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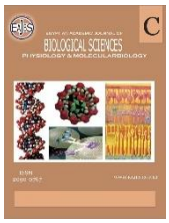

Evaluation of Post Covid- 19 Biochemical Alterations in Normal and Chronic Diseased Egyptians: Possible Mechanisms and Role of Vaccines

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ABSTRACT

Objective: COVID-19 survivors are either vaccinated or not usually afraid of COVID-19 side effects. This study aims to investigate post Covid-19 biochemical changes among healthy and chronically diseased either vaccinated or not subjects. **Material and Method:** 144 patients (72 males and 72 females) previously (two years ago) diagnosed with SARS-CoV-2 contagion by RT-PCR were enrolled as cohort group of this research. Major biochemical alterations of post Covid-19 infection among healthy, diabetic and heart-diseased Egyptian males and females either vaccinated or not were examined. **Result and discussion:** Results revealed that COVID-19 infection caused antioxidant levels to decrease significantly ($p \leq 0.05$) in association with a significant increase in oxidative lipid peroxidation initiating inflammation leading to deterioration of organ function (liver, heart and kidney) associated with biochemical alterations in glucose and lipid metabolism with improper immunoglobulin level. **Conclusion:** Chronic diseased patients were more affected by post-COVID-19 biochemical alterations. Vaccination attenuated post-COVID-19 biochemical changes. The study is expected to motivate previously infected people to check their health status and not vaccinated people to take the appropriate vaccine.

INTRODUCTION

Coronaviruses are RNA viruses (positive-stranded) that affect the respiratory tract. Coronavirus illness-2019 (COVID-19) caused serious intense respiratory syndrome coronavirus 2 (SARS-CoV-2) that infected more than 97 million people and scored over 6 million deaths (WHO, 2023). The lungs are mainly affected by the virus by the aperture human sort two human alveolar cells through the angiotensin-converting enzyme 2 (ACE2) (Murgolo *et al*., 2021).

The SARS-CoV-2 has a glycoprotein surface named spikes. Spikes enter the host cell through a connection to the ACE2 receptor. The S-protein spike is considered the viral element that relates to the host pickup through the ACE2 receptors (Ysrafil,2020).

After the virus attaches to the ACE2 cell surface, it brings about leukocytic infiltration, the permeability of blood vessels and alveolar wall; lung surfactants reduction leading to respiratory distress and inflammation progressing to a cytokine storm and finally an orderly inflammatory response syndrome (Walls *et al*., 2020).

COVID-19 main symptoms resemble fatigue, fever, muscle aches, airway infection, and morbid pneumonia, causing death in certain cases (NICE, 2021). COVID syndrome is recognized by markers correlated to grave acute respiratory syndrome profound at least one-month post-infection (Kingstone *et al*., 2020).

Moreover, persistent symptomatic COVID-19 lasts 1 to 3 months or post-COVID-19 syndrome from 3 months afterwards (Velavan and Meyer, 2020). Significant morbidity is linked with prolonged standing COVID-19 symptoms (Zeng *et al*., 2021).Post-COVID-19 syndrome characteristics are connected to oxidative stress, reduced antioxidants and mitochondrial dysfunction (Gedefaw *et al*., 2021).

Through this research article, post-COVID-19 biochemical alterations were characterized, and the role of gender, chronic diseases and vaccination on these alterations would be illustrated.

MATERIALS AND METHODS

Study Design and Population:

This study was cross-sectional in which RT-PCR diagnosed SARS-CoV-2 144 patients (72 males and 72 females) on 12 November 2020 and 28 January 2021, at EL Demerdash Hospital, Cairo, Egypt and Abassya Chest Hospital, Cairo, Egypt was enrolled as cohort group of this research. The following criteria were noted: gender, age, linked comorbidities (diabetes mellitus and chronic heart disease (hypertension and valve disorder)) and vaccination or not after treatment. Subjects were picked out following the implication and relegation criteria. Implication criteria: positive PCR test, age; 18-50 years and patients who sign the study agreement. Relegation criteria: pregnant, lactating females and psychiatric disease patients.

Patients were divided as following: Healthy Vaccinated -Ve Covid-19 (H.V.-Ve Covid-19); Healthy Vaccinated +Ve Covid-19 (H.V.+Ve Covid-19); Healthy not vaccinated -Ve Covid 19 (H. Not V.-Ve Covid-19); Healthy not vaccinated +Ve Covid 19 (H. Not V. +Ve Covid-19); Diabetes mellitus vaccinated -Ve Covid-19 (D.M. V.-Ve Covid-19); Diabetes mellitus vaccinated +Ve Covid-19 (D.M. V.+Ve Covid-19); Diabetes mellitus not vaccinated -Ve Covid-19 (D.M. Not V.-Ve Covid-19); Diabetes mellitus not vaccinated +Ve Covid-19 (D.M. Not V.+Ve Covid-19); Heart disease vaccinated -Ve Covid-19 (H.D.V.-Ve Covid-19); Heart disease vaccinated +Ve Covid-19 (H.D. V.+Ve Covid-19); Heart disease not vaccinated -Ve Covid-19 (H.D. Not V.-Ve Covid-19); Heart disease not vaccinated +Ve Covid-19 (H.D. Not V. +Ve Covid-19).

World Health Organization (WHO) COVID-19 disease intensity ranking was considered as follows: mild sort (symptomatic patients affirmed with SARS-CoV-2 contagion but without signs of viral pneumonia or hypoxia), moderate sort (patients with clinical signs of pneumonia but no signs of severe pneumonia on chest X-ray and SpO2 ≥ 90% on room air), severe sort (patients with clinical and radiological signs of severe pneumonia in addition to SpO2 < 90% on room air or respiratory rate > 30 breaths/min) (WHO,2021).

Studied subjects were treated according to the sort of the disease; mild-form patients took symptomatic medication (antipyretics, nasal decongestants, anti-inflammatories), moderate-form patients dread antivirals, while severe-form patients took antivirals and corticosteroids.

Ethical Principles:

During the research, a written informed agreement was taken out from all participants concerning dealing with data for scientific intent. The research was performed in accordance with the guidelines of the Declaration of Helsinki and approved by the Local Ethics Committee of the Ain Shams University- Women Faculty-Science branch (approval code# ASU/W/Sci-6R/23-4-58). All the study data were used only for this research and remained confidential.

