Egypt. J. Chem. **Vol. 65**, No. 4,. pp. 221 – 229, (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Evaluation of Biochemical and Hematological Parameters in Glucose-6-Phosphate Dehydrogenase Deficiency Patients Associated Covid19 infection

Sarmad Ajeel Hazzaa[a] ,Nashwan Ibrahem Al-lehebe[b*], Amel Taha Yaseen[c], Alaa Younis Mahdy Al-Hamadany[d]

a. Department of Community Health/ Baghdad Medical Technical Institute/ Middle Technical university.

b. Department of chemistry/College of education for pure sciences/University of Mosul.

c. Department of Chemistry, College of science, Mosul University, Mosul, Iraq

d.Technical institute/Mosul

Abstract

G6PD-deficiency is the most prevalent enzymopathy over the world and this deficit is expected to impact about 400 million individuals worldwide. Africa, Southern-Europe and the Middle-East, including Iraq, have the greatest incidence rates in this deficiency. Aim of study: The main objective of the current research study the relationship between specific biochemical parameters and Covid19 infection associated G6PDD patients in Mosul City. A cross study in a group of 43 as 21 males and 22 females participants with Covid19 positively infection associated G6PDD, 51 Covid19 patients with any chronic diseases as 24 males, 27 females and 40 healthy controls as 21 males and 19 females participants by paid a visit outpatient clinics and private hospitals in Mosul city from the date of 15/1 to 15/2 of 2021. Whole blood samples were collected from all volunteers' patients and healthy to be analyze for serum G6PD activity, GOT, GPT, ALP, LDH and also analyze CBC. The results were showed that the majority patients of the Covid-9 with G6PDD indicated lower levels of serum G6PD activity in Covid19 patients with G6PDD more than Covid-19compared to healthy control, Also Covid19 with G6PDD having an effect increases of Total WBC and decreases in levels of Hb and PCV more than Covid19 patients.

Key words: Covid-19, Immunological parameters, CRP, IL-6, IL-10, antioxidants, blood profile .

Introduction

G6PD (glucose-6-phosphate dehydrogenase) is a major enzyme in the pentose phosphate pathway that catalyzes the first step. It transforms glucose to ribose-5-phosphate and produces NADPH as a reducing equivalent [1]. G6PD deficiency's effect on viral infections might be due to its function in the metabolism with oxidative stress(OS). Pentose phosphate pathway is limiting by G6PD enzyme, accountable for the synthesis of the nicotinamide adenine dinucleotide phosphate(NADPH) in both the cytosol and mitochondria, involving a reduced-glutathione(GSH) and oxidized-glutathione balance (GSSG) [2]. G6PD is the most common and importance enzyme deficit is insufficiency, affecting a predicted outcome about 400 million people globally. The most common locations are the Mediterranean, Africa, Southern China and Southeast Asia [3]. Iraq is located in an area with a high prevalence of the G6PD deficient genotype, with 6.3 percent of the population carrying the mutation. For a variety of reasons, determining the prevalence of G6PD deficiency in the general population is critical: rising health-care expenditures linked to frequent hospitalizations [4]; the significant illness in terms of psychosocial load and a disrupted family life style and environment for parents of children with chronic illnesses, as well as the need to develop preventative actions [5]. G6PD deficiency was

*Corresponding author e-mail: nashwan78ibrahem@uomosul.edu.iq

Receive Date: 28 July 2021, Revise Date: 06 October 2021, Accept Date: 07 October 2021

DOI: 10.21608/EJCHEM.2021.88082.4240

©2022 National Information and Documentation Center (NIDOC)

discovered in patient, who had biochemical symptoms of haemolytic anemia. The absence of reticulocytosis was attributed to a severe inflammatory condition that impeded marrow regeneration. [6]

