Evaluation of COVID-19 Patients with Diabetes in Nineveh Governorate

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Abstract

Background: The world witnessed a major crisis when the new Corona virus (Covid-19) appeared, and its effects are still continuing, as no gender, race, age, or color was excluded from infection, and given the disease represented by a pandemic that spread in most parts of the world in recent years and still poses a threat to Therefore, it is a fertile field for studies and to delve into it extensively.

Methods: the study was conducted in Nineveh governorate on (113), samples of (34) for patients, Covid-19 with diabetes patients (29), and a healthy group (50), whose ages ranged between (35-70) years. They measured (15) parameters of some enzymes, levels of oxidants and its antioxidants, and indicators of kidney function and minerals.

Results: The results showed that there was a high significant increase in all the measured enzymes lactoperoxidase (LP), lactate dehydrogenase (LDH), aspartate and alanine aminotansferases (AST, ALT), as well as an increase in the level of interleukin-6(IL-6) when compared between groups of patients COVID-19 with diabetes, and that there was a very high oxidative stress in patients with COVID-19 and diabetes when compared with COVID-19 patients and control group. It was also observed that there was a high significant increase in the levels of total cholesterol, urea, creatinine, and iron, and a high significant decrease in the level of calcium in patients with COVID- 19 and diabetes.

Conclusion: The study concluded that there are clear effects of the levels of measured enzymes (LP, LDH, ALT and AST) and the level of IL-6 in patients with COVID-19, especially those with diabetes, as well as a high oxidative stress state, and there is a clear effect on the kidneys and their functions in patients with (Covid-19), especially those with diabetes.

Keywords: Covid-19, diabetes, Oxidative Stress, Antioxidants, Lactoperoxidase, Interleukins, Enzymes.

Introduction

Corona viruses have diameter between (65-125) nanometers, and possess a simple positive-sense single-stranded RNA as a relatively large nuclear material, whose size ranges between (26-32) kb, and there are four genera of the coronavirus family, which are α, β, γ and δ viruses[1], bats and mice are a source of alpha and beta corona viruses while birds are a source of delta and gamma coronaviruses[2]. Covid-19 disease caused by a new strain of corona viruses that was not previously known, and it was called Severe Acute Respiratory Syndrome-2 (SARS-Cov-2) depending on the evolutionary relationship with the coronavirus that It was the cause of the outbreak of SARS in 2003, and Covid-19 disease was first discovered during its outbreak in late December (2019) in Wuhan, Hubei Province, and this virus is one of the new strains of coronaviruses[3], the clinical symptoms of Covid-19 are similar to those of SARA & MERS[4], and the incubation period of the virus between 2 to 7 days and may sometimes reach 14 days[5], and symptoms vary between common symptoms: fever, cough, and shortness of breath, in addition to diarrhea and enteritis, and may reach a more severe condition such as heart failure and death[6].

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A Diabetes Mellitus is a chronic metabolic disorder characterized by persistent high blood sugar. It may be due to impaired insulin secretion, resistance to the peripheral actions of insulin, or both[7]. People with DM in all its forms are liable to contamination, so the high rate of sugar in people with severe Covid-19 could affect the increase in the prevalence of type 2 DM in the elderly. Which in itself could assist provide an explanation for the affiliation with deadly outcomes for Covid-19 patients[8].

Chronic hyperglycemia down regulates ACE2, which makes cells more vulnerable to the inflammatory and harmful consequences of the virus. Moreover, ACE2 in pancreatic cells can result in a direct impact on mobile function[9]. First, virus to enter target cells, SARS-CoV-2, Hijacks an endocrine pathway that performs an crucial function in regulating blood strain, metabolism, and infection[10]. ACE2 is considered as a receptor for the coronavirus protein. The second potential mechanism is where thedipeptidyl peptidase-4 enzyme has been diagnosed as a functional receptor of human coronavirus, as it plays a first-rate function in glucose and insulin metabolism[11].

The look at objectives to evaluate the situation of Covid-19 patients with type 2 diabetes disease in Nineveh governorate, and examine them with patients with Covid -19, via measuring 13 biochemical parameters.

Materials and Methods
Samples collection:

Collecting blood (serum) samples from patients with Covid-19 disease after they were clinically diagnosed, as well as the result of PCR examination was positive and under the supervsion of doctors specilizing in respiratory diseases at Al-Shifa Hospital for Chest Diseases and Fever (Isolation Hospital) in the city of Mosul for the period between August 2022 and end of January 2023, and after recording the required information from the patients, (113) samples were collected, including (34) samples for Covid-19 patients only, (29) samples of patients Covid-19 with diabetes, and (50) samples from healthy individuals considered as a control group with ages ranging from (35-70) years, in whom (15) parameters were measured from some enzymes, levels of: oxidants, antioxidants, indicators of kidney function and minerals.