Blood Pressure Estimation:

The blood pressure of all individuals

was measured using *Beurer BC28 Blood Pressure Monitor Wrist, Italy.*

Biochemical Measurements:

Blood samples were obtained by vein puncture using a standard sterile technique; serum was separated for doing the biochemical examinations. Reduced glutathione (GSH) and malondialdehyde (MDA) levels as oxidative stress parameters were determined (Owens and Belcher,1965; Lefevre *et al*., 1996). Insulin level (Andersen *et al*., 1993) and random blood glucose level were obtained by *Sanda Care Blood Glucose Meter Adura Kit-China*. Liver functioning enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) activities, total protein, albumin, and globulin were estimated using *calorimetric Biodignostic kits, Giza, Egypt*. Inflammatory marker as C - reactive protein (CRP) and immunoglobulin (IgG and IgM) levels were measured using *abcam enzyme-linked immunosorbent assay (ELISA) kits, Cambridge, UK*. Also, creatine kinase-MB (CK-MB) activity and cardiac troponin I (cTnI) level were determined using *Mybiosource ELISA kit, San Diego, USA* as a heart function test. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) as well as triacylglycerol (TAG) levels were measured (Allain *et al*., 1974; Lopes-Virella, *et al*.,1984; Fassati and Prencipe, 1982) respectively. Urea, uric acid and creatinine levels were measured as kidney function indicators using *calorimetric Biodignostic kits, Giza, Egypt* in Science and Technology Center Lab, Cairo, Egypt.

Statistical Analysis:

The SPSS package version 21 was used to review the differences between means for statistical significance by a one-way study of variance at $p \leq 0.05$. Results were expressed as mean ± standard deviation of the mean (Levesque, 2007).

RESULTS AND DISCUSSION

Age Distribution Among Studied Patients:

144 patients participated in this study divided into 72 males and 72 females. The average age for COVID-19 infection was 41 years for males and 33 years for females (Fig.1a and b).

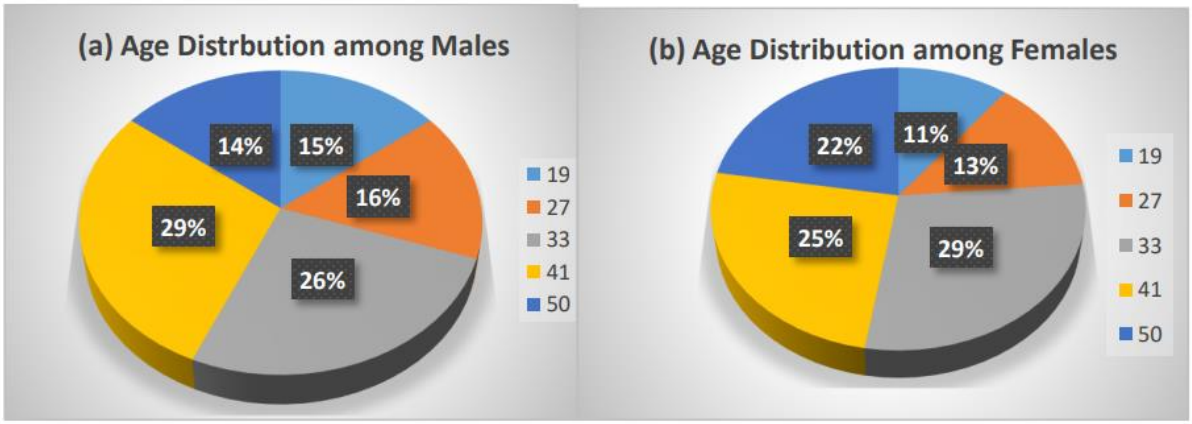

Fig. 1: Age distribution among studied patients [males (a) and females (b)]

COVID-19 Disease Forms and Types of Vaccines Among Studied Subjects:

Male patients suffered from COVID-19 in different forms and were classified as follows; 46% mild form, 35% moderate form and 19%sever form while female patients were classified as 50% mild form, 36% moderate form and 14%sever form; Figure 2(a). Vaccinated patients used one of the commonly used vaccines in Egypt. 50% of vaccinated males used Sinovac, 31% used Sinopharm and 19% used the Astrazeneca vaccine. While 56% of females used Sinovac, 33% used Sinopharm and 11% used Astrazeneca vaccine (Fig. 2b).

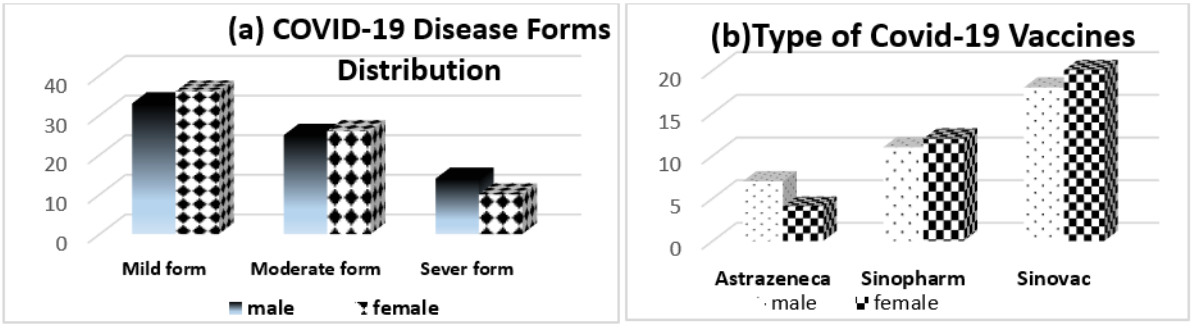

Fig. 2: COVID-19 disease forms distribution (a) and types of vaccines (b) used among studied patients.

Post Covid-19 Alterations in Oxidative Stress Parameters in All Studied Groups:

Data illustrated in Figure 3 (a and b), revealed that COVID-19 initiated a state of oxidative stress by decreasing non-enzymatic antioxidant GSH levels with increasing lipid peroxidation marker MDA content in infected patients, especially in chronically diseased patients with diabetes and heart disease. Vaccination controlled oxidative stress by preserving GSH levels and preventing MDA formation as much as possible in all vaccinated groups. Diabetic patients recorded the lowest GSH and highest MDA levels in comparison with all studied groups ($p \leq 0.05$).

