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Association between vitamin D3 and glutathione levels in COVID-19 individual

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ABSTRACT

Background: COVID-19 is an infectious disease associated with a high rate of infection and death, especially for the older males when they have low levels of glutathione (GSH) and vitamin D. The GSH status is positively associated with the bioavailability of vitamin D. The GSH deficiency is correlated by increased oxidative stress and inflammatory markers which implicate the increase in the severity of the disease.

Objective: To verify the vitamin D–GSH levels interaction among healthy and COVID- 19 patients.

Method: Control healthy group (166) individuals and (171) COVID-19 patients were involved in this study. Oxidative stress and antioxidant parameters, vitamin D, and inflammatory markers were estimated in both groups.

Results: The COVID-19 patients showed significantly higher levels of malondialdehyde (MDA), protein carbonyl group (PC), interleukin-6 (IL6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) and significantly low levels of GSH and vitamin D compared to the healthy control group, the aged and male COVID-19 group display significantly higher levels of MDA, PC, and significantly low levels for GSH compared with younger and women group.

Conclusion: The COVID-19 patient correlated with higher oxidative stress, inflammatory marker, and low level of antioxidant GSH and vitamin D which occur with advancing age, especially within the male.

Keywords: *COVID-19; oxidative stress; reduced glutathione (GSH); vitamin D3*

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INTRODUCTION

COVID-19 still spreading across different countries, has affected many people. The severity of this disease ranged from mild, moderate to severe critical illness to asymptomatic.1 This virus enters the human body with its spike protein and attaches to human cell receptors (ACE2), later it starts replicating within the lungs which leads to difficulty in breathing and death may also occur.2 Rapid growth of COVID-19 invades the human immune system and to overcome this virus, the body's mechanism of defense and "cytokine storm" will develop.3

The old-age people with COVID-19 have a higher rate of serious illness, which suggesting the implication of age which make human more sensitive to the environmental stress factors, such as infection with the COVID-19.4 Different studies show that the COVID-19 severity was associated with gender. Women are at a lesser risk of infection and death compared to men, and this is due to higher glutathione (GSH) in females than in males.5

Oxidative stress (OxS) is excess reactive oxygen species (ROS) and it correlates with different disorders such as COVID-19 disease.6 Under a normal physiological state, OxS is balanced by an antioxidants system. GSH is considered the major endogenous antioxidant.7–9 It has different functions which include the elimination of free radicals and also has antiviral properties. The level of cellular GSH keeps varying with sex and age.10

Vitamin D plays a key role in regulating many cell pathways which play a key role in the antioxidant system.11 Low levels of vitamin D are also associated with increased cell damage caused by ROS.12 Several studies indicated that vitamin D deficiency is associated with increased COVID-19 severity as vitamin D is positively correlated with the levels of GSH.13,14

COVID-19 and glutathione

The cellular deficiency of GSH may result from decreased biosynthesis or increased depletion of GSH which leads to the development of OxS, immunity dysfunction, and viral invasion.15–17 Different data confirm that GSH deficiency is directly correlated with the increased rate of COVID-19 infection. Old people are more susceptible to the damage caused by oxidative stress due to viral infection with decreased GSH levels as the root cause. This phenomenon is clearly evident in COVID-19 patients.18,19 So the inflammation in the lungs gets exacerbated and results in severe infection.20

COVID-19 and vitamin D

Vitamin D is a steroidal hormone.21 It plays a significant role in increasing cell immunity by preventing cytokine storms through influencing tumor necrosis factor-alpha (TNF-α) and interferon-γ22 and regulating immunity.23 It also plays an important role in inhibiting the replication of respiratory viruses.24 Studies suggest that its deficiency can stimulate the Renin-Angiotensin system, which may cause cardiovascular disease with decreased lung capacity. People with these comorbidities possess a higher risk of severe COVID-19.25

Glutathione and vitamin D

Many recent observations state that higher GSH is parallel with excellent levels of active vitamin D.26 Low level of L. cysteine, which is considered a precursor for reduced GSH, is correlated with low vitamin D level and vitamin D binding protein.27 Thus, administration of cysteine will improve rGSH level and will consequently increase the regulation of VDBP expression, 25-hydroxylase, and vitamin D receptor. So increased levels of vitamin D will lower the biomarkers of inflammation.28

