JOURNAL OF BIOMEDICINE AND BIOCHEMISTRY
Volume 1 Issue 3 (2022), pp. 1–5

Journal JBB
ISSN:2958-0528

ORIGINAL ARTICLE

A Possible Role for COVID-19 Infection in the Development of Thyroid Disorder

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Received:August 28, 2022,
Revised:September 05, 2022,
Accepted:September 05, 2022,

DOI: 10.57238/jbb.2022.5461.1008

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Abstract

Background Coronavirus is the new millennium's pandemic, with widespread consequences that include pneumonia and systemic contagion, as well as various clinical diagnoses affecting the endocrine system.

Objectives To investigate the impact of covid-19 infection on thyroid stability and disease through measuring some biochemical marker that are related to thyroid.

- Determine the level of inflammatory marker such as IL-6 and INF- γ

Patients & Methods Eighty patients were involved in this case control cohort study all of them attended the isolation wards at Marjan Teaching Hospital in the province of Babylon-Iraq, from September 2021 to February 2022. The group of patients was divided into forty participants were apparently healthy individual without history of any diseases and with negative PCR results. The rest of the participants include: First group forty patients tested positive for Covid-19 infection with no history of thyroid disorder. Following those patients blood sample were collected at different time incident 5th ,10th ,15th and 25 day after diagnosis. Second group after following the patient for $2^n d$ month five of them have symptoms of thyroid disease and after investigation it was confirmed to have thyroid problems. Blood was drawn from the patients for measurement the level of IL-6 and INF- γ concentration using ELISA technique.

Results Our analysis of 80 Covid-19 patients and control , it was confirmed IL-6 and INF- γ were significant increase than control group and second

Conclusion In this cohort research of patients infected with covid-19 infection, both IL-6 and INF- were shown to be significantly higher than in the control and second groups.

Keywords: Covid-19 ,Thyroid gland, PCR, ELISA technique

1 Introduction

Severe Acute Respiratory Syndrome Virus 2 (SARS-CoV-2) is a beta-coronavirus family that is positive-sense, single-stranded, enveloped RNA virus, is the virus that causes the extremely contagious viral disease coronavirus disease 2019 (COVID-19)[1]. The disease quickly spread, forcing COVID-19 pandemic to be declared by World Health Organization General-Director Doctor Tedros Adhanom Ghebreyesus on March 11, 2020 [2]. The pathophysiology of the COVID-19-induced thyroid dysfunction is still unknown. The virus may directly affect the thyroid gland, according to one idea[3]. Through direct penetration from the upper respiratory tract, SARS-CoV-2 appears to be capable of infecting the gland. Pathological changes in a number of organs, such as the thyroid gland, were discovered during post-mortem investigations of people who died with COVID-19. Surprisingly, however, thyroid follicles have not shown any major morphological abnormalities or damage. In the thyroid's histological examination, significant apoptosis, a sign of destructive thyroiditis, was found in the absence of a lymphocytic infiltrate, suggesting that this condition may be the source of thyrotoxicosis[4,5].And indirect damage (caused by abnormal immunological inflammatory responses to the virus, most likely involving the coagulation, cytokine, and complement systems) [6]. The severe form of COVID-19 is characterized by uncontrolled systemic inflammation and immune response involving the complement and coagulation systems, is characterized by a high release of proinflammatory cytokines, and causes a systemic hyper inflammatory state that can result in multiorgan injury/failure and even death [7, 8].The interleukin-1 (IL-1) family, IL-6, IL-8, IL-10, IL-17, tumor necrosis factor-alpha (TNF-α), and interferon (IFN-γ), as well as chemokines (CXCL8, CXCL9, CCL2, CCL3, CCL4, and CCL10, are all implicated in the formation of a cytokine storm. IL-1 and IL-6, as well as TNF-α and IFN-γ, have been identified as major pathogenic cytokines involved in COVID-19 cytokine storm [9]. Thyroid inflammation might be caused by the cytokine storm associated with COVID-19, . In the acute phase, increased concentration of pro-inflammatory cytokines, and in particular of IL-6 and interferon gamma may trigger thyroiditis and related thyrotoxicosis [10].

