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Association of physiological levels for Glutathione with some clinical symptoms in COVID-19 patients

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Abstract

Maintaining optimal glutathione (GSH) levels is essential for preserving cellular integrity, preventing oxidative damage, and mitigating inflammation, thereby safeguarding against a wide range of diseases. The present study was suggested to evaluate GSH level in COVID-19 cases and analysis some associations with disease biomarkers and characteristics, including D-dimer, ferritin, age, BMI, sex, Ct-scan, duration, and severity of infection. The results found that GSH was decreased in infection cases than the control group in a significant change (p= 0.011). D-dimer and ferritin showed significant elevation in cases with significant differences (p=0.003, p=0.000). The Ct-scan in the cases group was 33.18%, and infection duration (11.08) days, non-significant (non-sig) changes between both groups in BMI (p=0.346). GHS was higher in males than females in both groups, with non-significant differences. In the cases group, D-dimer was significantly higher in males, while in control, non-sig differences were observed according to sex, while ferritin levels and the clinical parameters displayed non-sig changes. GSH level showed elevation in simple and sever infection level in non-sig changes (p=0.291), D-dimer increased with severity of infection significantly (p=0.008), and ferritin also increased with infection severity significantly (p=0.000). The correlation analysis between GSH level and D-dimer revealed a significant inverse correlation (p= 0.037*) in COVID-19 cases. In contrast, the correlation of GSH with the remainder of the study variables showed a non-significant correlation in both groups (cases and control). Conclusion: The present finding concluded that GSH has a significant depletion in many COVID-19 cases and a negative correlation with D-dimer, suggesting a potential link between GSH levels and disease severity.

Keywords: Glutathione levels, clinical symptoms, COVID-19 infection patients, GSH

ارتباط المستويات الفسيولوجية للجلوتاثيون ببعض الأعراض السريرية لدى مرضى كوفيد-19

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الخلاصة

يعد الحفاظ على مستويات مثالية من الجلوتاثيون أمرًا ضروريًا للحفاظ على السلامة الخلوية، ومنع الأكسدة، وتخفيف الالتهاب، وبالتالي الحماية من مجموعة واسعة من الأمراض. تم اقتراح الدراسة الحالية لتقييم مستوى الجلوتاثيون في حالات كوفيد-19 وتحليل بعض الارتباطات مع المؤشرات الحيوية للمرض وخصائصه بما في ذلك D-dimer، الفيريتين، العمر،مؤشر كتلة الجسم، الجنس، الأشعة المقطعية، ومدة وشدة الإصابة. وجدت النتائج أن الجلوتاثيون انخفض في الحالات المصابة مقارنة بمجموعة السيطرة بوجود فروق معنوية (p=0.011)، وأظهر D-dimer والفيريتين ارتفاعا معنويا في مجموعة المصابين بوجود فروق معنوية (p=0.003، p=0.000). كانت نسبة الأشعة المقطعية في مجموعة الحالات 33.18% ومدة الإصابة (11.08) يومًا، مع تغيرات غير معنوية بين المجموعتين في مؤشر كتلة الجسم (قيمة الاحتمال = 0.346). وكان الجلوتاثيون أعلى في الذكور من الإناث في كلا المجموعتين لكن الفروق لم تكن معنوية. في مجموعة المصابين، كان D-dimer أعلى بكثير في الذكور بينما في مجموعة السيطرة كان منخفضًا بدرجة معنوية عند الذكور، بينما أظهرت مستويات الفيريتين والمعلمات السريرية تغيرات غير كبيرة بين الذكور والإناث في كل من حالات كوفيد-19 والاصحاء. أظهر مستوى الجلوتاثيون ارتفاعا في مستوى العدوى البسيطة والشديدة بفروق غير معنوية (P=0.291)، وارتفع d-dimer مع شدة الإصابة بشكل معنوي (P=0.008)، كما زاد الفيريتين مع شدة الإصابة بشكل معنوي (P=0.000). كشف تحليل الارتباط بين مستوى الجلوتاثيون وD-dimer عن وجود ارتباط سلبي معنوي (*p= 0.037) في حالات كوفيد-19؛ بينما أظهرت علاقة الجلوتاثيون مع متغيرات الدراسة المتبقية ارتباطاً غير معنويا (p>0.05) في كلتا المجموعتين (المصابين والاصحاء). الاستنتاج: استنتجت الدراسة الحالية وجود نقص معنوي لمستوى الكلوتاثايون مع الإصابة بكوفيد-19 وارتباط سلبي للكلوتاثايون مع D-dimer مما يشير إلى وجود صلة محتملة بين مستويات الكلوتاثايون وشدة المرض. وهذا يؤكد أهمية إجراء مزيد من الأبحاث حول دور الكلوتاثايون في الفيزيولوجيا المرضية لـCOVID-19 وإمكانية استخدامه كمؤشر حيوي لخطورة المرض.

