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Identification of some variable parameters in serum of COVID-19 patients in comparison with control group

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Abstract

The study intended to determine the correlation among coronavirus disease 2019 (COVID-19) infection and variable abnormalities in liver function test, lipids, and thyroid hormones. The study included 160 infected COVID-19 patients (80 females and 80 male) and 100 subjects as a control group (50 females and 50 males), attended the Al-Sader Medical City in Al-Najaf, Iraq during the period between January 2021 to October 2021. The patients' age ranged from 16-80 years old. Liver enzymes, lipid profile and thyroid hormone were tested. The results revealed a significant increase in liver function levels including alanine transaminase, aspartate aminotransferase, alkaline phosphatase, and Albumin (p<0.05). Also, there was an increase in lipids levels including total cholesterol, low-density lipoprotein, and triglycerides. The result showed significant difference in levels of thyroid hormones triiodothyronine, thyroxine and thyroid stimulating hormone between COVID-19 infected patients and the control group. As well the antithyroid antibodies (thyroglobulin antibody, thyroid peroxidase antibody and thyrotropin receptor antibodies) were increased. There was a correlation between increasing thyroid hormones and their antibodies with infection by COVID-19. This study concluded that COVID-19 infection can induce disturbances in liver and thyroid function tests and changes in the lipid metabolism.

Keywords: COVID 19; lipid profile; Thyroid hormones; Liver function tests; Thyroid antibody.

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Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an infection mainly infects the respiratory system with acceleration rates associated with increasing morbidities and mortalities.[1] However, COVID-19 may affect all organs of the human body. Multiorgan dysfunction occur such as acute kidney injury, liver dysfunction, myocarditis, thromboembolism, sudden cardiac arrest, hospital acquired infections, glycemic variability,

thyroid dysfunction and other organ failure may be caused by infection with COVID-19.[2,3] In fact there are many factors, play important role in pathogenesis of COVID-19 in multiorgan involvement such as angiotensin-converting enzyme-2 receptors, (autoantibodies), mediators of inflammation and immune status of person response.[4] Many studies indicated that COVID-19 infection and liver injury are commonly involved after lung infection.[5,6,7] Additionally, abnormality in liver function tests had not been noted with a high prevalence of liver injury in infected COVID-19 patients.[8,9,10,11]

Liver injury may be caused by attachment of COVID-19 virus with target cells that have angiotensin-converting enzyme 2 on cholangiocytes, hepatocytes and hepatic endothelial cells as in SARS-CoV-2 infection.[12,13]

The lipid levels have also been altered in COVID-19 infected patients. Many studies have documented alteration in the metabolism of lipid in COVID-19 infected patients and various research studies reported elevation in plasma triglyceride (TG) levels in COVID-19 patients.[14-17] Other studies recorded low levels of high-density lipoprotein (HDL) compared with normal controls.[18-21] The correlation between the levels of plasma lipids in infected patients with COVID-19 and body mass index (BMI) have been recorded, one study assessed the correlation between lipid level and severity of infection.[22]

There are evidence suggested that infection by COVID-19 can cause dysfunction of the thyroid gland, however many published studies reported thyroid disorder and a higher prevalence of disturbance of thyroid hormones level.[23-27] Thyroid injury may be caused by cross linked COVID-19 virus on thyroid cells that express angiotensin converting enzyme 2 protein (ACE2). ACE2 is expressed in many endocrine cells, as well imbalance in level of thyroid hormone as preexisting or occurs with infection like triiodothyronine (T3) syndrome or related to infection severity. There are few studies conducted to assess the concentration of free T3 in patients with hypothyroidism and COVID-19 infection.[28-30]. In the present study, we aimed to shed light on a possible long-term consequence of SARS-CoV-2 infection, causing COVID-19, on infected patients. Therefore, we measured clinical variables including lipid profile, liver function tests, thyroid hormones profile and anti-thyroid antibodies. We also attempted to determine if there is a correlation between COVID-19 with organ dysfunction.

Subjects and Methods

This case control study was conducted at Al-Sader Medical City in Al-Najaf, Iraq during the period between May 2021 to November 2021. The study included 160 hospitalized COVID-19 patients (80 females and 80 males), and 100 apparently healthy persons (50 females and 50 males) admitted to the same hospital without history of SARS-CoV- 2 infection as a control group. For selection of the control group, we excluded subjects with diseases such as diabetes, autoimmune disorder, thrombosis, cancer, or history of hypercholesterolemia, and no specific medication for liver dysfunction and thyroid dysfunction.