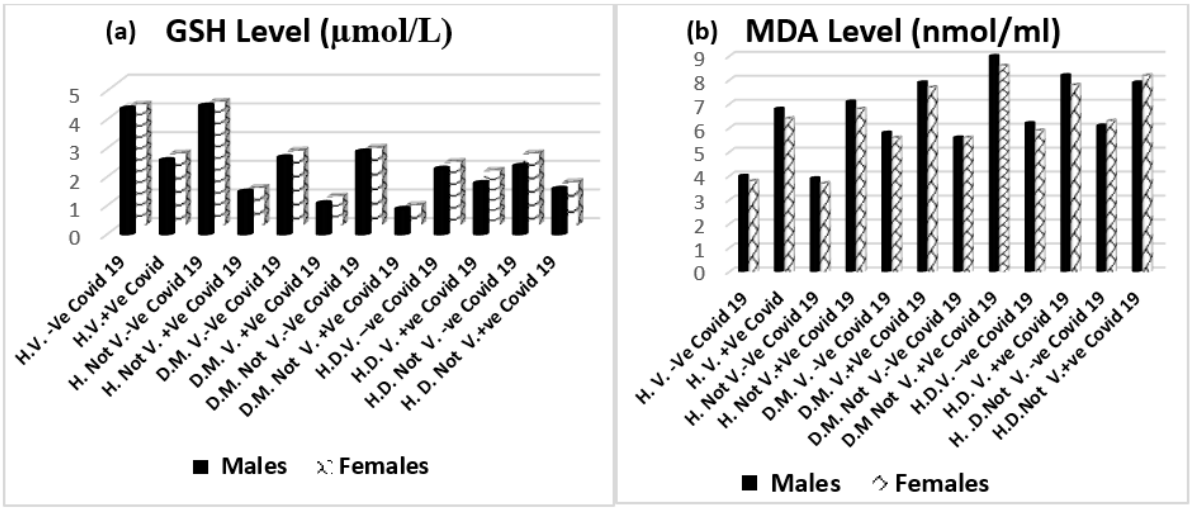

Fig. 3: Post-COVID-19 alterations in oxidative stress parameters in all studied groups [GSH (a), and MDA (b)] levels in all studied groups. Values are expressed as means ±standard deviation, n=6.

Post Covid-19 Effects on Insulin and Glucose Levels in All Studied Groups:

Results shown in Figure 4 (a and b), illustrated that infection with COVID-19 caused a diabetic-like status by increasing levels of insulin and glucose in all infected patients. Impaired glucose metabolism was aggravated in chronic diseased patients, especially with diabetes. Vaccination improved insulin action and controlled glucose levels in all vaccinated groups. Diabetic patients recorded the highest insulin and glucose levels in comparison with all studied groups ($p \leq 0.05$).

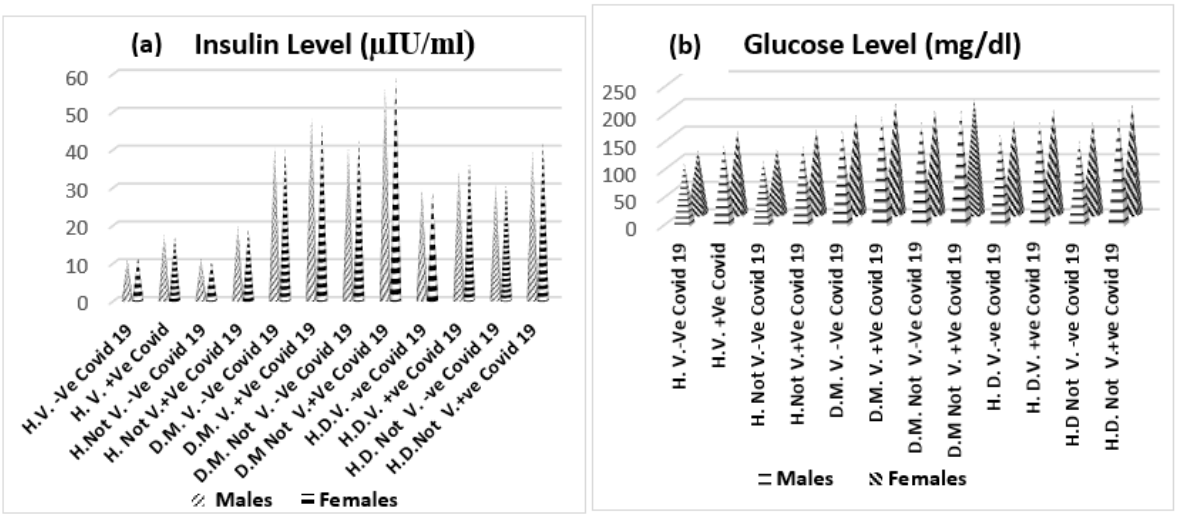

Fig. 4: Post-COVID-19 effects on insulin and glucose levels in all studied groups [Insulin (a), and Glucose (b)] levels in all studied groups. Values are expressed as means ±standard deviation, n=6.

Liver Function Status Post Covid-19 Infection in All Tested Groups:

Liver function deteriorated as a result of COVID-19 infection as illustrated in Figure 5 (a, b, c, d and e). Activities of AST and ALT increased significantly ($p \leq 0.05$) in all +Ve Covid-19 groups in comparison with –Ve Covid-19 groups. Also, increasing levels of total protein due to increasing levels of globulin, not albumin were observed. Hepatic tissues are more deteriorated in infected patients especially chronic diseased patients with diabetes and heart disease. Liver function was preserved by vaccination in all vaccinated groups. Liver tissues more deteriorated in diabetic patients in comparison with all studied groups ($p \leq 0.05$).