(G6PDD) enzyme deficiency, which is the common prevalent enzyme deficit globally and causes a range of illnesses, is one health condition that could be raising the chance of death in COVID-19 patients. [7]. G6PD deficient Human coronavirus was used to infect cells (HCoV) 229E at a greater rate of normal cells, according to Wu *et al*. G6PD status also affects the prognosis and other viral infections' survival, such as hepatitis and HIV [8]. According to Onori *et al*., G6PDD is one of the most frequent enzymopathies, and COVID-19, a major pandemic, have been linked, G6PDD disrupts redox equilibrium, impairs a variety of cellular immune responses, and boosts viral infection. As a result, in G6PD-deficient COVID-19 individuals, Hemolytic anemia, a severe phenotype caused by G6PDD, can develop [9]. COVID-19 has the potential to affect a variety of organ systems in its host., hematological profiles vary during SARS-CoV-2 infection. Neutrophils play a significant role in the early stages of antiviral defense. Neutrophils, on the other hand, become cytotoxic during severe pneumonia due to degranulation and lysis [10]

The aim of the study to determination and evaluation the values of G6PD as well as certain biochemical and hematological tests in G6PD-deficient COVID-19 patients.

2.Materials and Method

2.1 Study design

From January to July 2021, 43 (21 males, 22 females) patients with positively Covid-19 associated with G6PDD, 51 (24 males, 27 females) COVID-19 patients, and 40 (21 males, 19 females) healthy controls were included in this study by paid a visit outpatient clinics and private hospitals in Mosul city. The age ranged from 20 - 72 years, with the average age being 34.13 years. All patients had Covid-19 symptoms and indicators, and all patients or their families gave informed consent and were tested for COVID-19 using a rapid and molecular test.

2.2 Sampling

In this study, fresh venous whole blood was collected from study groups (patient and control groups). The drawing blood samples were then divided into two parts. 2 mL into anticoagulant (EDTA) tubes once for complete blood count assessment. The second part was retained in plan tubes and allowed to clot before being centrifuged for 10 minutes at 3000 rpm to separate the serum, which was then frozen at -20 °C for use in immunological testing.

2.3 Determination of G6PD activity **:**

The activity of G6PD was measured by using a standard technique to quantitative testing using a G6PD analysis-Kit (Randox-Laboratory, Crumlin, Antrim, UK) according to the scientific group's recommendations [11]. This test is based on the chemical process reported by [12], which is based on the measurement of absorbance caused by NADPH production. The NADPH production was spectrophotometrically monitored a specified period more over of time at 340nm and 37°C after a specific quantity of hemolysate is added to an assay the mixture which was containing glucose-6-phosphate) as a substrate (and its cofactor NADP).

2.4 Estimation of Complete Blood counts (CBC)

Anticoagulant whole blood samples were sent to the central laboratory of the hospital, where a complete hemogram was estimated automatically for study groups (patient and control groups) using an instrument of Beckman Colter (Ac•T 5diff CP, USA).

2.5 Estimation of Biochemical parameters

Using RANDOX kits (united kingdom manufacturer), the biochemical parameters of GOT and GPT were measured through the spectophotometry technique. Serum ferritin levels were determined using bioMerieux kits through the ELFA technique (Enzyme Linked Florescent Assay). On the Cobas Integra 400 Analyzer [Roche Diagnosis, GmbH, Mannheim, Germany], activity of lactatedehydrogenase (LDH), and alkaline phosphatase (ALP) were measured using kinetic and colorimetric assays.

2.6 Statistical analysis

Data was collected, collated, and statistically analyzed to produce cross-tabs and make appropriate findings using the SPSS statistical program version 26. An independent t-test and one-way ANOVA were used to tabulate the observed data and evaluate the variable groups. When the

t-test (p) result was less than 0.05, it was judged significant, and when it was greater than 0.05, it was considered non-significant. The impacts of continuous variables were expressed using the Mean±Standard Error [13].

3. Results and discussion

Coronavirus-19 has been identified as the second most common cause of common cold infections with a high incidence, after influenza and rhinoviruses, and it has been shown to be more easily transmitted horizontally from one person to another, potentially leading to a worldwide epidemic through rapid spread across countries [13].