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GSH deficiency associated with increased OxS changes the regulatory genes of vitamin D that lead to gene expression suppression and consequently decreases vitamin D biosynthesis, and the lead to secondary vitamin D deficiency. Finally, we conclude that GSH is vital to control the endogenously vitamin D biosynthesis and may be used as a treatment for vitamin D deficiency.29

METHODS

Study design and patient collection

A total of 337 individuals participated in this study and were registered from the Hospital of Al-Hakeem, 166 of them were considered as a healthy control group, and the remainder 171 were marked as case study group and confirmed with COVID-19 infection.

Once again, the case study group (171 patients) was subdivided into two subgroups, the first subgroup (129 patients) was made on the basis of their age and the second subgroup (171 patients) was made on the basis of gender. The objective of these subgroups was to show the influence of both factors on OxS product malondialdehyde (MDA), protein carbonyl (PC) and antioxidant stress including reduced GSH, vitamin D. Inflammatory markers including IL6, C-reactive protein (CRP), and TNF-α were measured for all participants.

Biostatistical analysis

Our data were expressed as mean ± standard deviation, and participant's T-test was done to verify the differences among healthy and COVID-19 patients, and among the subgroups of COVID-19 individuals for all estimated parameters. Significant differences were accepted when P-value was less than 0.05.

RESULT

After analysis, the results from Table 1 display significantly higher levels of MDA (4.51 ± 1.6, p = 0.001), PC (1.81 ± 0.92, p = 0.003) and significantly low levels for GSH (2.89 ± 0.42, p = 0.001) in the patient group when compared with the healthy group, while the data in Table 2 exhibit significantly higher levels of fasting glucose (141.1 ± 11.32, p = 0.001), IL6 (8.94 ± 1.21, p = 0.001), TNF (5.32 ± 1.03, p = 0.001) and CRP (10.11 ± 2.01, p = 0.001), and significantly low levels of D3 (19.71 ± 8.72, p = 0.001) in patients in the patient group when compared with the healthy group. In Table 3, the data demonstrate the age influence on the disease, it shows significantly higher levels of MDA (4.02 ± 1.12, p = 0.004), PC (2.05 ± 0.02, p = 0.028) and low level for vitamin D (18.01 ± 6.89, p = 0.004) and GSH (2.01 ± 0.33, p = 0.001) in the aging group (67 ± 12 years) when compared with the other group (62 ± 14 years). On the other hand, the gender factor displays significantly higher levels of MDA (4.34 ± 1.81, p = 0.03), PC (2.15 ± 0.11, p = 0.002) and significantly low level for GSH (2.36 ± 0.53, p = 0.003) in males when compared to females and fail to show significant differences for D3 (21.91 ± 6.96, p = 0.51) among two subgroups as shown in Table 4.

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TABLE 1. Oxidative stress and antioxidant value among healthy and COVID-19 patients.

Parameters	Healthy (Control group) N = 166	COVID-19 (Case group) N = 171	P-value
BMI (kg/m2)	23. 8 ± 1.8	24.1 ± 2.2	0.17
MDA (mmol/L)	1.41 ± 0.09	4.51 ± 1.6	0.001
PC (nmol/mg protein)	0.722 ± 0.3	1.81 ± 0.92	0.003
GSH (mg/gHb)	4.01 ± 0.61	2.89 ± 0.42	0.001

TABLE 2. Biochemical and inflammatory markers for healthy and COVID-19 patients.

Parameters	Healthy (Control group) N = 166	COVID-19 (Case group) N = 171	P-value
Glucose (mg/dL)	96.4 ± 8.31	141.1 ± 11.32	0.001
25 (OH) vitamin D (ng/mL)	33.42 ± 10.13	19.71 ± 8.72	0.001
IL6 (pg/mL)	3.15 ± 0.11	8.94 ± 1.21	0.001
CRP (mg/L)	2.97 ± 1.1	10.11 ± 2.01	0.001
TNF-α (pg/mL)	1.31 ± 0.93	5.32 ± 1.03	0.001

TABLE 3. Oxidative stress, antioxidant, and vitamin D3 values among COVID-19 patients on the basis of age.