All the patients were aged between 19-80 years. A venous blood sample (5 ml) was aspirated from each study subject and serum samples were separated after centrifugation. All patients infected with COVID-19 were diagnosed using the real-time polymerase chain reaction (RT-PCR) technique at the laboratory of Al-Sader hospital.

We performed laboratory investigations, including hepatic enzymes, lipid profile and thyroid hormone tests for patients and control group. Liver function tests (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, albumin, total. bilirubin and total protein) and lipid profile (total cholesterol, high-density lipoprotein, and triglycerides) were assessed using commercial clinical chemistry kits (manufactured by Fuji DRI-CHEM SLID, Tokyo, Japan) on an auto analyzer (Fujifilm, Japan), according to the manufacturer's instructions. Low-density lipoprotein was calculated using the Friedewald equation: LDL = (TC-HDL-[TG/5]).[31]

Levels of thyroid hormones (triiodothyronine, thyroxine, thyroid stimulating hormone, thyroglobulin antibody, thyroid peroxidase antibody and thyrotropin receptor

antibodies) were quantitatively assessed by using an automated immunoassay machine (AFIAS-6 automated fluorescent immunoassay system, Boditech Med Inc., South Korea), according to the manufacturer's instructions. Finally, BMI was calculated by using the equation BMI = Weight (in kilograms) / Height^2 (in meters).

Statistically Analysis

Data were collected and analyzed by a statistical package of social sciences (SPSS, Inc., Chicago, IL, USA) version 24. Parametric data were expressed as mean ± standard error of the mean (SEM). It was statistically analyzed using the student t-test and ANOVA test for data comparison. Correlations between all the studied variables were evaluated using the Pearson correlation. A *p* value of <0.05 was considered significant.

Results

The study included 260 participants, grouped in to two groups. The first group included 160 COVID-19 infected patients (80 females and 80 males). The second control group included 100 subjects (50 females and 50 males). Overall, the participants in the two groups were aged between 16-80 years. The weight of COVID-19 patients and the control group ranged between 27-83 Kg and, 30-85 Kg, respectively. While the BMI was 24.65 Kg m^2 for COVID-19 patients and 23.50 Kg m^2 for the control group. The demographic characteristics of the study participants are summarized in Table.1.

Table 1. The Demographic characteristics of study participants.

Characteristics	Patients with COVID-19 n= (160)	Control group n= (100)
Age (years)	16-80	17-70
Male	80	50
Female	80	50
Weight Kg	27-83	30-85
BMI kg M^2	24.65	23.50

BMI: body mass index.

In this study some liver function tests were assessed. There was a significant difference in the mean of these variables between the COVID-19 patients and the control group. However, there was no singinificant difference in the total protein between the two study groups (Table 2). The mean of AST in male patients was (42.13 ± 4.74), the mean of ALB (2.77 ± 0.457), the mean of ALB (2.77 ± 0.457), mean of total bilirubin (2.88 ± 0.564) and mean of total protein (6.56 ± 1.75). While the mean of ALT and ALP were found higher in female (48.48 ± 4.96 and 132.54 ± 10.65, respectivly).

Table 2. Liver function tests in infected patients with COVID-19 and the control group.

Variables	COVID-19 infected patients (n=160)	COVID-19 infected male patients (n=80)	COVID-19 infected female patients (n=80)	Control group (n=100)	*p value
ALT (μl)	44.54 ± 4.88	41.88 ± 6.88	48.48 ± 4.96	26.48 ± 3.86	<0.05
AST (μl)	41.55 ± 1.35	42.13 ± 4.74	39.44 ± 2.88	21.94 ± 3.67	<0.05
ALP ((μl)	122.55± 4.88	126.54 ± 8.66	132.54 ±10.65	84.11 ± 5.83	<0.05
ALB (mg/dl)	2. 72 ± 0.77	2.77 ± 0.457	2.66 ± 0.767	3.60 ± 0.97	<0.05
T bilirubin (mg/dl)	2.65 ± 0.99	2.88 ± 0.56	2.50 ± 0.66	1.11 ± 0.06	<0.05
T Protein (mg/dl)	6.55 ± 1.55	6.56 ± 1.75	6.54± 1.35	6.48 ± 1.66	NS

ALT: alanine transaminase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, ALB: Albumin blood test, *p values indicate comparison between patients and controls. $p > 0.05$ is not significant (NS).