Aside from Covid-19-related mortality in the elderly and those with chronic conditions, COVID-19 deaths account for 0.9 % of all deaths. Elderly people and who have pre-existing chronic conditions such heart disease, cancer, hypertension, respiratory issues, gastrointestinal problems, and diabetes clearly to be at a higher risk of developing complications and death [14]

This study included 134 participants who were divided into three groups based on clinical symptoms of G6PDD and validated by COVID-19 tests to compare some biochemical parameters: Covid-19 patients with G6PD deficiency (43.09 %), Covid-19 patients (51.80 %), and healthy group (40.85 %). COVID-19 patients with G6PDD, COVID-19 patients, and healthy controls had a mean age of 40.01years, with a range of 18 to 74 years. The G6PDD patients exhibited fixed symptoms and signs of COVID-19, such as difficulties in breathing, fevering, coughing, and organ dysfunctions, sharing with symptoms and signs of D6PDD, but the healthy controls had no symptoms or signs of either G6PDD or virological illnesses.

In the present study, the prevalence of COVID-19 with G6PDD patients according to gender was 21 (48.84%) males and 22 (51.16%) females. With COVID-19 patients, the prevalence of males was 24 (47.06 %) and females were 27 (52.94 %). While healthy controls were 21 (52.5%) males and 19 (47.5%) females (See Figure 1).

Furthermore, Figure 2 depicted the age distribution of the research participants (study groups). The distribution of the different age groups was inconstant among COVID-19 with G6PD patients and COVID-19 compared to healthy controls. Covid-19 patients with G6PDD with the lowest percentage of age group (60-70) years were 1.49 %, while the greatest percentage of age group (40-50) years was 10.44 % (see Figure 2). Our study found that patient who have G6PDD have severe COVID-19 infection with severity signs and symptoms. Iraq is located in an area with a high prevalence of the G6PD deficient genotype, with 6.3 % of the population carrying the mutation. G6PD deficiency might have a role in the acuteness of COVID-19-related sickness and mortality in these people. G6PD deficiency has been a role in increased ability to COVID-19 infection and more severity of illness.

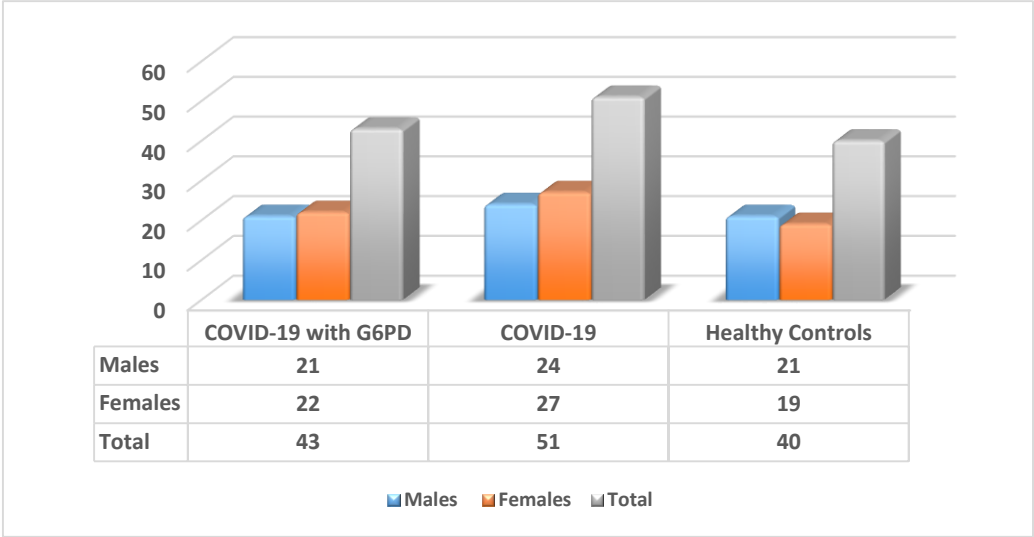

Figure 1: The gender distribution of study group participants.