The activity of lactoperoxidase (LP) was estimated using the colorimetric method used by the researcher Tayefi-Nasrabadi*et al*.[12], as the enzyme oxidizes pyrogallol in the presence of hydrogen peroxide to purpurogallin. LDH was estimated using kit from the Spanish company (Spinreact REF:1001261) depends on the spectroscopic method through decrease in NADH concentration[13], and activity of ALT & AST were estimated using kit from Randox company (Cat.No.HNI530) which depends on the colorimetric method[14]. The level of (IL-6) was estimated using kit from Boditech Korean company (REF:FPRR020 (AFIAS) IL-6 based on the (FIA) method using the sandwich method for immunological detection.

Peroxynitrite(ONOO-) was estimated using the researchers' modified method Vanuffelen*et al*. [15], which relies on nitration of phenol to nitrophenol by ONOO-. MDA was estimated using Guidet and Shah method[16]. GSH was estimated using the modified method used by the researchers Sedlak and Lindsay [17], it is reduced by the thiol group (SH group), forming a colored product. Uric acid level is estimated using kit from Biolabo company (REF:80001), which is basd on the enzymatic method[18]. Albumin was estimated using Bromocresol green method by kit from Biolabo company (REF:80002). Cholesterol level was estimated using Biolabo (REF:87356) Kit, which is an enzymatic method based on converting cholesterol and cholesterol esters into quinoneimine form[19]. The determination of urea using kit from the Spanish company (Biosystem) (REF: COD11537), using the enzymatic method (Berthelot Reaction Urease-Modified)[20]. Kit from the German company (Human)(REF:10051) was used to estimation of creatinine by Jaffe method, when creatinine reacts with a solution of picric acid to form a yellow-reddish complex of creatininepicrates[21]. Calcium was estimated using the colorimetric method, and kit from Biolabo company (REF: 80004) was used, which depends on the interaction of the compound ortho-crysophthalene with calcium ions[22]. Iron is estimated using kit from Biolabo company (REF: 92108) is used, which depends on the separation of ferric ions and formation of a colored complex with ferrin[23].

All results were analyzed statistically using the SPSS 25 statistical program, the difference between the groups at P≤0.05 significant difference.

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Results and Discussion

1. Enzymes (LP, LDH, ALT, AST) and interleukin-6 levels:

High significant increase (P≤0.0001) in the activity of all measured enzymes (LP, LDH, ALT, AST) and in level of IL-6 when comparing Covid-19 patients and diabetic patients with control group, as it was higher in patients with DM, and these results match the results of previous studies indicated that there is an increase in activity of LP in Covid-19 patients, and a study that indicated an increase in LDH[24], and an increase in activity of liver enzymes (ALT & AST)[25], and an increase in the level of IL-6 [26].

Diabetes mellitus is a major factor for severe pneumonia and the septic course due to viral infection and occurs in about 20% of patients[27], and health centers and hospitals showed an increase in mortality in patients with Covid-19 by up to 50% in diabetics than those without diabetes[28]. The high activity of LP in Covid-19 patients, especially in diabetics, are due to the effect of antivirals such as halide oxides generated by the LPO-Duox Halide system and also include an increase in (SCN-) resulting from Covid-19 infection. LPO, which is concentrated in saliva and bronchial secretions, also increases the production of SCN- in cigarette smokers. Also, increased production of haloiodide in saliva is positively associated with LP levels, which enhances the defense ability against viral infection[29, 30]. On the other hand, the high activity of the LDH enzyme, which is one of the predictive markers for Covid-19 infection, as many systematic reviews and statistical analyzes have indicated the association of LDH with respiratory function and predicting its failure[31], according to studies, LDH is better a reliable measure of intensive care admissions (ICU) or deaths, as LDH increases six-fold in patients with Covid and mortality increases by 16-fold in those with Covid and diabetes[32, 33].

Table 1: Shows the activity of enzymes (LP, LDH, ALT, AST) as well as the level of IL-6.

Some enzymes and IL-6	Control		Covid-19 patients only		Covid-19 patients with DM		P value
	Mean	S.D	mean	S.D	Mean	S.D	
LP (U/mL)	a 51.38	13.88	b 102.27	18.66	112.87 c	26.4275	***0.0001
LDH (U/L)	a 296.04	27.23	b 673.72	68.764	789.06 c	75.5155	***0.0001
ALT (U/L)	a 7.37	0.87	b 24.56	4.90	34.38 c	5.631	***0.0001
AST (U/L)	a 5.64	0.73	b 22.45	19.22	26.00 c	11.02	***0.0001

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IL-6 (picogram/ml)	a 2.87	0.32	b 71 0.94	31.40	987.48 c	74.33	***0.0001

*** indicates that there is a significant difference at a probability level less than 0.0001 between the studied groups.

Covid-19 causes damage to hepatic cells, which increases the activity of ALT & AST, and is often asymptomatic, as evidenced by laboratory tests. Liver injury caused by Covid-19 has many causes[34]. Drug-induced liver injury in patients[35]. Some studies inside the United States of America determined that the ratio of ALT & AST enzymes turned into (3 times) better than the top restrict of the ordinary cost in sufferers with chronic liver illnesses. Compared to patients without chronic liver sickness, numerous research also said that severe cases of Covid-19 had been much more likely to have extreme liver harm in comparison to moderate instances[36].

