Evaluation of Tau, amyloid beta, dynorphin levels and number of biochemical variables in covid-19 patients

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Abstract
The study aimed to determine the levels of Tau,amyloid beta, dynorphin, and number of biochemical variables in men with COVID-19. The study groups included 30 men with COVID-19, 30 men who recovered from COVID -19, and 30 healthy men as a control group. Protein and biochemical assays include: tau, amyloid beta, dynorphin, zinc, triglycerides, HDL-C, VLDL-C and cholesterol. The results were a significant increase (P 0.05) in the levels of amyloid beta, dynorphin, HDL-C, cholesterol and LDL-C in patients. Those infected with COVID-19 compared to the control group, while in the recovery group, amyloid beta was low compared to the control group, while zinc and lipid profile were high in the recovered. While tau protein, zinc, triglycerides and VLDL-C showed a significant decrease at (P≤ 0.05) in the affected men group compared to the control group.
Keywords: COVID-19, Tau, amyloid beta, dynorphin

1. Introduction

Corona viruses belong to the genus Coronavirus, the Coronaviridae family, and the order Nidovirales (Paules and Marston,2020), which are enveloped viruses containing single-stranded non-segmented RNA due to the presence of superficial protein protrusions in a crown-like appearance (Ksiazek, 2003). Cornaviruses are classified into four important genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, and the former two species usually infect mammals, while the latter two species mostly infect birds (Weiss and Leibowitz, 2011; Li, 2016; Schwartz and Graham, 2020).
The COVID-19 virus can be transmitted through droplets and contact in two ways: direct contact with infected people and indirect contact with surfaces used by an infected person through coughing or sneezing or entry of the virus into the mucous membranes of the mouth, nose or conjunctiva (eyes) It can also be transmitted from Through household items such as clothing, utensils and furniture around the affected person (Ong et al,2020: iu et al,2020). The most common symptoms of COVID-19 can be fever, dry cough and fatigue (Dhama et al, 2020).
COVID-19 and AD share many biochemical processes, and similar to Alzheimer's disease, SARS-CoV-2 can alter the balance of the blood-brain barrier, induce hypoxia and stimulate neuroinflammation. It is noted that the virus uses the ACE receptor. 2 (ACE2) Angiotensin-covering enzyme 2 as a point of entry into human cells, and in Alzheimer's patients, appears to correlate with levels of oxidative stress (Ding et al,2021; Rahman et al ,2021) .Since olfactory loss is a hallmark symptom of COVID-19, the olfactory epithelium proximal to the frontal cortex could represent a potential pathway for SARS-CoV-2 entry into the brain (Politi et al, 2020).
Amyloid beta peptides generated by enzymatic cleavage of the amyloid precursor protein (APP) (Serrano-Pozo et al, 2011; Holtzman et al. 2011)
, and amyloid plaques can be divided into two groups: diffuse and neuroblastoma (Yamaguchi et al, 1988b, Holtzman et al, 2011). Rangan et al. 2020 researchers suggested that nanofibrils composed of proteins in SARS-CoV-2 are involved in neurological symptoms in COVID-19 and thus, that amyloid-forming proteins of SARS-CoV-2 virus could be involved in the central nervous system of patients with COVID-19. Cytotoxic and inflammatory functions similar to amyloid assemblies that are molecular features of amyloid-Aβ-related neurodegenerative diseases such as Alzheimer's disease AD.
Tau protein, discovered in 1975, has been identified as a key protein in the assembly and stabilization of microtubules in the brain. Tau protein belongs to the family of microtubule-associated proteins (MAPs) (Weingarten et al, 1975). Tau protein is involved in many diseases, such as between Alzheimer's disease, Down syndrome, frontotemporal dementia, chromosome 17-associated Parkinsonism (FTDP), frontotemporal dementia and parkinsonism linked to chromosome 17, progressive supranuclear palsy (PSP), and corticobasal degeneration disease (CBD) corticobasal degeneration (Kovacs,2015; Hutton et al, 1998). Tau protein promotes the assembly of tubulin into microtubules, a major component of the neuronal cytoskeleton that determines normal morphology and provides structural support for neurons (Kosik, 1993).