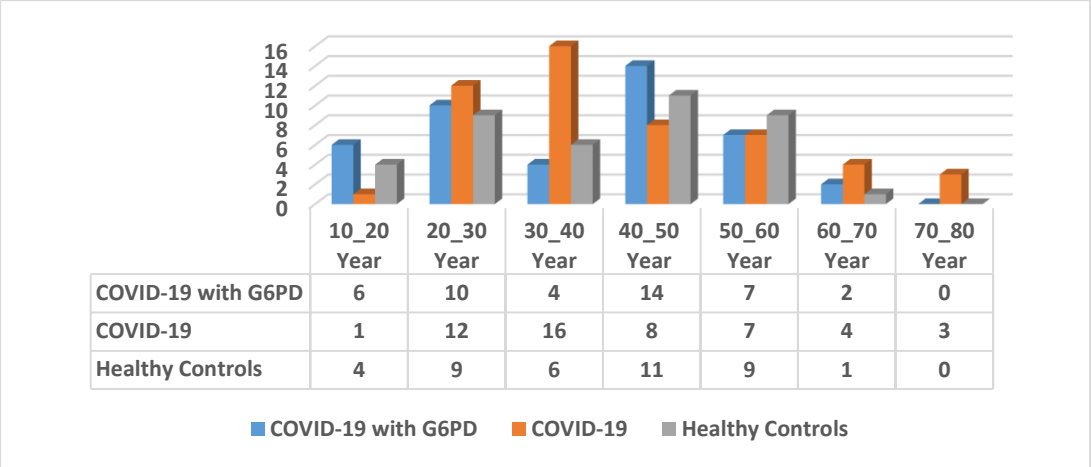

Figure 2: The age distribution of study participants.

In this study, When compared to controls, the counts of Hb and PCV in COVID-19 patients with G6PDD were and exhibited the lowest value in both females and men (Table 1).

G6PD-deficient may infected lung cells of human coronavirus 229E produce and replicate more virus than normal cells. With secondary tissue hypoxia, increased susceptibility to infection and hemolysis may result in increased disease severity and possibly death[3].

In the present study, The results of Hb and PCV reveals of G6PDD withe COVID-19 patients significantly lowered in Hb and PCV than COVID-19 patients and healthy as 11.869 mg\dl, 13.388 mg\dl, and 15.620 mg\dl respectively in Hb levels, in PCV as 35.609%, 40.164%, and 46.862% respectively. On another side, the results showed a slight increase in Total WBC in COVID-19 patients than COVID-19 patients with G6PDD compared to healthy subjects (see Table1).

Depending on the gender variable. The results revealed significant increases in Hb and PCV in males than females in COVID-19 patients without and with G6PDD compared to healthy controls. In contrast, the results of WBC revealed a slight increase in females of COVID-19 patients and COVID-19 patients with G6PDD than males as comparing to healthy control (Table 1). In addition, when comparing healthy subject to Covid-19 patients with G6PDD, our study found that total WBC counts were lower and exhibited low counts in both men and females in Covid-19 patients with G6PDD. These findings are consistent with the findings of other previous studies done in various locations, which show that COVI-19 patients with G6PDD had greater complications with decreased Hb and PCV than COVID-19 when compared to healthy controls [16,2].