This study showed that mean level of total cholesterol was higher in serum of infected male patients with COVID-19 (5.26 ± 1.77) than in sera of infected female patients (4.98 ± 1.75), however the difference did not reach statistical significance. Also, the mean level of total cholesterol in serum of COVID-19 infected patients was not different than control group (5.12 ± 1.66 vs. 4.50 ± 0.98). However, levels of the triglycerides were significantly different between the COVID-19 infected patients' group and the control group (2.47 ± 0.06 vs. 1.42 ± 0.1) (Table.3). The details of the lipid profile is shown in (Table.3).

Table 3. Lipid profiles of patients infected with COVID-19 and control group.

Variables	COVID-19 infected patients (n=160)	COVID-19 infected male patients (n=80)	COVID-19 infected female patients (n=80)	Control group (n=100)	*p value
T Ch (mg/dl)	5.12 ± 1.66	5.26 ± 1.77	4.98 ± 1.75	4.50 ± 0.98	≥ 0.05
LDL (mg/dl)	2.91 ± 0,54	2.90 ± 0.32	2.93 ± 0.86	2.85 ± 0.88	≥ 0.05
HDL (mg/dl)	1.32 ± 0.65	1.32 ± 0.42	1.33 ± 0.57	1.66 ± 0.26	< 0.05
TG (mg/dl)	2.47 ± 0.06	2.53 ± 0.08	2.46 ± 0.07	1.42 ± 0.1	<0.05

T Ch: Total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: Triglycerides, *p values are indicating for comparison between patients and controls. $p > 0.05$ is not significant (NS).

This study showed decreased serum levels of T3 in infected patients (3.89 ± 0.97 P mol) than the control group (4.55 ± 1.09 P mol). There was a significant difference in serum T3 levels between COVID-19 patients and the control group (p<0.05). Also, infected male patients had lower levels of T4 (21.38 ± 3.96 µg/dl) than females. COVID-19 patients had more T4 levels than the control group (Table 4). While the mean level of TSH was significantly increased in serum of females (5.28 ± 1.08 mg/dl) than in males (4.90 ± 0.99 mg/dl). There was a statistically significant difference in TSH between pateints infected with COVID-19 and the control group (p <0.05). Finally, the mean levels of Tg Ab, Tbo Ab and TSHR Ab in serum of patients infected with COVID-19 were significantly higher than the control group (p < 0.05) (Table.4).

Table 4. Thyroid hormone profiles of patients infected with COVID-19 and the control group.

Variables	COVID-19 infected patients (n=160)	COVID-19 infected male patients (n=80)	COVID-19 infected female patients (n=80)	Control group (n=100)	*p value
T3 P mol	3.89 ± 0.97	3.2 ± 0.86	3.84 ± 0.78	4.55 ± 1.09	≤ 0.05
T4 µg/dl	21.35 ± 2.87	21.38 ± 3.96	21.25 ± 4.66	10.68 ± 1.89	≤ 0.05
TSH mg/dl	5.13 ± 1.98	4.90 ± 0.99	5.28 ± 1.08	2.08 ± 0.01	≤ 0.05
Tg Ab IUL	55.56 ± 2.97	55.50 ± 5.77	55.54 ± 5.66	32.98 ± 2.88	≤ 0.05
Tbo Ab UL	9.84 ± 2.58	10.25 ± 3.98	9.55 ± 1.59	5.81 ± 1.99	≤ 0.05
TSHR Ab UL	2.94 ± 0.02	2.98 ± 0.03	2.98 ± 0.01	1.44 ± 0.02	≤ 0.05

T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid Stimulating Hormone, TG Ab: Thyroglobulin antibody, Tbo Ab: Thyroid peroxidase antibody, TSHR Ab: Thyrotropin receptor antibodies, *p values are indicating for comparison between patients and controls. *$p \leq 0.05$ is significant.