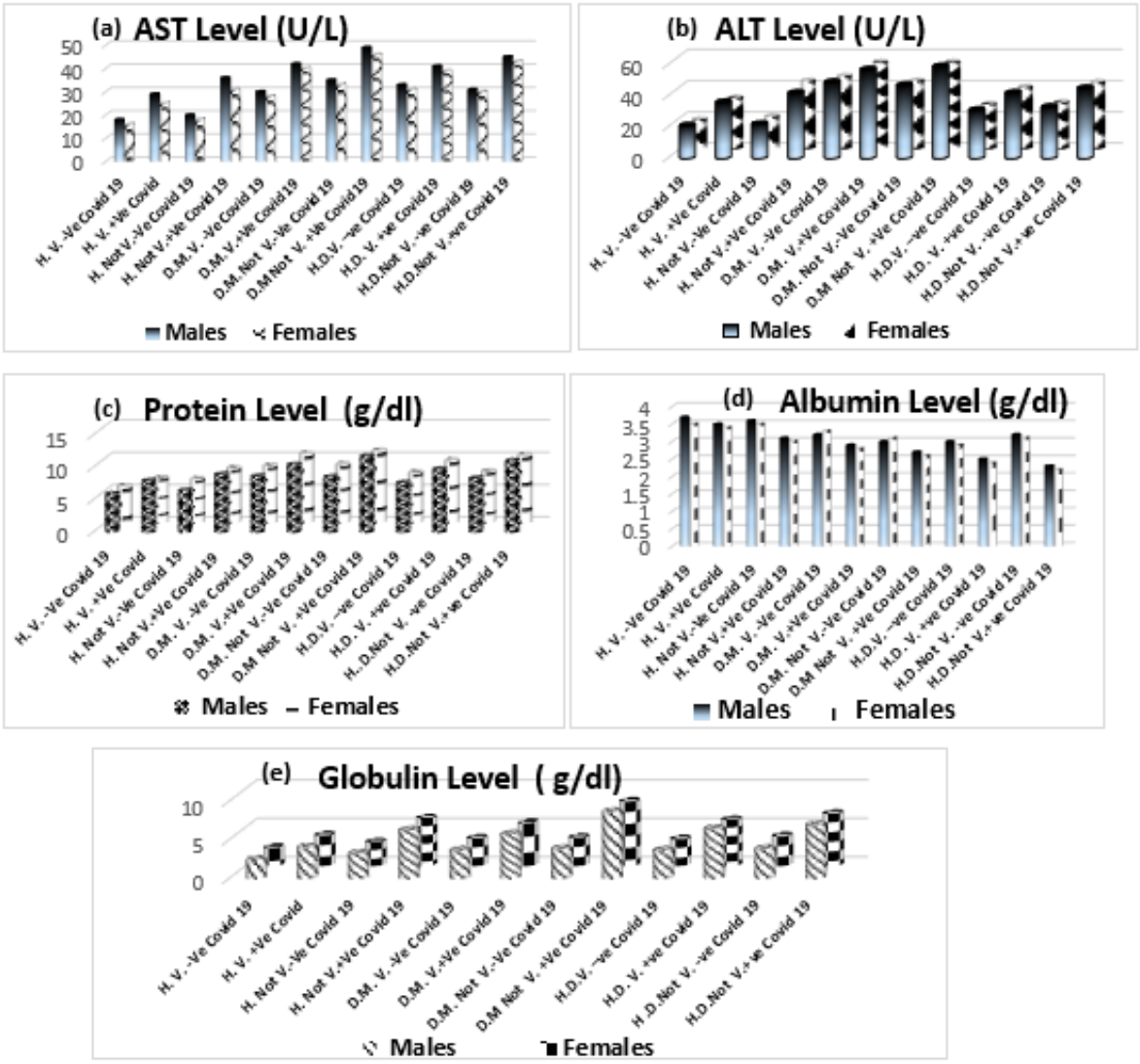

Fig. 5: Liver function status post-COVID-19 infection in all tested groups [AST (a), ALT (b) activities, total protein (c), albumin (d) and globulin (e) levels] in all tested groups. Values are expressed as means ±standard deviation, n=6.

Post Covid-19 Impact on Kidney Function in All Tested Groups:

Kidney function affected by COVID-19 infection as illustrated in Figure 6 (a, b and c) as urea, creatinine and uric acid values increased significantly ($p \leq 0.05$) in infected patients in comparison with non-infected subjects. Chronic diseased patients with diabetes and heart disease kidney function more deteriorated especially in diabetic one. Urea, creatinine and uric acid levels were more preserved in vaccinated groups.

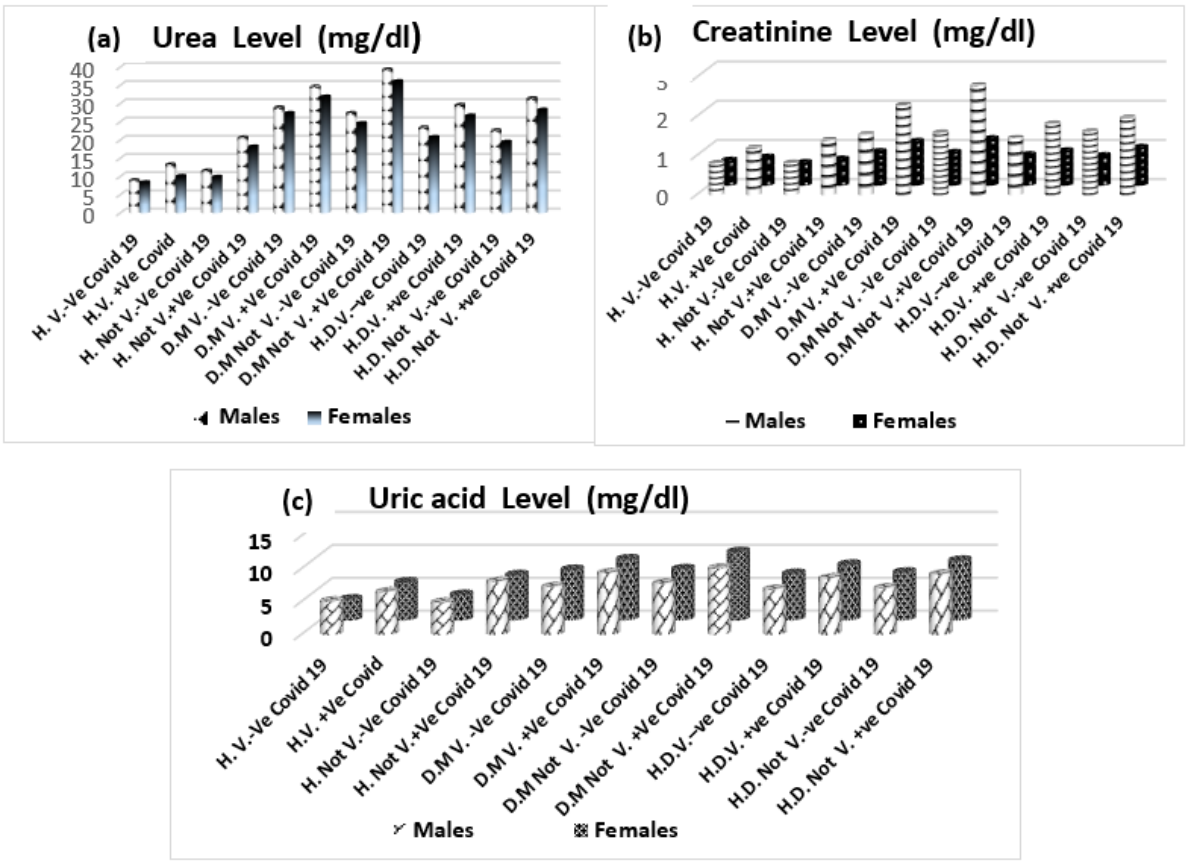

Fig. 6: Post-COVID-19 impact on Kidney function in all tested groups.
[Urea (a), Creatinine (b) and Uric acid (c) levels] in all tested groups. Values are expressed as means ±standard deviation, n=6.

Effect of Covid-19 Infection on Lipid Profile in Healthy and Chronic Diseased Subjects:

Total cholesterol and triacyl glycerol values were increased significantly ($p \leq 0.05$) in all previously infected persons. The most significant increment was recorded in heart disease followed by diabetic ones. Cholesterol fractions are also affected by increasing LDL-C and decreasing good cholesterol (HDL-C) levels. Vaccination attenuated hyperlipidemia in all infected subjects. Female sex hormones preserve lipid fractions in female subjects in comparison with males (Fig. 7 a,b,c and d).

