok, and the related document sent to the editorial office of the journal.

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ORCID
Kajeen Hassan Jasim: 0000-0001-6961-9424
Ronak Haj Ersan: 0000-0001-6651-5910
Noor Adnan Naeem: 0009-0005-3704-3834
Lana Ziyad Sulayman: 0009-0009-5676-4361
Rayan Sadiq: 0009-0008-2986-7448
Nechervan Waheed: 0009-0000-1053-2711
Jihan Hasan Jasim: 0009-0008-1456-8891
Azheen Qasem: 0009-0003-0036-2538

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