Discussion

In this study, we aimed to analyze some variables of liver, lipid, and thyroid hormones to determine the correlation of the abnormality of these variables with infection with COVID-19. The study found that liver function tests were increased more in COVID-19 infected patients than in the control group. Similar findings were reported by Wang et al., 2021, that revealed elevated AST levels as its percentage recorded (33.3%) in COVID-19 infected patients and also elevated ALT (24.1%).[32] The study by Cai et al., 2020, pointed out to increased levels of serum bilirubin, liver enzymes, and other liver parameters in patients suffering of severe COVID-19 infection.[33] However, Fan et al., 2020, noted that 37.2% of COVID-19 patients had abnormal liver function tests while the percentage was 27.4% in the patients with normal liver function test.[34] However, findings of the current study disagreed with those of a study done by Abhishek et al., 2021, that included 600 patients and 44.16% of the patients had liver dysfunction while 55.83% of the patients had normal liver function.[35] Another study done by Abdelrahman et al., 2021, showed that the abnormalities appeared in liver function test accounted for 44% of patient with COVID-19 infection.[36]

According to lipid profile our results showed that the level of TG was elevated in serum of COVID-19 infected patients, however, there was no significant difference between COVID-19 infected patients and the control group. This result is similar to that reported by Shahab et al., 2022, who showed no significant difference appeared in TG levels among the studied groups. Findings of a study by Xu et al., 2023, showed increased levels of LDL cholesterol, triglyceride, total cholesterol and decreased levels of HDL cholesterol in COVID-19 survived patients when compared with negative COVID-19 controls.[37,38]

Total cholesterol levels in serum of infected COVID-19 patients were significantly elevated in comparison with control group ($p< 0.05$). This result is different than that reported by a study of Shahab et al., 2022, they noted no difference in the level of total cholesterol between patients attending intensive care units and a group of outpatients, and a study of Angelo et al., 2021, which showed that patients hospitalized with severe COVID-19 disease had lower total cholesterol levels.[37,39]

This current study observed significant elevation in serum LDL level in COVID-19 infected patients (2.91±0.54) than the control group, and significant decrease of HDL level in serum of COVID-19 infected patients. This finding agreed with other studies including Xu et al., 2023, Angelo et al., 2021 and Chien et al., 2005.[38-40]

In the present study abnormalities of thyroid hormones and their antibodies were detected. The result showed a significant difference between levels of thyroid hormone (T3, T4 and TSH) in serum of COVID-19 infected patients and the control group. This result agreed with data obtained by Chen et al., 2021, who showed lower TSH level than normal range in 56% of the patients.[41] Significantly lower levels of TSH and T3 were observed in patients infected with COVID-19 than in the healthy control group. Also, the study of Muller et al., 2020, found correlation between low level of TSH and the frequency of hospitalization in patients with COVID-19 infection.[42] Another study showed decreased TSH levels in COVID-19 patients, however, there was no significant difference noted in total thyroxine level of patients with COVID-19 from the control group.[43] While the report by Tee et al., 2020, recorded elevated levels of TSH after COVID-19 infection in serum of patients without any symptoms of thyroiditis before infection.[44]

The current study clarified that antibody titers of TG Ab, TPO Ab and TSHR Ab in serum of COVID-19 infected patients were significantly elevated than control group. These findings agreed with those of a study conducted in Hong Kong by David et al., 2021, that pointed to increased TPO Ab levels at baseline of Gravies disease and Hashimoto's thyroiditis patients after getting COVID-19 infection. Also, in the same study researchers documented increased TPO antibody and TG antibody titers in serum of patient three month post-infection with COVID-19.[45] Another study by Kaushik et al., 2020, found that 15% of COVID-19 patients were anti-

TPO antibody positive, suggested that COVID-19 may trigger hyper inflammatory syndrome leading to autoimmune thyroid disease.[46] The results of a study by Tee et al., 2020, when examined the thyroid function observed elevation in anti-thyroid antibody in patient infected with COVID-19.[44] Finally, the report by Mateu et al., 2020, showed anti-thyroid antibody positive result in COVID-19 infected patient.[47]

In conclusion, the present study illustrated that infection with COVID-19 may play a role in induction of disturbances in the liver and thyroid functions. Levels of thyroid hormones and liver function tests appear to be changed in patients infected with COVID-19. In addition, COVID-19 infection may lead to changes in lipid metabolism and lipid profiles.

Author Contributions

ECA, ACA, Conceptualization. AZA, Data collection and curation. ECA, contributed data Formal analysis. AZA, ECA, Methodology. ECA, MMS, Project administration. ECA, ACA, Resources. ACA, ECA Software. MMS, ECA, Validation. ECA, MMS, Visualization. ECA, ACA, Wrote original draft. MMS, Wrote & edited the review.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Ethics Committee, Faculty of Medicine University of Kufa (Ref. No.: MEC-43, dated 23/5/2021).-

Informed consent

A written informed consent was obtained from each patient before included in the study.

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