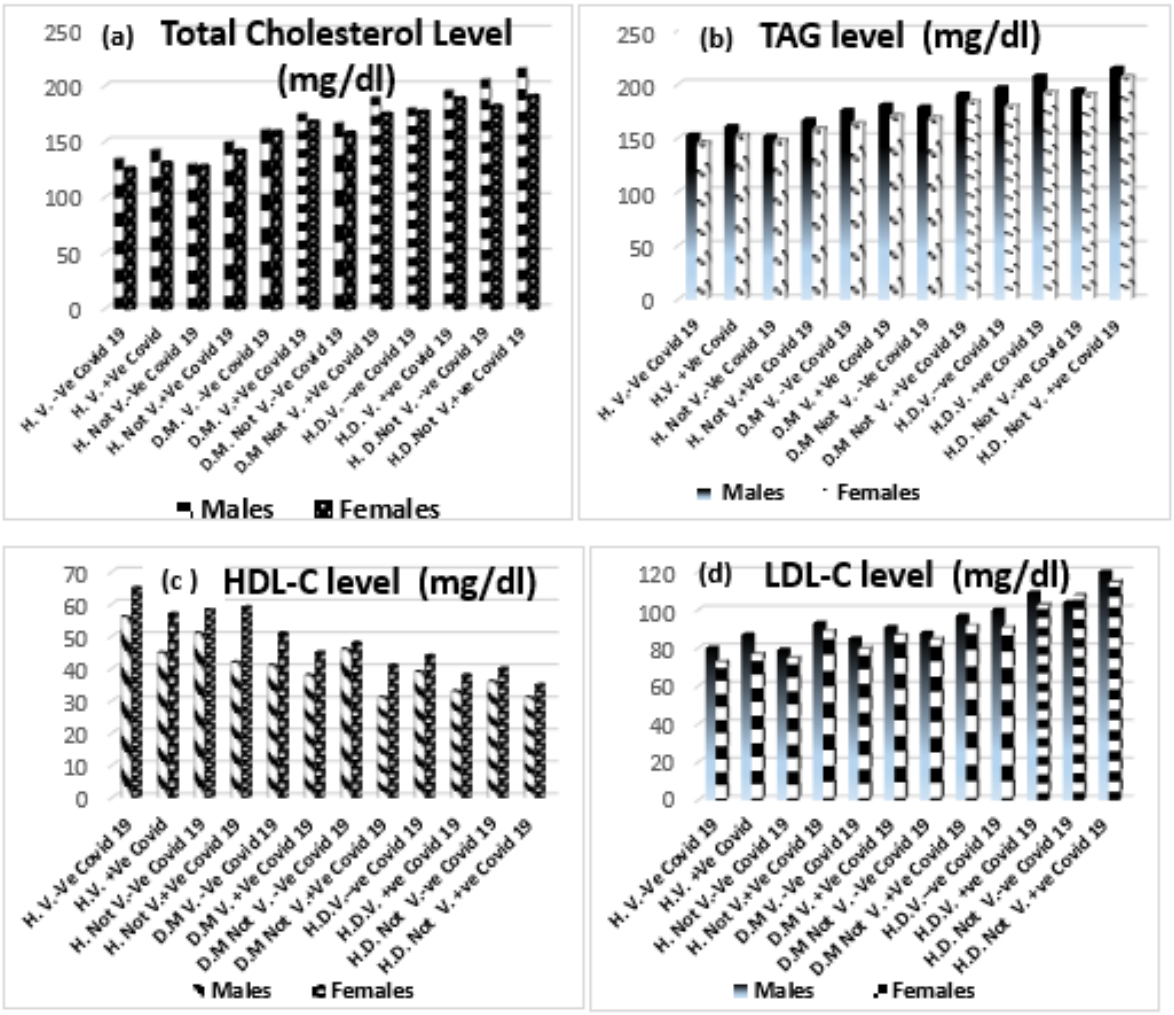

Fig. 7: Effect of COVID-19 infection on lipid profile in healthy and chronically diseased subjects [Total cholesterol (a), TAG (b), HDL-C (c) and LDL-C (d) levels] in all tested groups. Values are expressed as means ±standard deviation, n=6.

Post Covid-19 Effects on Cardiac Function in All Studied Subjects:

cTn I level and CK-MB activity as well as blood pressure were determined in all studied subjects (Fig. 8a,b,c and d) and results demonstrated that cardiac function was affected badly by COVID-19 infection in both males and females also blood pressure increased significantly post covid-19 infection. Heart diseased subjects were more affected followed by diabetic patients. Vaccination preserved cardiac function and controlled blood pressure in all vaccinated subjects.

Post Covid-19 syndrome associated body inflammatory conditions in all studied groups

CRP level in Figure 9 revealed that infection with COVID-19 caused inflammatory circumstances inside the body. Inflammation increased in chronic diseased patients. Vaccination opposed inflammation by controlling CRP content in all vaccinated groups. Diabetic patients recorded the highest CRP value in comparison with all studied groups ($p \leq 0.05$).