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Dynorphin(DYN) is an endogenous opioid neuropeptide produced from Peprodynorphin and has since been shown to be widely distributed throughout the central nervous system (Civelli et al 1985, Evans et al ,1988), although dynorphin is an opiate peptide that has A specific role as inhibitory neurotransmitters in reducing pain, but there is increasing evidence that exposure to high concentrations of dynorphin can lead to hyperalgesia or may contribute to neurodegeneration(Faden, 1993; Faden and Salzman , 1992). Hernández-Fernández et al. 2020 suggested Loss of ACE2 activity caused by SARS-CoV-2 infection has an important role in hematologic insufficiency, endothelopathy, and neuropsychiatric manifestations of COVID-19 (2020).

Zinc is an element found in nature. It is one of the most important elements in the body and is indispensable for the growth and development of microorganisms, plants and animals. It is found in all tissues and secretions of the body in relatively high concentrations. 85% of the zinc in the body is concentrated in muscles and bones and 11% in the skin and liver. In all other tissues, the average amount of zinc in an adult human body is about 1.4-2.3 g of zinc (Stefanidou et al, 2006; Prasad,2009; Bhwmik et al, 2010.

Cholesterol is an essential fat for the cells of the human body and is either obtained from the food source or is synthesized by an internal pathway that occurs in most cells of the body, especially in the liver Acetyl-CoA (Acetyl coenzyme A) is a precursor to the synthesis of cholesterol that can be produced from glucose or fatty acids or amino acids (Hampton et al, 1996).

Triglycerides (TGs) are non-polar fat molecules consisting of a glyc-erol molecule bound to three fatty acid (FA) molecules and are the main form of fat and energy storage in the human organism and are synthesized primarily through the glycerol phosphate pathway. In certain tissues such as muscle, liver, and tissues on the nutritional status of the individual and is a process necessary for life, an imbalance in this process may lead to many metabolic disorders, such as obesity, fatty liver or high triglycerides (Zhang, 2015; Wu,2015).

High density lipoprotein (HDL) It is a type of lipoprotein with a very heterogeneous structure, density and particle size containing cholesterol, phospholipids, triglycerides and lipoproteins. It was first isolated from the blood in the 1960s by ultrafast speed. Of all the types of human plasma lipoproteins, the high-density lipoprotein (HDL) complex Mainly in the liver and small intestine has the highest density and smallest volume in the circulation Apolipoprotein AI (ApoA-I) is the main component of the structural protein of HDL (Gordon et al,1989; Ginsberg,1998; Trajkovska and Topuzovska,2017).

2. Materials and Methods

Samples

In this study, (30) blood samples were collected in the period from 1/11/2021 to 1/2/2022. All samples were males, their ages ranged between (20-70) years for people infected with COVID-19 virus and present in the isolation hall. In Balad General Hospital and some clinics in the cities of Dhuluiya and Samarra. They are treated in Balad Hospital.

Blood collection

A sample size of 5 milliliters (ml) was taken from venous blood of the study groups (the control group, the patients infected with COVID-19, and the group of patients who had recovered). The samples were placed in tubes containing silica gel tube glass for the purpose of separating the blood serum from the coagulated blood by centrifugation at a speed of 3000 (cycles/minute) for 10 minutes, and the blood serum was taken through a micropipette, then stored the blood serum at a temperature of -20 Celsius until the required tests were performed, and other samples were drawn (5 ml) for the same patients after fasting for a period of 12 hours to check lipids.

Protein analysis

The levels of Tau protein, Amyliod Beta, Dynrophine and in serum were measured using Reader Elisa device manufactured by German company Human.

Biochemical assay

Lipid profile (Cholesterol, Triglycerides, High density lipoprotein- cholesterol (HDL-C)) was quantified by followed the given procedure with kit (biolabo, France), Low density lipoprotein-cholesterol (LDL-C) estimated by the equation: LDL-C= Chol-HDL-C-VLDL-C Very low-density lipoprotein- cholesterol (VLDL-C) estimation by the following equation: VLDL-C = TG/5 (Buritis and Ashwood, 1999).