1. Introduction

The risk determinants that determine the severity of Coronavirus disease 19 (COVID-19) disease in some patients and not others are still obscure [1]. Laboratory parameters like ferritin and D-dimer have been proven to prophesy the intensity of COVID-19 [2]. High-resolution computed tomography (CT) for the chest is usually employed for COVID-19 pneumonia detection in the course of the disease. Increased levels of D-dimer along with ferritin in COVID-19 cases were correlated with high-resolution CT intensity scores [3, 4]. Indeed, mounting evidence suggests that oxidative stress and the related inflammation could originate from a boost assembly of reactive oxygen species (ROS) and/or reduced antioxidant barrier engaged in various chronic pathology [5], inclusive of diabetes mellitus, cardiovascular and respiratory diseases, which are famed to augment the risk of severe disturbances as well as death in COVID-19 cases [6]. In this context, antioxidants have a safeguard role averse to oxidative stress; they have a significant interest in the field of cognizance of the pathways of underlying non-specific sensitivity or impedance to the infectious agents [7]. One of the most antioxidant molecules is glutathione (GSH), which is characterized by low molecular weight and appears near the cell to prevent oxidative stress effects on cell components like protein, lipid, and nucleic acids [8]. Maintaining optimal GSH

levels is essential for preserving cellular integrity, preventing oxidative damage, and mitigating inflammation, thereby safeguarding against a wide range of diseases. Strategies aimed at enhancing glutathione synthesis and/or replenishing its levels through dietary interventions, supplementation, and lifestyle modifications may offer therapeutic benefits in various pathological conditions that are related to oxidative stress and inflammation [7]. It can also be observed in the cytoplasm, mitochondria, and nucleus, in addition to extracellular spaces like fluids. GSH is elevated during body exposure to some oxidant factors. The decrement in GSH has been found to be associated with some diseases like chronic pulmonary inflammation and smokers [8].

Glutathione is involved in thrombosis and thrombotic events by many mechanisms, like in the activity of the coagulation cascade and platelet attenuation [9, 10]. Glutathione peroxidase (GPX) used GSH to decrease lipid hyper oxides and free hydrogen peroxide; one study demonstrated that plasma GPX, GPX-3 knock-out lead to platelet-dependent thrombosis increase in *murine* models [11], the GPX-3 deficiency causes a reduction in ROS metabolism, partly due to NO reduction that increased platelet adhesion and aggregation. COVID-19 is the most vital pathogen infecting the respiratory system. The previous coronaviruses are prevalent, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) have been elucidated as important common health threats in the last decades. [12, 13]. COVID-19 was reported at the end of 2019 in China [14]. It has detrimental effects on the human body, such as organ damage to the liver, kidneys, heart, immune system, and blood [15-18]. GSH depletion may also allow a virus to replicate; thus, it's a major factor in COVID-19 pathology. Evidence found when the virus invades the body, the pro-inflammatory markers are elevated, as well as TGF-β and IL-6, which prevent the GSH formation [19]. The virus COVID-19 infection also reduces GSH via intracellular radical expression and BRCA1 inhibition, damage in DNA repair protein that mediates the production of antioxidant gene important in the synthesis of GSH [20]. The low level of GSH can further magnify the positive thrombus-inflammatory feedback loop in immune-thrombosis via potentiating platelet activation and aggregation and high D-dimer levels [19, 21]. The main goal of the current investigation is to evaluate GSH levels in COVID-19 cases alongside D-dimer levels and clinical symptoms to understand the potential roles of oxidative stress and coagulation abnormalities in the pathogenesis of COVID-19 infection to the best understanding of the pathophysiology of this infection and potentially identify novel curative objectives for ameliorating patients administration and outcomes.

2. Methodology

2.1. Sample collection and ethical approval:

A total of 57 samples (28 males, 29 females) of COVID-19 infected cases were included in the current investigation, and they were receiving treatment at Marjan Hospital city during the third era of the pandemic in Iraq. They had a mean of age 49.95 (standard error = 2.04); in addition, 40 healthy subjects (34 males, 6 females) were not infected with this virus, with a mean of age 32.35 (standard error = 2.08) who were used as control group. All data were collected from cases by written consent from each case. This project has been considered and approved by the department's council and the Academic Research Committee at the Faculty of Science for Women (FS), The University of Babylon (BU). The approval ID is 31.