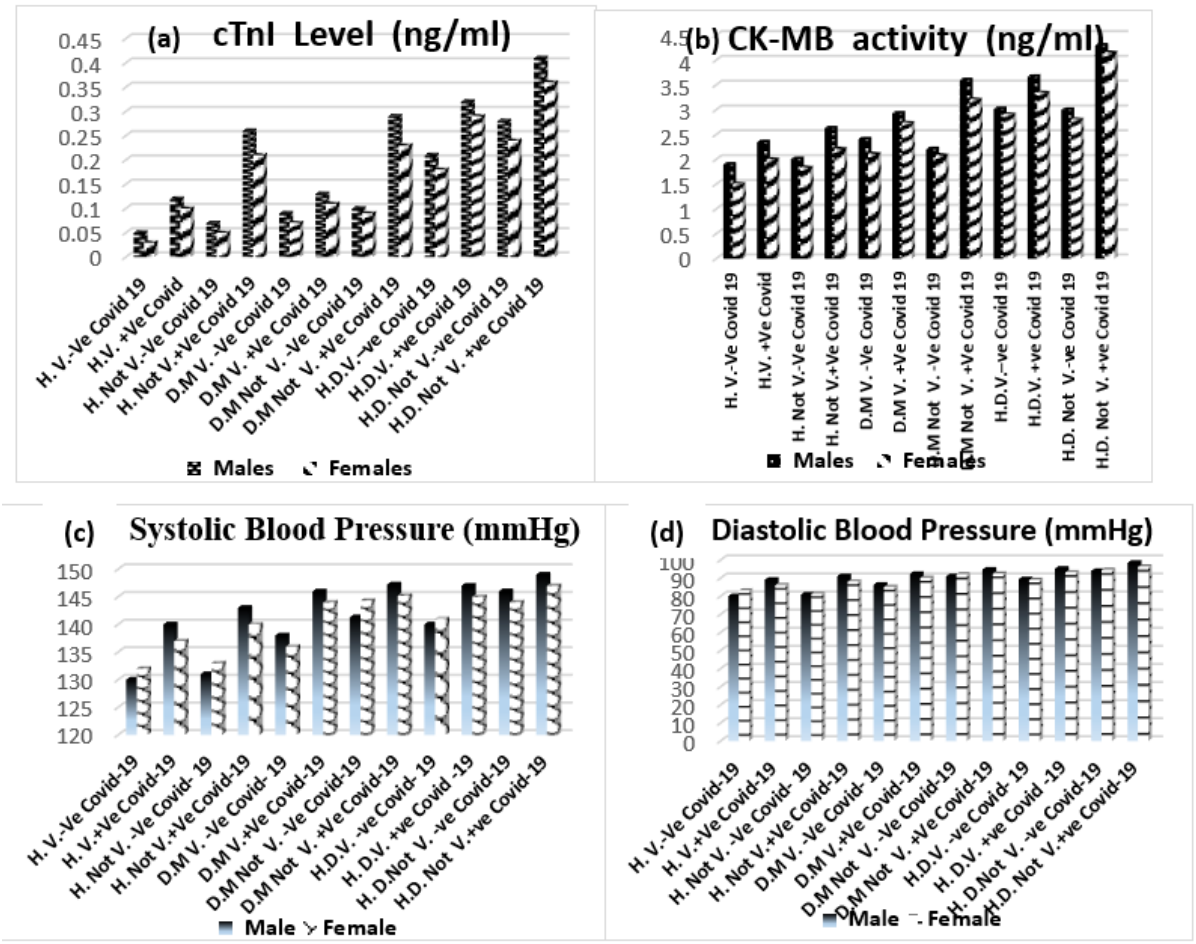

Fig. 8: Post-COVID-19 effects on cardiac function in all studied subjects [cTnI (a) level, CK-MB (b) activity, Systolic and Diastolic blood pressure (c and d)] in all tested groups. Values are expressed as means ±standard deviation, n=6.

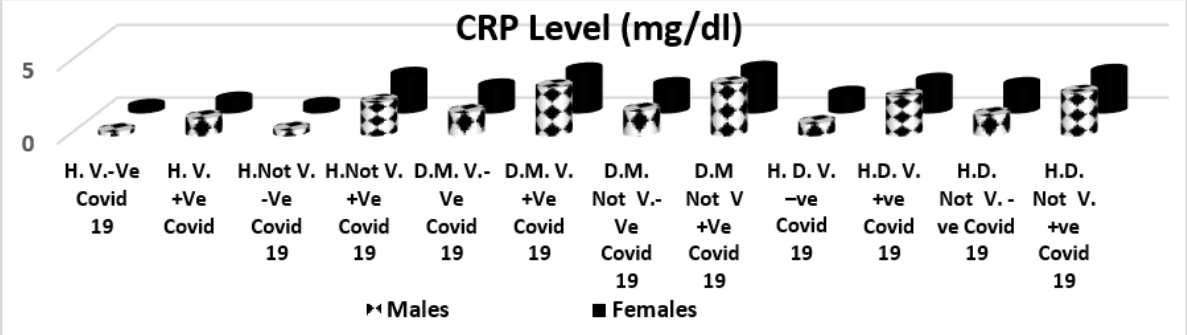

Fig.9. Post-COVID-19 syndrome associated body inflammatory CRP level in all studied groups.Values are expressed as means ±standard deviation, n=6.

Levels of Immunoglobulin Post Covid-19 Infection in All Tested Groups

Immunoglobulin levels (IgG and IgM) increased significantly post-COVID-19 infection (Fig. 10 a and b) due to inflammation and infection in +Ve COVID-19 subjects. Vaccination controlled immunoglobulin levels but on the other hand diabetes and heart disease populations were more affected.

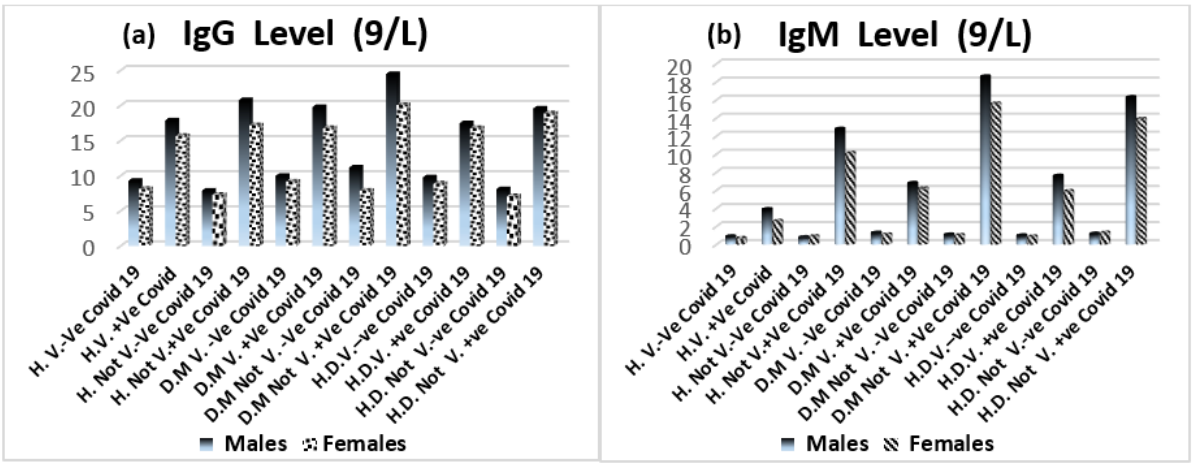

Fig. 10: Levels of immunoglobulin post-COVID-19 infection in all tested groups [IgG (a) and IgM (b) levels] in all tested groups. Values are expressed as means ±standard deviation, n=6.

DISCUSSION

COVID-19 caused many biochemical alterations in affected subjects. COVID-19 pathogenesis is dependent on oxidative stress and the defense against reactive oxygen species (ROS) (Ebrahimi *et al.*,2021). Once the virus spike is attached to the ACE2 cell membrane receptor, it enters the cell by endocytosis. This leads to RNA replication, viral structural protein translation and viral open reading frames. Activation of oxidative stress and inflammatory pathways result from these cascades.

ROS are generated; nuclear factor erythroid-2 related factor2 and glutathione contents are decreased, leading to antioxidant capacity decrement. Also, nuclear factor kappa B levels are increased by ROS and stimulate the nucleotide-binding domain-like receptor family pyrin domain containing 3 inflammasomes, leading to cytokine expression and inflammation (Schieber and Chandel,2014)

The imbalance between ROS and antioxidants leads to oxidative and nitrosative stress that holds up cellular pathways through DNA strand breaks, protein modification, lipid peroxidation, progressing to dysfunctional mitochondria, death of the cell, and inflammatory response increment. COVID-19 patients were observed with, increased oxidative damage markers in comparison to controls (Galaris *et al*., 2019).