Zinc was quantitative by followed the given procedure with kit (biolabo, France).

3. Statistical Analysis

Values expressed as mean ± SD. data analyzed done by using and analysis of variance (ANOVA).

4. Results and Discussion

The results shows in Table 1 a significant increaseat (P≥0.05) Amyloid Beta Protein, Dynrophin, TC, LDL-C, HDL-C, compared to control, while TG, zinc,VLDL –D, Tau protein, shows significant decrease at (P≥0.05) in compared to control.

Table 1: Amyloid Beta Protein, Dynrophin and Tau protein, lipid profile levels in patients and follow up and control.			
Groups	Control	Follow –up	Pation in COVID -19
Tau protein	286.80±59.04 B	394.06±58.6 B	150.99±56.94 C
Amyloid Beta Protein	199.959± 50.95 B	189.744±55.44 B	295.274±54.43 A
Dynrophin	79.270 ±24.38 C	95.341±22.09 B	265.291±54.45 a
Zinc	0.76267±0.15 B	1.04233±0.34 A	0.52133±0.16 c
TriGlyceride	126.218±25.23 B	171.79±47.32 A	118.909±35.73 b
Cholestrol	152.653±24.13 B	178.153±32.65 A	163.200±31.48 b a
HDL	42.800±9.55 A	43.172±12.89 A	44.228±9.74 a
VLDL	25.243±5.05 B	34.36±9.46 A	23.781±7.15 B

The rise in amyloid-beta in the case of COVID-19 patients, may be attributed to the systemic inflammation characterized by the so-called 'cytokine storm' to disruption of the blood-brain barrier and neuronal and glia damage that could be involved in long-term outcomes. Systemic inflammation is recognized as a pathophysiological mechanism. Underlying Alzheimer's disease (Akiyama et al, 2020).

The SARS-CoV-2 infects astrocytes in the brain and causes deposition of amyloid beta (Aβ), i.e., its levels increase. They also indicated that Aβ acts as an antimicrobial peptide that can be overproduced in immune mechanism (Crunfli et al. 2020 and Soscia et al. 2010).

While in the recovering, a decrease in amyloid-beta was observed and it is in agreement with (Matias-Guiu et al,2021).

Decreased ability to concentrate and other cognitive difficulties in patients after the acute phase of COVID-19, these complaints have been categorized as "brain fog" (Wijeratne and Crewther,2020: Kingston et al, 2020).

Reduced tau protein may be caused by decreased appetite in COVID-19 patients or in the event of starvation, as Turner and Rogers 2022 indicated. Six participants reported weight loss in line with evidence linking decreased appetite to inflammation in the body.

Coronaviruses express a nucleocapsid (N) protein essential for the treatment of viral replication, transcription and viral assembly. N phosphorylation of SARS-CoV is by glycogen synthase kinase 3 (GSK-3) for its function and inhibition of GSK-3 with lithium impairs N phosphorylation, and viral transcription, we report here That the SARS-CoV-2 N protein contains GSK-3 sequences and that this motif is present in diverse coronaviruses, raising the possibility that SARS-CoV-2 may be sensitive to GSK-3 inhibitors including lithium (Liu et al,2021)).

Medina and Castro2008, Selenica et al. 2007 indicate that manipulation of kinases by means of drugs is an effective way to reduce tau levels; For example, a small molecule inhibitor of GSK-3β kinase was effective in reducing phosphorylated tau.

The Dynorphin is elevated in people with COVID-19 and the reason may be that the affected cells are in turn weaker and their contents leak into the periphery, leading to the stimulation of inflammatory cytokines. This "cytokinin storm" in turn raises levels of dynorphin and is neurotoxic, leading to the death of neurons, as the lobe and olfactory bulb form the "center" of infection with a crucial loss of smell after virus removal, which is temporary in most cases but can also be permanent (Bikdeli et al, 2020: Mustafa,et al,2020;Netland et al, 2008) and this is in agreement with Dixon and Diep, 2020.