Samples were collected according to the instructions of the Ministry of Health and Environment in Iraq. Blood samples were collected with sterile conditions, and under specialist nursing, all cases were diagnosed by PCR and CT-scan methods (which were conducted by the hospital staff as part of the routine methods to confirm infection with this virus), in addition to clinical symptoms; physician detected the level of infection as a simple,

moderate and severe infection. The serum was isolated, and then biomarkers (GSH, D-dimer, and ferritin) were detected using routine lab procedures. Glutathione level was estimated in the serum according to the method of Moron *et al.* [22]. D-dimer level reflects abnormal coagulation function and has been revealed to be implicated in the disease progression of COVID-19 [4]. Its levels have been estimated using the AFIAS kit/Korea. Ferritin is a mediator for immune dysregulation and is linked to disease severity [4]. Levels of ferritin were evaluated using an ELIZA kit (BT Lab /China).

2.2 Statistical analysis

Data were displayed as mean ± SE and were analyzed employing SPSS statistical program version 26. Independent sample t-test and ANOVA were applied to ensure a significant analysis.

3. Results

In the present work, some variables were detected in cases of COVID-19 infection compared with those of healthy subjects. Table (1) shows study characteristics: glutathione showed a significant decrease in infection cases compared to the control group (P= 0.011), the GHS in patients fluctuated, and several patients had higher levels than others.

D-dimer showed significant elevation in the case group with significant differences (P=0.003). Ferritin also increased significantly in the case group (P=0.000). The CT scan in the case group was 33.18% during the duration of infection, 11.08 days, and there were non-significant changes between both groups in Body mass index (BMI) (P=0.346). The infected cases have an age mean of 49.59 years, while the control group was 32.35 years. There were slight changes between males and females in the case group (49.12 and 50.87%), respectively. In contrast, in the control group, the males (84.21%) were more frequent than females (15.78%). The infected case group included three infection levels (simple, moderate, and severe), and the severe level was the most common in the present study (38.59%).

Table 1: Study characteristics in COVID-19 infected cases and control group (P<0.05)

Variables	Mean ± SE		P value
	Healthy subjects	COVID-19 cases	
Glutathione (µmole/l)	16.83±2.09	11.78±1.15	0.011*
D-dimer (ng/mL)	140.37±10.67	1503.52±316.07	0.003*
Ferritin (µg/L)	108.59±14.80	454.83±63.96	0.000*
CT-scan	-	33.18±3.048	ND
BMI (kg/m2)	26.22±1.08964	27.33±0.62800	0.346^{NS}
Duration (days)	-	11.80±1.86510	ND
Age (year)	32.35±2.08	49.95±2.04	0.000*
Sex **Male** **Female**	(34) 85% (6) 15 %	(28) 49.12 % (29) 50.88%	0.007*
Covid-19 infection level **Simple** **Moderate** **Sever**	-	16 (28.07%) 19 (33.33%) 22 (38.6%)	ND
***(P≤0.05); NS: No Significant; ND: non-detected; SE: standard error**			

The study variables according to sex were elucidated; GHS was higher in males than females in both groups with non-significant differences. In the case group, D- dimer levels

were significantly raised in males, while in the control group were non-significantly lower. Ferritin level was higher in females in the control group but lower in the case group with non-significant changes. CT scan was higher in males than females with non-significant differences, and BMI showed slight changes in both sexes of study groups. The duration showed non-significant changes, and finally, the age of the case group showed non-significant changes, as shown in Table 2.

Table 2: The study characteristics differences according to sex in COVID-19 infected cases and control group.

Variables	Healthy subjects		P value	COVID-19 cases		P value
	Males	Females		Males	Females	
Glutathione (µmole/)	18.54±2.32	13.00±2.78	0.42^{NS}	12.48±1.80	11.11±1.47	0.55^{NS}
D-dimer (ng/mL)	125.60± 11.09	217.00±67.22	0.022^{NS}	1895.66±555. 65	1148.13±327. 55	0.024*
Ferritin (µg/L)	198.83±11.81 9	195.68±112.00	0.071^{NS}	565.10±92.49	354.90±86.12	0.10^{NS}
CT-scan	-		-	37.00±4.45	29.71±4.14	0.23^{NS}
BMI (kg/m2)	26.50±1.57	28.48±1.030	0.60^{NS}	28.04±0.79	26.69±0.95	0.28^{NS}
Duration (days)	-		-	9.13±2.05	7.75±1.13	0.98^{NS}
Age (year)	31.06±2.17	45.00±15.87	0.94^{NS}	52.82±3.36	47.34±3.49	0.27^{NS}
*(P≤0.05); NS: No Significant; SE: standard error						

The study variables differences according to COVID-19 infection level (simple, moderate, and severe) were clarified in Table 3. GSH showed elevation in simple and severe infection levels with non-significant changes (P =0.291), D-dimer increased with severity of infection significantly (P= 0.008), ferritin also increased with infection severity significantly (P= 0.000), same results with CT scan (P= 0.000), BMI (P= 0.015), age (P=0.000) and duration (P=0.002).