Several studies were done on COVID-19 patients and concluded that all patients from mild to severe forms of infection suffered from oxidative stress characterized by decreased glutathione, vitamin C, thiol proteins, selenium levels with increased lipid peroxidation (MDA), H_2o_2 and damaged albumin contents (Badawy *et al*., 2021; Zendelovska *et al*., 2021; Kryukov *et al*., 2021; Pincemail *et al*., 2021).

Enzymatic or non-enzymatic antioxidants prevent or reduce oxidative damage. Massive increments in the level and activity of antioxidants and reduced thiol levels associated with total antioxidant capacity decrement were observed in COVID-19 patients. This worsens disease severity and outcome. GSH defends against oxidative stress. It acts as an antioxidant enzyme (glutathione peroxidase) cofactor and a reducing reactive species compound. GSH prevents the virus's replication at the viral life cycle's distinct stages. It also aids the antiviral defense by attenuating the viral load and the upcoming cytokine storm (Tsermpini *et al*.,2022)

COVID-19 also results in insulin resistance (impaired tissue sensitivity and inability to excrete enough insulin to regulate blood glucose); leading to up normal metabolic changes developments (Dimitriadis *et al*., 2011; Tam *et al*., 2012; Davids, *et al*.,2020.; Govender *et al*., 2021).

ACE-2 transforms angiotensin-2, (vasoconstrictor, pro-inflammatory and pro-fibrotic molecule) to angiotensin one to seven, causing vasodilation (Dominici, *et al*.,2014). Infection with SARS-CoV-2 leads to ACE2 decreased expression associated with Ang II activity and immunological response increment and insulin resistance (Govender *et al*.,2021).

Patients with SARSCoV-2 infection recorded pancreatic β-cells damage and increased fasting glucose levels in individuals who had not received glucocorticoids resembled non-SARS pneumonia patients (Yang *et al*.,2006). Also, the viral infection worsens the diabetic status in type 2 diabetics (Yang, *et al*.,2010). These alterations might cause the onset of type one or two diabetes (Rubino, *et al*.,2020).

SARS-CoV-2 links to ACE-2 receptors present in the pancreas, intestine and adipose tissue cells. SARS-CoV-2 infection disrupts glucose metabolism and augments the intensity of COVID-19 (Li *et al*.,2020).

Pulmonary epithelial cells exposed to hyperglycemia, had viral contagion and replication, marking the function of hyperglycemia in the *in vivo* enhancement of viral contagion (Collier *et al*., 2008; Fiaschi-Taesch *et al*., 2009). Resistance to insulin has critical health wages affecting the brain, vasculature, and cardiac and renal systems (Artunc *et al*.,2016).

Diabetic patients are more prone to the severity of COVID-19. This is due to (1) hyperglycemia, which initiates the formation of pro-inflammatory cytokines and advanced glycation end products (AGEs); (2) insulin resistance; (3) oxidative stress; (4) adhesion molecules production that intermediate tissue inflammation; and (5) an aggressive pro-inflammatory reaction (Tilg and Moschen,2008; Nowotny *et al*.,2015; Tomás *et al*.,2002). Diabetics showed slowed-type hypersensitivity responses, dysfunction complement activation, inhibited lymphocyte proliferative reaction, and impaired macrophage and neutrophil jobs (Geerlings and Hoepelman, 1999; Ilyas *et al*.,2011).

COVID's long-term effects comprise pulmonary and extra-pulmonary organs and cause various diseases evolution as diabetes (Al-Aly, *et al*.,2021). COVID-19 post-acute phase patients resembled an increased incidence of different non-communicable diseases like diabetes and cardiovascular diseases. People aged 65 years or more with a high BMI are at an increased risk of diabetes (Xie and Al-Aly,2022).

Diabetes may be developed in long-COVID patients as a result of (a) exocrine and endocrine cell destruction; (b) pancreatic beta cell trans-differentiation by eukaryotic initiation factor 2 signaling pathway activation; and (c) low-grade inflammation and induced auto-immunity (Dallavalasa, *et al*., 2023).

Elevated markers of liver injury, such as AST, ALT, alkaline phosphatase, and gamma-glutamyltransferase were found in COVID-19 patients (Bertolini *et al*., 2020; Phipps *et al*.,2020; Goyal *et al*.,2020; Richardson *et al*., 2020)associated with decreased albumin level (Cai *et al*.,2020). Direct hepatic virus infection, cells damaged by the immune-mediated inflammatory response mainly cytokine storms and treatment drug-induced liver injury are the main mechanisms of liver injury (Siddiqui *et al*., 2021; Alexander *et al*., 2021). Also, ischemic hepatitis may occur, in cases of respiratory failure. ACE2 receptor of the virus, is existent in biliary and hepatic endothelial cells, affording an accepted explication for the observed liver hurt. Also, liver injury caused the severity of symptoms in COVID-19 diseased patients (Bertolini *et al*.,2020).

15%-53% of infected patients developed liver injury. Elevated liver enzyme activities, monocyte count decrement, and prolonged prothrombin time were recorded. Hepatomegaly on ultrasound, liver hypo density, pericholecystic fat stranding and ground-glass opacity on chest computed tomography, were observed. While managing the patients, liver function must be recognized (Su *et al*.,2021).

As a result of the presence of ACE-2 in

cells; COVID-19 affects other organs than the lungs especially the heart, liver, intestine, brain, testicles, and kidneys (Chen *et al*.,2020).

The presence of the virus itself in the proximal tubule of the kidneys is due to the migration of SARS-CoV-2 through the bloodstream, facilitated by the circulating ACE-2 and a large amount of the ACE-2 enzyme in the kidneys (Su *et al*.,2020). Infected patients were observed with some laboratory alterations indicating kidney injury as elevated urea, uric acid, decreased serum albumin, proteinuria, decreased glomerular filtration rate, high lactate dehydrogenase and CRP levels (Lim *et al*., 2020; Neves *et al*., 2020; Xia *et al*., 2020; Cheng *et al*., 2020; Peng *et al*., 2020; Ouahmi *et al*., 2021;).

Chronic diseases act as a risk factor in infectious diseases. During the COVID-19 pandemic; chronic disease patients' bodies have a larger amount of the ACE-2 enzyme with a great affinity to SARS-CoV-2 (Hoffmann *et al*., 2020). Risk factors for developing kidney diseases in infected patients were age, male gender, African descent, heart failure, hypertension, diabetes, immunosuppression, cerebrovascular diseases, obesity, use of mechanical ventilation, sepsis and use of diuretics (Marchiori *et al*.,2021).

Atherosclerotic cardiovascular disease occurrence is elevated either during severe COVID-19 contagion or for an indefinite time afterwards. Dyslipidaemia in the post-acute strep infection was assessed. Elevated total cholesterol, LDL cholesterol, triglycerides and decreased HDL cholesterol in survivors were recorded. Dyslipidaemia was greatest in most severe infections that required intensive care admission (Iqbal *et al*., 2020; Xie *et al*., 2022).