The elevated level of IL-6 being produced in COVID-19 sufferers that precdes the development of acute lung damage suggests its usability as an early marker of acute ailment[37], as it's miles believed that IL-6 increases capillary permeability, pulmonary blood clots that power the improvement of ARDS also stimulate the coagulation pathway of the pulmonary movement and growth the threat of thrombosis, and in a study via researchers Giamarellos-Bourbboulis*et al.* [38] propose that sufferers with acute respiration failure in COVID-19 be afflicted by immune dysregulation.

2. Levels of oxidant and antioxidants:

The results in Table (2) indicated that there was a high significant increase at $P \leq 0.0001$ in ONOO-, MDA and uric acid, and decrease for GSH in patients, as the results were identical to a study De Flora *et al.* [39] in an increase in level of ONOO- and also in a previous study in which an increase in MDA was observed Rojas *et al*. [40] and in a study an increase in uric acid was observed[41].

Table 2: Shows a comparison of oxidative stress and antioxidants.

Some oxidants and antioxidants	Control		Covid-19 patients only		Covid-19 patients with DM		P value
	mean	mean	S.D	mean	S.D		
ONOO- (µmol/l)	a 44.27	b 90.78	7.37	102.81 c	10.34		***0.0001
MDA (µmol/l)	a 3.46	b 8.93	1.31	9.40 c	1.93		***0.0001
GSH (µmol/l)	c 13.5	b 8.	0.8	6.25 a	0.7		***0.0001

	Control	Covid patients	Covid patients with DM	P value
UA (mmol/l)	243.42 a	263.324 a 24.65	358.12 c 39.34	***0.0001
Alb (g/l)	40.09 a	40.79 2.85	40.88 a 2.59	0.803

*** indicates that there is a significant difference at a probability level less than 0.0001 between the studied groups.

ONOO⁻ an oxidizing agent that can damage a wide range of molecules in cells due to its oxidative properties. ONOO - results from the reaction of the free radical nitric oxide $^\bullet NO$ with superoxide anion radical $O^\bullet_2$, as this phenomenon increases in infections resulting from viral infection and a weakened immune system, and the high levels of ONOO- are an indication of the severity of infections as a result of viral infection with Covid-19 [42].

Elevated MDA has been associated with several pathological conditions such as cardiovascular disease as well as diabetes[43, 44, 45], and several studies have indicated a link between oxidative stress (OXS) and COVID-19 disease[46, 47, 48]. A high level of MDA in people with Covid, as it is an important pointer of the severity of oxidative stress resulting from viral infection, especially RNA viruses[49].

Decrease in the level of GSH, as it participates directly in the removal of ROS, through the protection processes it uses from oxidative stress, in addition to having a role in preserving external antioxidants [50]since every organ in the body can be affected by GSH cycle, especially the immune system, nervous system, digestive system, liver and lungs. Previous studies, which include a common pathway affecting all of these danger elements, have tested a measure of low GSH degrees[51-53]. COVID-19 sufferers display changes inside the glucose-insulin axis, main to hyperglycemia and extensive decreases in vitamin D and thiols[54]. GSH depletion can result in immune machine failure and positioned the body's organs at hazard from oxidative pressure resulting from the buildup of ROS that could be a commonplace hallmark in all situations assocated with COVID -19 [34].

High levels of uric acid above the normal rate lead to health problems, so that the kidneys cannot filter it, and it is deposited in it, forming kidney stones, and it also leads to diseases such as diabetes and bone diseases, and goes to the joints, especially the joints of the toes, and is deposited there causing arthritis and severe pain in it [55]. Previous research showed that the uric acid stage increased consistent with the standards in pressure in Covid-19 sufferers who obtained Favipirvir (antiviral remedy), because the signs and symptoms and signs associated with this elevation have been no longer observed. After comparing the biochemical parameters of Covid sufferers, multiplied uric acid tiers had been defined as an unexplained increase because it is in touch with antiviral capsules [41].

3. Levels of some biochemical Parameters and minerals:
The results in Table (3) indicated that there was a significant increase in the levels of cholesterol, urea, and creatinine in patients with Covid-19 and patients with DM, and these results were identical to previous studies in high cholesterol[56].

Table 3: Some biochemical and mineral variables.