Table 3: The study characteristics differences according to COVID-19 infection level (simple, moderate, and severe) in infected case and control group (P<0.05)

Variables	COVID-19 cases Mean ± SE			P value
	Simple	Moderate	Sever	
Glutathione (µmole/l)	14.04±2.58	9.43±1.14	12.18±2.08	0.291^{NS}
D-dimer (ng/mL)	397.38±128.66	1114.97±455.28	2675.86±657.11	0.008*
Ferritin (µg/L)	78.82±20.24	192.55±53.68	972.22±84.93	0.000*
CT-scan	9.29±0.69	23.23±1.22	59.91±3.15	0.000*
BMI (kg/m2)	25.63±0.76	26.23±0.99	29.60±1.15	0.015*
Duration (days)	5.52±0.478	8.04±1.00	19.86±4.39	0.002*
Age (year)	38.88±3.47	46.14±4.32	61.60±3.18	0.000*
*(P≤0.05); NS: No Significant; SE: standard error				

The correlation between glutathione level and study variables in infected cases and control group was explained in Table 4. A few changes were observed in the correlation

between GSH with age, D-dimer, ferritin, and BMI, which have a positive correlation in the case group and an inverse correlation in the control group with a non-significant correlation.

Table 4: Correlation between glutathione and study variables in infected cases and control group ($p<0.05$)

Groups		Age	d-dimer	Ferritin	CT-scan	Duration	BMI
COVID-19 cases	r	0.056	-0.785-	0.021	-0.024-	-0.103-	0.095
	P	0.680	0.037*	0.879	0.859	0.444	0.481
Control	r	-0.172-	-0.080-	-0.187-	-	-	-0.195-
	p	0.481	0.743	0.442	-	-	0.424

4. Discussion

Oxidative stress is a non-specific pathological status that has emerged as a critical issue contributing to various diseases [23]. It involves an imbalance between the production and scavenging of ROS by the antioxidant defense, which comprises antioxidant enzymes, vitamins, and minerals. It serves as a crucial protective mechanism against the detrimental effects of oxidative stress [24]. GSH is an important antioxidant enzyme, and its importance in COVID-19 infection cases was reported by numerous studies [25-27]. The relation of GSH with COVID-19 was demonstrated by the mediated immune response, which contributed to viral replication and scavenger ROS [28, 29].

According to current results, statistical analysis indicated a significant GSH deficiency in COVID-19 cases. The endogenous GSH scarcity reduces the biosynthesis and/or intense exhaustion of GSH, which could be a significant contributor to COVID-19 pathogenesis via the mechanisms related to oxidative stress and inflammation. Numerous studies agree with the present study that found GSH deficient in COVID-19 cases [20, 30-32]. Oxidative stress leads to pro-inflammatory cytokines activation [33], increased levels of IL-6 and TGF-β, and blocked GSH synthesis enzymes [19]. Polonikov found that GSH depletion is a vital factor in COVID-19, especially in correlation with more severe manifestations [7]. Previous studies have also indicated that low GSH concentration was the most common factor among COVID-19 cases and one of the risky factors detected to be related to high death rates like age, Coronary artery disease, hypertension, diabetes mellitus, Bechet's disease, and chronic respiratory disease [34, 35]. Notably, the low level of GSH can be used as a risk biomarker for the disease course of COVID-19, developing severe COVID-19 and severe lung damage [32].

The findings of the present study showed that non-significant depletion in GSH in COVID-19 cases decreased in female groups. Moreover, it decreased with the severity of infection. In infection cases, the decrement of GSH started with the COVID-19 protein binding with angiotensin-converting enzyme 2 (ACE2) that causes decreased or blocked expression of ACE2 and toxic over accumulation of Angiotensin II (ANGII) [36], high level of ANGII via linked to Angiotensin II receptor type 1(AT1R), stimulating NADPH oxidases (NOX) that transport an electron to O_2 from NADPH, making many radical species that scavenged using GSH and deplete GSH, lead to increases ROS-mediated oxidation. In spite of the COVID-19 proteins being produced in the cytosol, several of them, such as Non-structural protein (Nsp)1, 5, 13, 14, and 16, are indeed found in the nucleus [37]. This was proved by research that suggested the S protein is also found in the nucleus and impedes

DNA repair by obstructing the essential DNA repair protein (BRCA1) and 53BP1 recruitment to the damage site [38].