Infection's acute effect is to decrease LDL cholesterol, sometimes significantly in association with triglycerides rise and decrease of HDL cholesterol. Restoration of LDL cholesterol to premorbid levels as the acute aliment abates was recorded. On the other hand in chronic inflammation; inflammatory cytokines cause increased triglyceride and decreased HDL persistence (Soran *et al*., 2018; Feingold and Grunfeld, 2000). During COVID-19-associated inflammation, HDL composition and functional capacity changed and it has been named pro-inflammatory or pro-atherogenic HDL. Serum amyloid A, emitted over inflammation, interferes with the capability of HDL to protect LDL from pro-atherogenic modulations like glycation and oxidation. Moreover, decrement in apolipoprotein A1 in HDL minimizes its ability to extradite overflowing tissue cholesterol, which is approved to happen during the ATP adherence cassette A1 and to be a remarkable early phase of inverse cholesterol transport (Phetsouphanh *et al*., 2022; Frere *et al*.,2022).

Low HDL-C levels are linked with elevated infection susceptibility and *vice versa*. Also, non-surviving severe patients recorded higher TAG levels. Elevated TAG content in COVID-19 patients is an index of uncontrolled inflammation and a higher risk of death (Kowalska, *et al*.,2022).

COVID-19 cardiac impairment is not fully known. However, studies illustrated that COVID-19 increased the risk of acute coronary syndrome, asymptomatic myocardial injury, stress cardiomyopathy, myocarditis and cardiogenic shock (Tersalvi *et al*.,2020).

Elevations of troponin and acute myocardial infarction in COVID-19 patients were recorded. Higher levels were observed in those admitted to ICU. An association between elevated serum troponin levels and disease severity was reported (He *et al*.,2020).

People diagnosed with SARS-CoV-2 showed induced programmed cell death, inflammation and vascular damage (Huang *et al*.,2020). COVID-19 contagion not only affects the lungs but also affects the cardiovascular and nephropathic rhythm, interfering with the vascular-endothelial cells and other body parts (Zhou *et al*.,2020).

COVID-19 virus could instantly infect the blood vessels of human calvarial osteoblasts due to the presence of ACE2 (Chen *et al*.,2019). Endothelial cells of COVID-19-influenced people showed the

occurrence of inflammatory cells and viral compartments inside; that eventually cause cell death (Wang, *et al*.,2020). SARSCoV-2 infection has the capability to launch endothelial inflammation, followed by pyroptosis, leading to inflammatory host response and cell harm (Monteil *et al*.,2020). Endothelial dysfunction is linked with endothelial inflammation, vascular lesions and vasoconstriction making diabetics more prone to endothelitis of other organs (Wang, *et al*.,2020).

Diabetics with endothelial dysfunction participate in cytokine storms and pulmonary lesions (Varga *et al*.,2020). Glycemic oscillations have the affinity to promote the formation of adhesion molecules and endothelial cytokines. This causes extravasation of the leukocytes in the alveoli during the infection, leading to morbidness of respiratory job and lung damage eventually (Avogaro *et al*.,2011).

Arterial hypertension after COVID-19, either newly verified or worsened existing, is a common occurrence (Delalić *et al*.,2022). COVID-19-associated cytokine storm can result in a severe clinical complexity known as acute respiratory distress syndrome (ARDS). That is caused by an exaggerated immune reaction rather than the viral load (Erener,2020). Pro-inflammatory cytokines role in COVID-19 etiology and related complications is documented (Hulme *et al*.,2017).

Virus replication leads to pyroptosis, which initiates the release of pro-inflammatory cytokines and affects macrophage and lymphocyte roles (Fara *et al*., 2020; Grasselli *et al*.,2021) leading to peripheral lymphopenia (Channappanavar and Perlman, 2017).

Innate immunity changes caused by interferon (INF)-1 which is a pivotal contributor to viral replication and promoting the adaptive immune systems. COVID-19 impacts the host's innate immune response and weakens the role of INF-1(Wang *et al*., 2020; McGonagle *et al*., 2020). Macrophages, neutrophils and dendritic cells begin the immune response as the body's first-line defense after infection. Patients who died of COVID-19 lung autopsies illustrated a big macrophage infiltration into the bronchial mucosa (Yang,2020). Also, the massive production of certain cytokines, such as IL-6 may be the main reason for the inflammatory response to COVID-19 (Tavakolpour *et al*.,2020)

Immunoglobulins (Ig) could bind to the S protein and initiate inflammatory cascades. This linkage can collect monocytes and pro-inflammatory macrophages in the lungs via the release of IL-8 and monocyte chemoattractant protein (MCP)-1. Fc receptor (FcR) interaction mediates the inflammatory reaction on monocytes/macrophages surface with the virus anti-S-IgG complex (Huang *et al*.,2020; Barton *et al*.,2020).

Viral load is cleaned by innate and adaptive immune systems. IgM is raised first followed by IgG with more specificity and viral neutralizing capacity. This makes antibody estimation a confirmed test to estimate the occurrence and trend of COVID-19 disease (Dispinseri *et al*., 2021). IgM and IgG and levels increased significantly in Covid-19 patients at the beginning of the infection and decreased afterwards but remained higher in non-infected patients (Ghasemi *et al*.,2022).

The humoral immune response is influenced by antigen firmness in the patients' bodies. Older individuals and severe symptoms patients showed higher median length of viral persistence. Because of this phenomenon, people exposed to SARS-CoV-2 antigens for long periods, maintain higher antibody levels (Luo *et al*., 2021; Menon *et al*., 2021).

Dysregulation of the immune system and increased inflammatory response are associated with diabetes. The enhanced severity of SARS-CoV-2 in diabetics is due to (1) immune response dysregulation, (2) cytokine response abnormalities, and (3) immune cell number irregularities (Graves and Kayal, 2008). Also, the elevation of glucose levels may suppress the antiviral responses (Nicolls et al., 2007; Tay *et al*.,2020; Revannavar *et al*., 2021). Moreover,

the severity of COVID-19 could be due to delayed interferon-gamma response, prolonged hyper-inflammatory state and lower CD4+ and CD8+ cell numbers (Huang, *et al*.,2019). Diabetics showed variations in the innate immunity components with impaired chemotaxis and phagocytosis (Lecube *et al*., 2011).

CONCLUSION

COVID-19 infection is associated with many biochemical alterations in vital body organs and essential human biological functions in infected subjects especially those with chronic diseases history as diabetes mellitus and heart diseases. Vaccination attenuated post-COVID-19 biochemical alterations. In the future study, we will study and investigate other comorbidities associated with the COVID-19 pandemic among Egyptians as infertility problems especially due to claims on vaccine effects on sex hormones.

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