Some Biochem	Control	Covid patients	Covid patients with DM	P value

ical parameters	only				
	mean	Mean	S.D	Mean	S.D
T.C (mmol/l)	a 4.44	b 5.90	0.96	8.77c	2.69	***0.0001
Urea (mmol/l)	a 4.60	b 5.50	0.65	8.12c	0.72	***0.0001
Cr. (µmol/l)	a 69.13	b 75.11	9.60	90.77c	10.42	***0.0001
Ca (mmol/l)	c 2.22	b 2.01	0.20	1.89a	0.18	***0.0001
Fe (µmol/l)	a 20.17	b 35.30	2.95	39.27c	3.18	***0.0001

*** indicates that there is a significant difference at a probability level less than 0.0001 between the studied groups.

Chronic infections cause cholesterol loading in tissues rich in macrophages[57], and pulmonary cells and macrophages work to absorb and flow cholesterol. This process is associated with lung diseases and dysfunction. Recently, it has been proven that cholesterol is one of the main factors in SARS-Covid infection[58]. A recent study showed us a cholesterol- depndent mechanism that regulates the transport of transmembrane proteins and between lipid group[59], and showed that ACE2 can bind to membranes, which are similar in structure to Monosialotetrahexosylgakglioside 1(GM1), as low levels of ACE2 appear here under normal conditions of a healthy lung, as cholesterol contributes to infection and death[56].

The excessive degree of urea negatively impacts patients with coronary heart failure, and the ratio of urea to albumin within the blood is an essential predictor of dying or sickness severity in aspiration pneumonia[60]. As urea has a role in estimating renal feature and is a marker for predicting renal failure, as preceding studies indicated that urea can cause death, mainly in seriously ill patients who're within the in depth care unit(ICU).

A small increase in creatinine shows bad kidney function, as creatinine is the stop product of

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nitrogen metabolism. It is the most not unusual marker for comparing kidney feature. COVID-19 enters cells the use of ACE2 as a receptor. According to the ultra-modern statistics, the attention of ACE2 is ready a hundred instances better within the kidneys in comparison to the lungs[2], where the Corona virus can affect kidney feature via getting into the kidney cells through angiotensin-changing enzyme 2 and activating the renin-angiotensin-aldosterone device. RAAS increases the reabsoption of H_2O and Na^+ in the renal tubules, inflicting passive reabsorption of urea. These systemic results purpose renal vasoconstriction and, therefore, glomerular filtration and urea excretion are reduced. However, the urea/creatinine ratio will increase as creatinine is filtered with the aid of the glomeruli and is not reabsorbed[61].

The effects additionally indicated that there was a high substantial decrease in calcium degrees and an increase iron for Covid-19 sufferers and Covid patients with diabetes. These outcomes were steady with previous studies of calcium level[62] and iron level[63].

Calcium as an vital secondary messenger in activated and unexcited cells controls important capabilities.The role of calcium in virus-host mobile interaction has been established for numerous kinds of viruses,inclusive of coronaviruses. For instance, in a have a look at from 2015, researcher Nieto-Torres et al. Discovered that the coronvirus envelope protein (E) of SARS-CoV activates a calcium channel within the intermediate compartment of the Golgi equipment and endoplasmic reticulum as well as the Golgi membranes[64]. Several specific, formerly regarded, and newly evolved calcium channel blockers target special types of channels, host cells, or viral cubicles/pathways. The default mode of movement using calcium channel blocker treatment is to lessen intracellular calcium degrees, which may additionally affect viral calcium handling of host cells and prevent entry into viral host cells. This is what promotes a lower in calcium tiers[65, 66]. This explains why there is a decrease in calcium stages in Covid-19 sufferers with diabetes more than people with Covid most effective.

To give an explanation for the high iron, studies have indicated that one of the most common headaches as a result of Covid -19 is acute respiration misery syndrome, wherein the virus multiplies inside the host cells and invades the floor of the lung, causing irritation and hypercoagulability. Moreover, the discharge of free iron may also result in blood circulate and an growth in its stages. Which reasons oxidative harm to the lung and other organs due to extended oxidative stress[67], this results in an growth in ferritin in the blood movement of sufferers with COVID-19, which can also lead to the destruction of hepatocytes and motive the disengagement of saved iron in these cells and its release to circulation.

Conclusions

It is concluded from the study that the Covid-19 virus that causes acute respiratory distress. Yes, the lung may be the target organ at the beginning of the infection, but as soon as the virus begins to penetrate and multiply, all organs of the body are targeted, no one is excluded from it, as it became clear to us through the difference in the levels of enzymes, biochemical Parameters and minerals between The infected and the healthy, and as it turned out that the chronic diseases of people with Covid-19, such as diabetes, have a very clear role in these changes, and thus exacerbate the infection and increase the death rate of Covid-19.

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Conflicts of interest

There are no conflicts of interest.

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