2 Materials and methods

Eighty patients, including (35) females and (45) males, were in this case control cohort study. All of them attended the isolation wards at Marjan Teaching Hospital in the province of Babylon-Iraq from September 2021 to February 2022 .The patients were chosen based on the following criteria: -All patients had laboratory confirmed Covid-19 and age above 18 years without history of chronic disease. The patients groups were divided into forty participants were apparently healthy individual with no history of any diseases and their PCR results negative . The rest of the participants include: First group forty patients tested positive for Covid-19 infection with no history of thyroid disorder. Following those patients blood sample were collected at different time incident 5th ,10th ,15th and 25 day after diagnosis. Second group after following the patient for 2 month five of them have symptoms of thyroid disease and after investigation it was confirmed to have thyroid problems.

Inclusion Criteria : Covid-19 infection patients (confirmed by PCR)

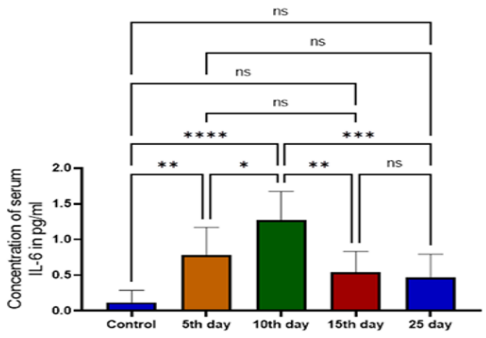
Exclusion Criteria : Patients with chronic disease .

Statistical analysis: The results were examined with graph pad Prism 9.2.1 and displayed as mean standard deviation. The estimation figures and table show how the degree of significance was determined using the T-test and ANOVA correlation comparison analysis..

3 Result

3.1 Measurement of IL-6 concentration

. For the 1st group IL-6 concentration in pg/ml was measured for all time incident . Third comparison was done, the first with the control group the results showed a significant increase in serum IL-6 concentration more than control at the 5th and 10th day after diagnosis (p=0.0018, and p=<0.0001) respectively, while no significant was found at 15th and 25 day as shown in Figure 1. The second comparison was done between the different time incident for the same group. The result showed that the highest level of IL-6 was found at the tenth day more than other time incident as shown in figure 1, while no significant difference was found among other time incident. The third comparison as shown in figure 2 was done between first group with second group the estimation of the IL-6 concentration for 2nd group showed no significant difference with 5th and 10th day after diagnosis , while a significant higher concentration (p=<0.001) was found at 15th and 25 day after diagnosis.



(a)

	Control	5th day	10th day	15th day	25th day
Minimum	0.02	0.06	0.34	0.21	0.11
Maximum	0.5	1.08	1.9	0.9	0.8
Mean	0.119	0.77	1.27	0.54	0.366
Std. Deviation	0.1677	0.39	0.39	0.288	0.32

(b)

Figure 1: Measurement of serum IL-6 concentration :- (**A**) a diagram shown the level of IL-6 for 1st group at all- time incident and control group.(**B**) Table showing the level of significance between the control group and the all-time of incidents for the first group.

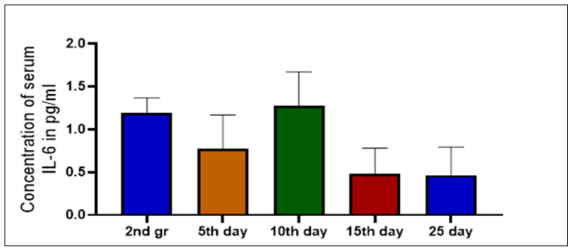
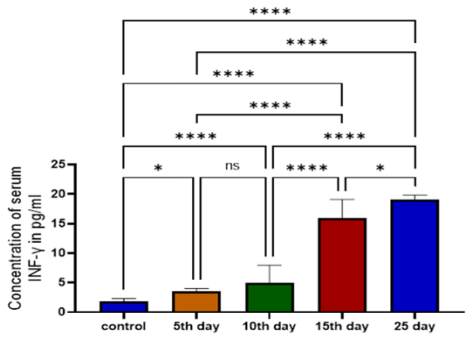


Figure 2: A diagram shown the level of serum IL-6 between second group and 1^{st} group at all-time incident ,significant (p=0.001) was found at 5^{th} and 10^{th}.

For the 1st group IFN-γ concentration in pg/ml was measured for all time incident . Third comparison was done, the first with the control group the results showed a significant increase in serum IFN-γ concentration more than control at all-time incident after diagnosis (p=0.01and p=0.0001) respectively as shown in Figure (3). The second comparison was done between the different time incident for the same group. The results showed that highest level of INF-gamma was found at 15th and 25 day more than other time incident after diagnosis as shown in Figure (3), while no significant difference was found between 15th and 25 day. Figure (4) illustrate the third comparison between 1st group and 2nd group. The estimation of INF-γ for the 2nd group showed no significant difference with the 25 day after diagnosis while significant increase at the 5th ,10th (p=<0.0001) and 15th (p=0.02).