Parameters	COVID-19 patient N = 64	COVID-19 patient N = 65	p-value
Age years	62 ± 14	67 ± 12	0.03
BMI (kg/m2)	24.21 ± 1.5	24.62 ± 1.22	0.091
MDA (mmol/L)	3.52 ± 0.81	4.02 ± 1.12	0.004
PC (nmol/mg protein)	1.91 ± 0.51	2.05 ± 0.02	0.028
GSH (mg/gHb)	2.77 ± 0.54	2.01 ± 0.33	0.001
25(OH) vitamin D (ng/mL)	21.61 ± 7.11	18.01 ± 6.89	0.004

TABLE 4. Oxidative stress, antioxidant, and vitamin D3 values among COVID-19 patient on the basis of gender.

Parameters	COVID-19 patient (Female) N = 84	COVID-19 patient (Male) N = 87	P-value
Age years	65 ± 10	66 ± 13	0.57
BMI (kg/m2)	24.32 ± 1.6	23.92 ± 1.17	0.06
MDA (mmol/L)	3.88 ± 0.81	4.34 ± 1.81	0.03
PC (nmol/mg protein)	1.91 ± 0.71	2.15 ± 0.11	0.002
GSH (mg/gHb)	2.61 ± 0.54	2.36 ± 0.53	0.003
25(OH) vitamin D (ng/mL)	22.68 ± 8.33	21.91 ± 6.96	0.51

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TABLE 5. The demographic properties for study.

Parameters	Healthy (N = 166) (Control group)	COVID-19 (N = 171) (Case group)
Mean age (year)	62 ±12	64 ±14
Gender Males Females	 87 (52.41%) 47.59 (79%)	 50.88 (87%) 49.12 (84%)
Symptoms Mild case Moderate case Severe case	 – 	 72 (42.11%) 59 (34.5%) 40 (23.39%)
Comorbidities None Hypertension Gall stone	 – 	 167 (97.66%) 1 (0.59%) 3 (1.75%)

DISCUSSION

This pandemic has spread extensively, mutated into new forms, alpha, sigma, etc., and there lack of knowledge, information, and efficient treatment.30 Therefore, it is required to identify certain factors that interact with the mechanisms of the pathogenicity of this virus to lower the time of hospitalization and mortality rate. Oxidative stress is correlated with disease severity especially when there is a decrement in the antioxidant level such as GSH, ascorbic acid, vitamin D, and others. Oxidative stress is associated with different diseases and certain infections such as COVID-19.31

Different evidence reported that the GSH dearth is the most caustic agent for harmful demonstration in addition to death due to this virus.32 The GSH has antiviral properties as it inhibits viral replication and this activity leads to a decrease in the massive inflammatory markers' liberation into the lung.1 Also GSH decrement the activity of ACE, reduction ROS synthesis so, GSH keeps cytokine storm will be under control.33

Different studies show the prevention role of vitamin D against COVID infection.34–36 Meltzer et al. concluded that there is a duplication in the rate of COVID-19 infection with vitamin D deficiency.37 So the role of vitamin D in keeping the redox status of the cell becomes essential, the vitamin D demonstrate a significant reduction in infected cells and it also lowers the levels of proinflammatory markers.38–40

The interaction of GSH and vitamin D deficiency and overproduction of ROS with the pathogenicity of this virus make us measure intracellular GSH concentrations, oxidative stress parameters, and vitamin D in those individuals.41

Our data in Table 5 exhibit a significantly higher level for MDA, PC, and significantly lower levels for GSH in the case group in comparison to the healthy group. It's not surprising that the depletion of GSH leads to increased OxS and more carbonylation of proteins resulting PC42–45, and the abnormal production of free radicals will destroy lipid cell membranes with MDA formation. It has been shown that the possible explanation for the severity and complication of COVID-19 is GSH deficit.