Gautier and Ravussin 2020 and Ahmadirad and Ghasemi 2020 and Chen et al. 2020 indicated that the concentration of dynorphin A (1-13) is increased in COVID-19 patients due to downregulation of ACE2 which can potentiate a neurotoxic effect in the brain. Thus, the dysregulation of ACE2 after SARS-CoV-2 entry, and the accumulation of Dynorphin A that may lead to loss of taste and smell as symptoms of COVID-19 may be attributed to the possible damage to neurons of the loss of taste and smell caused by coronaviruses to virus entry into the nervous system. and subsequent damage from hypoxia following pulmonary disturbances and production of inflammatory cytokines (cytokine storm).

In recoveries, Shiers et al. 2020 noted, neurological effects (for example joint pain and headache) can persist for at least months after injury, suggesting neurosensory involvement in persistent disease, and it has been linked to pain receptors, which are activated by dynorphin. The cause of these post-viral problems is due to PDYN regulation.

Jothiman et al. 2020 noted that COVID-19 patients had lower zinc levels compared to healthy controls, and that comorbidities had no significant effect on zinc levels in their study groups, and that lower serum zinc levels were associated with an increased risk of acute respiratory distress syndrome, and an increased risk of developing acute respiratory distress syndrome. Levels of non-inflammatory agents, increased mortality in adult patients.

Whereas in Heller et al. 2021 indicated an increase in serum zinc after hospitalization in zinc concentrations in both survivors. Patients in recovery experience asymptomatic after COVID-19 infection with periods of mental distress (Garner, 2020; AL-Samarraie,et al,2020).

Total cholesterol was elevated at 3% in subjects with COVID-19 (Nain et al, 2022; Alkanaani,et al,2020). Uyaroğlu et al. 2021 indicated that the levels of plasma total cholesterol, LDL-C, HDL-C, and triglycerides were significantly higher than those levels on the day of admission and may be attributed to the result of receiving steroid therapy. As Li et al.

2021 noted in a follow-up study we compared patients' lipid levels at 3-6 months after hospital discharge with those at the time of admission. LDL-c, HDL-c, and TC were all
significantly higher at follow-up than at admission time in severe/critical cases.
The level of TG will decrease as nutritional status decreases due to COVID-19 infection (Zhao et al. 2021).
Buschard 2020 indicated using fibrate as a treatment for COVID-19 because it helps increase the amount of sulfide that can reduce disease severity, and fiber reduces triglyceride levels and increases HDL levels by targeting fatty acid synthesis and increasing lipoprotein lipase activity.
Whereas in those recovering, Chen et al. 2020 suggested that the increase in lipid levels during hospitalization in severe COVID-19 patients may indicate an improvement.
That among patients infected with COVID-19 virus, the highest HDL-C had lower CRP levels after diagnosis of COVID-19, Chidambaram et al, 2022 and agrees with Choi et al. 2020.
Whereas in those recovering, Tanaka et al. 2020 and Meilhac et al. 2020 reported a gradual increase over time in both HDL-C and LDL-C concentrations, and these increases over time could be related to patient improvement, normalization of blood, and a decline in LDL-C. Inflammation, decreased capillary leakage or increased hepatic HDL synthesis, agrees with (Fan et al. 2020).
The COVID-19 patients have significantly higher levels of LDL-C than normal adults matched for age and sex, and immune imbalances are a common feature of SARS-2 infections and may be risk factors associated with the disease itself (Peng et al. 2020 and Zhang et al. 2020).
Nain et al. 2022 reported an 8% decrease in VLDL in people with COVID-19.
Whereas in convalescents, Acquafredda et al. 2021 indicated an increase in triglycerides caused by increased VLDL secretion as a result of lipolysis, by increasing hepatic synthesis of free fatty acids and by suppressing fatty acid oxidation.

5. Conclusion

COVID-19 may be related to increased levels of beta-amyloid and dynorphin, levels of HDL-C, cholesterol, LDL-C and decreased levels of tau protein, triglycerides, VLDL-C and zinc in the blood

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