Table 1. Mean±Standard Error of hemoglobin, Packed cell Volume Total WBC, among study groups according gender

Parameters		Hb (mg\dl)			PCV (%)			Total WBC ($\times 10^9$/L)		
Study groups	Statistics	**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**
COVID-19 with G6PDD Patients	**Males**	11.895	0.880	21	35.685	1.475	21	5.575	0.594	21
	Females	11.845	0.905	22	35.53	2.985	22	5.888	0.754	22
	Total	11.869	0.9574	43	35.609	1.892	43	5.735	0.702	43
G6PDD Patients	**Males**	13.482	0.461	24	40.447	1.593	24	6.741	1.090	24

	Females	13.281	0.638	27	39.845	1.942	27	6.869	0.959	27
	Total	13.388	0.581	51	40.164	1.723	51	6.802	1.023	51
	Males	15.624	0.882	21	46.872	2.077	21	6.526	1.181	21
Healthy Controls	**Females**	15.616	0.764	19	46.850	1.992	19	6.221	0.978	19
	Total	15.620	0.859	40	46.862	2.067	40	6.364	1.009	40

Table 2 compares Hb, PCV, and Total WBC levels between patients of Covid-19 with G6PDD, COVID-19 patients, and healthy controls by age group. In COVID-19 patients with G6PDD, the mean Hb levels and PCV were substantially lower in the age group 20-30 years as 11.597 mg/dl and 34.791 %, respectively, while with COVID-19 patients showed that lower mean Hb levels and PCV with age groups older than 70 years as 11.476 mg/dl and 34.430 %, respectively when compared to control.G6PDD in COVID-19 patients, however, the highest mean of Total WBC is found in the age group 30-40 years, followed by the age group 40-50 years, with 6.662 and 5.995 cells× 10^9/L, respectively. While with COVID-19 patients, the highest mean of total WBC was found in the age group 40-50 years, followed by the age group 20-30 years at 6.672 and 6.624 cells × 10^9/L, respectively When comparing to healthy control. Table 4 summarized the significant statistics of Hb, PCV, and Total WBC tests in the present study. However, the statistical significance of Hb, PCV, and Total WBC parameters estimated in all COVID-19 patients with G6PDD, COVID-19 patients, and controls group is compatible with clinical significances ($p < 0.005$) (See Tables 3,4 for details).

Table 2: Mean ± Standard Error of hemoglobin, Packed Red Volume Total WBC, among study groups according age groups

Parameters		Hb (mg\dl)			PCV (%)			Total WBC (× 10^9/L)		
Study groups	**Statistics Age groups (years)**	**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**
Covid19 with G6PDD Patients	**10-20**	12.321	0.185	6	36.965	0.577	6	5.900	0.895	6
	20-30	11.597	0.055	10	34.791	0.429	10	5.239	0.994	10
	30-40	11.692	0.844	4	35.077	0.732	4	6.662	0.151	4
	40-50	11.976	0.667	14	35.929	0.033	14	5.995	0.462	14
	50-60	11.708	0.364	7	35.125	0.215	7	5.432	0.908	7
	60-70	12.050	1.349	2	36.150	0.577	2	5.110	0.467	2
	70-80	-	-	-	-	-	-	-	-	-
Covid19 Patients	**10-20**	13.210	0.0	1	39.630	0.0	1	4.660	0.0	1
	20-30	13.469	0.848	12	40.407	0.364	12	6.624	0.950	12
	30-40	13.656	0.082	16	40.970	0.696	16	6.213	0.833	16
	40-50	13.473	0.333	8	40.421	0.500	8	6.672	0.932	8
	50-60	14.070	0.955	7	42.210	0.500	7	6.292	0.468	7
	60-70	12.182	0.508	4	36.547	0.000	4	6.170	0.161	4
	70-80	11.476	0.453	3	34.430	0.364	3	6.310	0.841	3
Healthy Controls	**10-20**	14.625	0.333	4	43.875	0.951	4	6.325	0.643	4
	20-30	16.178	0.712	9	48.536	0.589	9	6.980	0.308	9

30-40	16.401	1.000	6	49.205	0.512	6	6.941	0.839	6
40-50	15.112	0.906	11	45.338	0.235	11	6.684	0.980	11
50-60	15.575	0.856	9	46.726	0.593	9	7.100	0.500	9
60-70	15.890	0.0	1	47.670	0.0	1	4.890	0.0	1
70-80	-	-	-	-	-	-	-	-	-