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34 Different studies were compatible with our output data,46 Karkhanei et al.,47 Muhammad et al.,48 found elevated levels of oxidative stress and reduced antioxidant status GSH in the patient group.49,50

The data in Table 4 demonstrate significantly higher levels of TNF-α, IL-6, CRP in the patient group in comparison to the healthy group. In COVID-19 patients, the depletion of GSH increased OS resulting in increased TNF-α and IL-6.51,52

Also, the result shows significantly higher levels of D3 associated with the low levels of inflammatory markers and oxidative stress in the control group in comparison to the case group, and this explains the role of vitamin D in downregulating the synthesis of these markers and it also reduces oxidative stress.53–55 Studies show that the GSH stimulates the regulation of vitamin D gene and elevates the concentrations of vitamin D within the cell. Vitamin D also affects the biosynthesis of GSH through increased cellular GSH formation.14,56 So there is a positive interaction between D3 and GSH in lowering the severity of COVID-19.57

COVID-19 and age

Age, comorbidities, smoking history, and dietary deficiency are considered risk agents for COVID-19 infection.58 The age implicated in making such aged-subject highly exposed to stressing factors of the environment as infectious viruses such as COVID-19. In addition, aging involves normal immune response dysfunction and induced dysregulation pathways of inflammation.4 The deterioration of redox homeostasis and OxS come out to be critical biological processes that could account for enhancing human susceptibility to disease in the elderly patient.

59 The possible causes are depletion of GSH which is associated with age advancing.

Our observations are interesting because they exhibit significant GSH deficiency in the aged group in comparison to other groups of patient. Our study was in agreement with different studies.60–62 From this point, age may be considered a factor involved in the pathogenesis of COVID-19.63

Now we discuss the level of vitamin D in aged patient and its association with disease severity

The data exhibit significantly low levels of vitamin D in the aging group (≥67 years) in comparison to the other group. Many studies indicated that aged population is at higher risk of COVID-19 infection.64,65 Our data is in agreement with other studies which also say that COVID-19 incidence is significantly greater in older patients, especially with vitamin D deficiency.66–68

Less exposure to sunlight, absence of appetite, reduced absorption of vitamin D are common in old age patients and result in the deficiency of it. Our data indicate significantly low levels of vitamin D and GSH in association with significantly higher levels of oxidative stress (MDA and PC) in the aging group. Oxidative stress neutralized with GSH is the most intracellular antioxidant. Older age individual with COVID-19 is at high risk of elevated OxS combined with GSH deficiency and vitamin D deficiency.69,70

Recently vitamin D plays a significant role in lowering the OxS by activated of many antioxidant cascades and the block certain pathways which make ROS-activating. So there is a sincere interrelationship betwixt oxidative stress, vitamin D and GSH level, especially in old age.71

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COVID-19 and gender

The sex-associated COVID-19 infection will be used in our study as one of the commonest caustic agents responsible for the disease. It notices that male is more significantly to suffer from COVID-19 infection compared to women.72 In addition, our data show significantly lower plasma levels of GSH, which are associated with lower but non-significant vitamin D levels in men in relation to women.73 So men are more susceptible to OxS and inflammation34 which was observed through significant elevation of the MDA (4.34 ± 1.81, $p = 0.03$) and, PC (2.15 ± 0.11, $p = 0.002$) level in men compared to data MDA (3.88 ± 0.81, $p = 0.03$), (PC 1.91 ± 0.71, $p = 0.002$) in women.

Several studies were exhibited lower values for GSH in men due to rapid utilization of it compared` to the woman and the reasons may be due to implication of testosterone hormone in the male in exacerbation of free radicals and stimulation peroxidation of lipids.74 On the other hand, it was found the Estrogens female hormone could inhibit the synthesis ROS so women have less probability of depilation of GSH.75

From the above data and ample evidence we hypothesize that vitamin D supplementation and GSH or its precursor advise using decrement COVID-19 severity.76

LIMITATION

Small sample size, the data obtained from only one hospital, the recommendation for future studies should consider these limitations by increasing the sample size and measuring other antioxidants.

CONCLUSION

The COVID-19 patients display low vitamin D level associated with the low levels of GSH resulting from increment oxidative stress is implicated in lung injury and reflected the severity of the disease.

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