A study found the S protein perhaps lowered the intra-cellular and intra-nuclear of GSH protection. When the S protein in the nucleus depletes breast cancer 1 (BRCA1) recruitment, it becomes support for nuclear factor erythroid 2–related factor 2 (Nrf2) actions [39]. On the other hand, Interleukin 6 (IL-6) has been found to stimulate a dose-dependent reduction in intracellular GSH levels in some lung cell lines for humans. IL-6 causes an increase in superoxide radicals levels, resulting in intracellular GSH decrement [40]. The increased concentration of IL-6 is recorded in severe COVID-19 cases, which makes it a good indicator of disease infection [41]. In addition to the significant deficiency in GSH, the results of our investigation indicated a considerable increase in D-dimer values in COVID-19 cases than control individuals. D-dimer is indeed a protein fragment that appears in the bloodstream when there is degradation of blood clots through a process called fibrinolysis. Normally, faint levels of D-dimer can be found in the plasma due to the natural breakdown of fibrin, which is involved in clot formation [42]. However, raised levels of D-dimer can occur in numerous pathological conditions. This altitude in D-dimer levels is often utilized clinically as a marker for certain states, particularly those related to blood clotting and thrombosis [43]. Increased levels of D-dimer have been consistently recorded in severe cases of COVID-19 patients. Hakami *et al.* [44] found that mortality rates from COVID-19 increased with age, ferritin, and D-Dimer levels, which were significantly higher in deceased patients than in survivors. Increased D-dimer levels are often indicative of thrombosis increased risk along with reflecting a more severe inflammatory response or vascular damage in COVID-19 patients [45]. Kryukov *et al*. [32] found an inverse relation between levels of D-dimer and GSH and pointed out an association between GSH depletion and the severity of COVID-19. This is consistent with the results of the current investigation. These observations are secondary to the increased risk of thromboembolic consequences in COVID-19 cases. At this time, there is no reliable diagnostic technique to identify microemboli with precision. D-dimer testing may, therefore, be used to direct clinical suspicion and track therapeutic response.

Age is a well-known risk factor for COVID-19 infection-related serious illness, sequelae, and mortality. Interestingly, research on both humans and animals shows that endogenous glutathione levels gradually decrease with age, leaving cells in older adults more vulnerable to oxidative damage from various environmental causes than in younger people [46].

As for the significant increase of ferritin in COVID-19 patients recorded in the current study, these results agreed with a previous study, which indicated that a severe increase in ferritin levels is remarkably related to mortality in extremely ill patients who suffer from hyper-inflammation statement [47]. The present finding also agrees with the results reported by Gómez-Pastora *et al*., which showed that a boost of (1.5–5) times the upper range of normal was indicated with serum ferritin in COVID-19 cases [48]. The results of the current study are also consistent with a previous Bahraini study that indicated the ferritin and D-dimer precisely presage patients developing severe COVID-19 infections as well as those at risk of evolving COVID-19 pneumonia [49].

Despite the mounting body of evidence supporting and enhancing the beneficial impacts of GSH, its entire potential and clinical applications may still be underestimated. Further investigations are needed to articulate the mechanisms of action of GSH in several physiological processes and to scout its potential therapeutic implementations in greater depth. Also, grasping the factors that influence GSH levels in the body, such as diet, lifestyle, and genetics, may provide valuable insight for improving health and managing disease. Also,

the limitation of the current study is to identify one type of antioxidant in COVID-19 patients, and in subsequent studies, it will be better to include other criteria to determine the oxidative stress index, such as total antioxidant capacity and reactive oxygen species to explain the exact role of oxidative stress in COVID-19 disease.

5. Conclusion

The present finding concluded a significant depletion of GSH levels with COVID-19 infection and a positive correlation with D-dimer, suggesting a potential link between GSH levels and disease severity. This conclusion reinforces the role of oxidative stress in the development of the disease and the importance of maintaining a high level of antioxidants to suppress further free radicals that are formed as a result of the inflammatory processes associated with the disease. This emphasizes the significance of further research into the function of GSH as well as other antioxidant factors in the pathophysiology of COVID-19 to prove the potential to be important biomarkers for the severity of the disease.

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