Mendelian randomization results imply that the severity of COVID-19 is inversely related to basophil count, basophil percentage, and myeloid WBC count. [17]) COVID-19 individuals with catastrophic outcomes have had higher WBC and neutrophil counts, as well as a decreased lymphocyte count, and the neutrophil-to-lymphocyte ratio has been recommended as a predictive biomarker [18]. Immune cells may play an important role in the severity and susceptibility of COVID19, according to a rising number of studies [19]

Table 3 shows the number, gender, and results of some biochemical parameters tested in this study. As shown in Table 3and 4, the results revealed a significant increase of serum **ferritin** in COVID-19 patients with G6PDD more than COVID-19 patients compared to healthy controls as 226.44, 190.31 ng\ml respectively. Also, the results showed a decrease of G6PD activity in patients with COVID-19 associated with G6PDD more than COVID-19 patients compared to healthy controls as 9.974, 221.899 mU\109 Erythrocytes respectively (see Table 3and 4). The results of serum GOT, GPT, ALP, and LDH doesn't show any significant differences among study groups. According to gender, The results significantly reveal a slight increase of serum Ferritin in females of COVID-19 patients with G6PDD more than males as 249.45, 202.33 ng\ml respectively. In contrast, the results showed that elevated in males of Covid-19 patients than females compared to healthy controls as 236.13, 149.59 ng/ml respectively (Table 3). With G6PD activity, the results showed that the activity of enzymes increased in males of COVID-19 patients with G6PDD more than females as 10.137, 9.818 mU\109 Erythrocytes respectively while with COVID-19 patients, the results showed an increase in G6PD activity in females more than males as 236.583, 207.216 respectively. see Table 3and 4,

In mild COVID-19 patients, advanced age and a high LDH level were identified to be independent risk factors for deterioration. in this multicenter nested case-control analysis. Clinicians should give special note to elderly patients or those has a high LDH levels among the mild patients.[20]

Table 3. Mean ± Standard Error of Ferritin, GOT, GPT, among study groups ccording gender

Parameters		Ferritin (ng\ml)			GOT (U\L)			GPT (U\L)		
Statistics / Study groups		**Mean**	**S.E**	**No.**	**Mean**	**S.E**	**No.**	**Mean**	**S.E**	**No.**
COVID-19 with G6PDD Patients	**Males**	202.33	9.044	21	34.90	0.212	21	32.90	0.929	21
	Females	249.45	17.307	24	40.59	0.732	24	39.50	0.898	24
	Total	226.44	11.232	43	37.81	0.46	43	36.28	0.846	43
G6PDD Patients	**Males**	236.13	15.501	24	38.33	0.738	24	37.71	0.937	24
	Females	149.59	9.342	27	35.26	0.892	27	34.56	0.320	27
	Total	190.31	11.543	51	36.71	0.707	51	36.04	0.640	51
Healthy Controls	**Males**	80.38	7.193	21	38.48	1.023	21	35.86	8.440	21
	Females	86.68	4.657	19	35.05	0.923	19	33.21	5.817	19
	Total	83.38	5.406	40	36.85	1.034	40	34.60	7.344	40

Table 4. Mean ± Standard Error of G6PD activity , LDH, and ALP among study groups according gender

Parameters		G6PD activity (mU\10^9 Erythrocytes)			LDH (U\L)			ALP (IU\L)		
Statistics / Study groups		**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**	**(Mean)**	**[S.E]**	**No.**
COVID-19 with G6PDD Patients	**Males**	10.137	0.324	21	173.62	9.434	21	120.45	5.690	21
	Females	9.818	0.445	24	188.09	13.124	24	120.070	7.348	24
	Total	9.974	0..38	43	181.02	11.60	43	120.253	6.234	43
G6PDD Patients	**Males**	207.216	10.435	24	166.04	16.376	24	82.802	4.746	24
	Females	236.583	11.234	27	135.89	8.951	27	80.370	7.556	27
	Total	221.899	10.175	51	150.08	12.776	51	81.515	5.910	51
Healthy Controls	**Males**	217.307	13.079	21	120.43	6.776	21	61.206	11.403	21
	Females	255.527	9.098	19	108.26	7.984	19	60.877	13.878	19
	Total	235.462	11.527	40	114.65	6.765	40	61.050	12.730	40

Table 5 showed the statistical significance of some biochemical parameters measured in all COVID-19 patients with G6PDD, COVID-19 patients, and healthy controls is compatible with clinical significances ($p<0.005$).