(a)

	Control	5th day	10th day	15th day	25th day
Minimum	1.0	2.7	1.009	10.2	18.00
Maximum	3.0	4.0	9.950	18.00	20.00
Mean	1.80	3.56	4.96	15.88	19.10
Std. Deviation	0.51	0.45	3.001	3.20	0.74

(b)

Figure 3: Estimation of serum IFN- γ :(**A**) a diagram shown the level of INF-gamma for 1st group at all- time incident and control group.(**B**) Table showing the level of significance between the control group and the total number of incidents for the first group

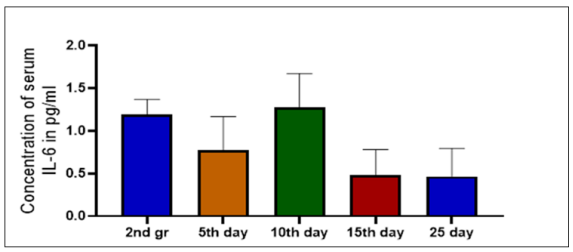


Figure 4: A diagram shown the level of serum IFN-gamma between second group and 1st group at all-time incident .

4 Discussion

Interleukin (IL)-6 is released at the site of inflammation and is required for the acute phase response, as shown by clinical and biological characteristics such as the synthesis of acute phase proteins (5). In COVID-19 patients, IL-6 is one of the major virus-related cytokine storm and inflammatory mediators(11). In this study, there was IL-6 higher significant than the control group and also significant with 2nd group (after recovery from covid-19). Numerous studies demonstrate that the estimated serum IL-6, Ilera, Verónica, et al.(2021) showed that in COVID-19 patients with a severe condition compared to those with control, IL-6 levels are significantly higher. Moreover, it was discovered that in individuals with SARS-CoV-2 infection, thyroid dysfunction, in particular thyrotoxicosis, was linked to a high level of IL-6(12).

IFN-gamma is a type of immune protein. It is required for the body's immune response to viral infections. It regulates immune and inflammatory response genes and activates macrophages, natural killer cells, and neutrophils. IFN-gamma induced protein 10 and monocyte chemoattractant protein 1 may also play a role in COVID-19 pathogenesis, particularly in the severe form of the disease(13). The results of the current study demonstrate that level of IFN-gamma was higher significant than the healthy group and also significant with other two groups, also IFN-γ has a positive association with T3, T4, and a negative correlation with TSH. Some previous studies were conducted to measure the level of interferon gamma , Croce, L., et al. (2021),was found when compared to controls, more common in COVID-19 patients, and Gadotti, Ana Carolina, et al.(2020) was found Higher IFN- γ levels were associated with a worse prognosis in this prospective cohort of patients. The death rate rose in those with persistent IFN- γ levels(14) .

5 Conclusion

Patients with severe COVID-19 disease may experience a cytokine storm, a condition in which cytokines play a major role in the progression of the thyroid problem seen in critically ill patients. . In this cohort of hospitalized patients with covid-19 infection, both IL-6 and IFN- γ were present with significant high level as compared with control and other group.

Acknowledgement

((Thanks to God for His entire blessing during the pursuit of my academic and career goals)) I would like to express my sincere thanks and gratitude and appreciation to my supervisor ((Professor Dr. Buthainah Abbas Al-Azzawi , College of Medicine, University of Al-Qadisiyah)), for her valuable guidance and advice throughout this research. My gratitude to all those who accepted to be part of this study, if it hadn't been for your participant nothing, of this would be possible.
I would like to express my deep thanks to all the staff of Biochemistry Department for their help and support and to the dean of the college of medicine. I express my deep thanks to staff of Marjan Teaching Hospital for their help to collection sample.

Conflict of Interest: None
Ethical consideration: from ethical committee in the in the Department of Clinical Biochemistry, College of Medicine, University of Al-Qadisiyah, Al Diwaniyah, Iraq

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How to cite

Ali M.S; Al-Azzawi B.A.; A Possible Role for COVID-19 Infection in the Development of Thyroid Disorder. Journal of Biomedicine and Biochemistry. 2022;1(3):1-5. doi: 10.57238/jbb.2022.5461.1008