Table 5. Statistically significant of parameters tests.

Statistics Tests	Mean Difference **No. (134)**	Std. Error Difference	Sig. (2-tailed)	*P* (t-test)	Df
G6PD activity	-7.646	0.697	0.000	- 10.962	132
GOT	1.108	2.140	0.606	0.518	132
GPT	0.240	2.107	0.910	0.114	132
ALP	-4.55482	.81202	0.000	-5.609	132
LDH	30.945	18.866	0.104	1.640	132
Hb	-1.51827	0.27067	0.000	-5.609	132
PCV	-4.55482	0.81202	0.000	-5.609	132
WBC	-.62932	0.21630	0.005	-2.910	132
Ferritin	36.128	22.132	0.106	1.632	132

The possible involvement of G6PD deficit in oxidative stress metabolism may play a part in the complications caused by G6PD deficiency's influence on viral infections. The rate-limiting enzyme in the pentose phosphate pathway, G6PD, and it is responsible for the synthesis of pentose phosphate of the NADPH in both the cytosol and mitochondria by balancing reduced (GSH) and oxidized GSSG) glutathione. Reduced

G6PD levels promote oxidative stress and alter redox balance equilibrium, since metabolism of glutathione is a significant composed of defense mechanism as antioxidant system [21,22]

On other side, the results of our study showed that serum of GOT, GPT, ALP, and LDH within normal range with significantly differences among study groups (Table 3). This finding was not acceptable with other study documented by **Bresolin *et al*** . that revealed GOT, GPT, CK, and LDH elevated in patients with G6PDD [23], and is identical to what is found in a pedestal showing the height of alanine transaminase and gammaglutamyl transpeptidase [24]

Although the G6PD activity showed low level in COVID-19 patients with G6PDD in our study with no significant difference between the means of activity in males and female groups was seen in our study (Table 3) which acceptable with other studies that documented lower means of G6PD activity with non-significant between males and females among study groups[25]. In contrast , A Cambodian study done by Kim et al., on G6pDD patients indicated a significantly elevated activity of G6PD enzymes in males more over females [26]. Several recent publication of data imply that (G6PD) deficiency may enhance ability to COVID-19 infection and the degree of diseases that are associated with it.[27]

However, this study indicating that COVID-19 with G6PDD had been more complicated than COVID-19 with any chronic disease compared to healthy controls. There is evidence that the production particles of viral was also greater in the G6PD-inaducate cells over time, suggesting that G6PD activity regulates this production, implying that G6PD-deficient cells were more vulnerable to COVID-19-mediated cell death. [28]

Conclusion

In this research, we founded that decrease of G6PD activity in patients with COVID-19 associated with G6PDdeficiency, although lower in a count of Hb and PCV in COVID-19 with G6PD deficiency more than COVID-19 indicating that G6PDD may increase complication and severity of illness. However, during Covid-19 infection, it is critical to monitor biochemical and hematological testing, particularly in individuals with a chronic illness like G6PDD, in order to possibly help in the improvement of disease outcome.

Acknowledgment

I extend my thanks to University of Mosul and Middle Technical university in Iraq for providing the facilities in carrying out this research, as well as to the hospitals in Mosul city**.**

References

1- Pandolfi PP, Sonati F, Rivi R, Mason P, Grosveld F, Luzzatto L. EMBO J(14) (1995):5209–15

2- Duygu Aydemir & Nuriye Nuray Ulusu. Pathogens and Global Health, (114)3 (2020) 109-110

3- Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. Blood Cells Mol Dis (42) (2009):267–78.

4- Hilmi FA *et al*. Eastern Mediterranean Health Journal, 8(1) (2002) 42–48.

5- Merenstien D, Egleston B, Diener-West M. Pediatrics, 115(4) (2005)839–844.

6- Mastroianni F, Colombie V, Claes G, Gilles A, Vandergheynst F, Place S. EJCRIM (**7)** (2020) doi:10.12890/2020_001875.

7- Ulusu N.N. Med Hypotheses. (85) (2015) 219–223. Epub 2015 May 11.

8- Wu YH, Tseng CP, ML C, et al. J Infect Dis. 197 (15) (2008) 812–816.

9- Onori, M.E., Ricciardi Tenore, C., Urbani, A. *et al*. Mol Biol Rep. (48) (2021) 2973–2978.

10- Haick AK, Rzepka JP, Brandon E, Balemba OB, Miura TA.. J Gen Virol . (95) (2014) 578e90. doi.org/10.1099/vir.0.061986-0.

11- Laouini, N., Sahli, C. A., Jouini, L., Haloui, S., Fredj, S. H., Daboubi, R., Messsaoud, T. Clinical Chemistry and Laboratory Medicine (CCLM), 55(8) (2017) 1193–1201.

12- Beutler E, Blume KG, Kaplan JC, Lohr GW, Ramot B, Valentine WN. Br J Haematol (43) (1979) 465–7.

13- Bolton, S. & Bon, C., (2003). (4th ed.). CRC Press.

14- Wrapp D., Wang N., Corbett K.S., Goldsmith J.A., Hsieh C., Abiona O., Graham B.S and McLellan J.S. Science (367) (2020) 1260–1263.

15- World Health Organization. Situation Report (69) (2019) [cited 2021 July 2]. Available from: https://www .who. int/docs/

16- Beauverd Y, Adam Y, Assouline B, Samii K.. Eur J Haematol. (2020) 00:1–3.

17- Yitang Sun, Jingqi Zhou and Kaixiong Ye. J. Pers. Med. (11) (2021) 195. https://doi.org/10.3390/jpm11030195

18- Zhou F. Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang J., Wang Y., Song, B., Gu, X., et al.Lancet. (395) (2020) 1054–1062.
19- Qin C., Zhou L., Hu., Z., Zhang S., Yang S., Tao Y., Xie C., Ma K., Shang K., Wang W., et al. Clin. Infect. Dis. (71) (2020) 762–768.
20- Zhou, Q Zhang, X.Y., Zhengxing W.u., Xiangao J., Hongying Y., Lingyun S., Jing-Wen A., Haocheng Z., Bin., Feng. and Wenhong Z.. BMC Medicine (18) (2020) 168. https://doi.org/10.1186/s12916-020-01633-7
21- Aydemir D. and Nuray N U· Transfusion and Apheresis Science (60) (2021) 103080.
22- Aydemir D, Hashemkhani M, Acar HY, et al. Chem Biol Drug Des. (94) (2019) 2094–2102.
23- Bresolin N., Bet L., Moggio M. et al., Journal of Neurology, 4(236) (1989) 193–198.
24- Xuexiang G., Xiangyu L., Xusheng A., Shufeng Y., Shangnong W., Xiaozhong Y. and Honggang W. J Clin Lab Anal. ;(34) (2020) e23391.1-6.
25- Azma RZ, Hidayati N, Farisah NR, Hamidah NH, Ainoon O. Southeast Asian J Trop Med Public Health (41)(2010) 982–8.
26- Kim S, Nguon C, Guillard B, Duong S, Chy S, Sum S, et al. PLoS One . 6 (2011)e28357
27- Vick DJ. Mayo Clin Proc (95) (2020) 1803–4.
28- Vick D J, Mayo Clin Proc. 95(8) (2020) 1797-1809