**Association between Vitamin D3 and Glutathione levels**

**in COVID 19 individual**

Khalid Hassan Abdalruda , PhD, Department of biochemistry, Faculty of Pharmacy ,Jabir Ibn Hayyan Medical University, Al Najaf Al-Ashraf, Iraq ,+9647809364959. E-mail. [Khalid.hh.abdalruda@jmu.edu.iq](mailto:Khalid.hh.abdalruda@jmu.edu.iq),

ORCID:0000-0002-7179-4034

**Abstract:**

**Background:** COVID-19 is an infectious disease associated with high rate of infected and death specially for older male when they have low levels of glutathione (GSH) and vitamin D (vit D). The GSH status positively associated with bioavailability of vit D. The GSH deficiency correlated by increased oxidative stress and inflammatory markers which implicate in increase the severity of disease. **Objective**: To verify the vitamin D - GSH levels interaction among healthy and COVID- 19 patient. **Method** :Control healthy group (166) individual and (171) COVID 19 patient were involved in this study. Oxidative stress and antioxidant parameters, Vit D, and inflammatory marker were estimated in both group. **Results**: The COVID-19 patient show significant higher level for malondialdehyde (MDA),protein carbonyl group(PC), inturlukin-6 (IL6),Tumor necrosis factor alpha (TNFα) and C-reactive protein (CRP) and significant low level for GSH and vit D compare to healthy control group, the aged and male COVID-19 group display significant higher level for MDA,PC and significant low level for GSH compare with younger and women group. **Conclusion**: The COVID-19 patient correlated with higher oxidative stress , inflammatory marker and low level of antioxidant GSH and Vit D which develops by age advancing and especially within male .

**Key words:** COVID-19 ,Oxidative stress ,Reduced glutathione(GSH) and Vitamin D3

**Introduction**

The (COVID-19) still to spread throughout different country, influence many people. The disease severity of people varied from mild, moderate to severe critical illness to asymptomatic, (1).The virus enters to body of human through employed its spike protein and attach to human cell receptor (ACE2) ,later begin to replication within lung contributing to difficult of breathing al so death may be occur(2). Rapid growth of COVID-19 resulting in invasive immune system and overcome mechanism of defense and ‘cytokine storm’ will develops (3).

The infected older age people with COVID-19 has higher rate of harmful illness ,this

suggesting the implication of age which make the human more sensitive to the environmental stress factors, such as the infection with the corona virus SARSCoV-2 (4).different studies show that the COVID-19 severity was associated with the gender. The women are less risky ,worsen and death comparable to men. And this due to higher GSH in female than in males (5).

The oxidative stress(OxS) is excess reactive- oxygen species and its correlated with different disorder as COVID-19 disease,(6),Under normal physiological state, OxS is balanced by antioxidants system .The reduced glutathione (GSH) consider the major endogenous antioxidant (7,8,9). It has different function as elimination the free radicals and an antiviral property. The level of cellular GSH keeps varying with sex and age (10).

The vit D play a role in regulate many cell pathways which has magic role in antioxidant system (11). Low level of vit D may involve with increments damage of cell caused by the reactive- oxygen species (ROS) (12).Several studies indicated that vit D deficiency associate with increased COVID-19 severity and notice that vit D positively correlate with level of GSH(13,14).

**COVID 19 and Glutathione**

Thecellular deficiency of GSH may results from decrement biosynthesis or increased depletion of GSH lead to development the OxS, immunity dysfunction and viral invasion (15,16,17).Different data confirm that, GSH deficiency become the most acceptable clarification of increase rate of COVID-19 infection by aging. The old age human are more susceptible for damage cause by oxidative stress due to viral infection as a result for decrement in GSH level and this phenomena shown in COVID-19 patients (18,19).So the inflammation process in lung will be exacerbation resulting in increment disease severity (20).

**COVID 19 and Vitamin D**

Vit. D is steroidal hormone (21). Play significant role in increasing cell immunity achieve by prevention cytokine storm through influencing on TNF- α and interferon- γ [(22) and regulating the immunity (23), an important role in inhibiting the replication respiratory viruses (24). Studies suggest that this deficiency can stimulate the Renin- Angiotensin- system , resulted in cardiovascular disease with make lung function to be insufficient. People has like this comorbidities are possess a higher risk of severe COVID-19 (25).

**Glutathione and Vitamin D**

Many recent observation state , higher reduced (GSH) is parallel with excellent level of active vit D (26).Low level of L.cysteine which is consider precursor for reduced GSH was correlate with low vit D level and vit D. binding protein (27). Thus administration the one-cysteine will improve rGSH and consequence up regulation to VDBP expression , 25-hydroxylase, and vitamin D receptor , So VD value will increase and biomarkers of inflammation will be lower (28).

GSH deficiency is association with OxS increments causing alters regulatory genes of Vitamin D lead to the gene expression suppress consequence decreases in Vit D biosynthetic, and the net results leading to secondary vit D deficiency. finally we conclude that ,GSH is vital for control the endogenously vit D biosynthesis and may use as treatment for vit D deficiency (29).

**Method**

**Study design and patient collection**

A total of 337 individual were share in this study ,they were collected from Hospital of Al-Hakeem,166 of them were consider as healthy control group, and the reminder 171 marked as case study group and confirmed with COVID-19 infection.

Once again the case study group(171 patient) was subdivided in to two subgroup ,the first sub group (129 patient) designed considering the age and the second sub group (171 patient) considering gender and the aim to show the influence of both factors on OxS product MDA,PC and antioxidant stress including reduce glutathione (GSH) , Vit D, and inflammatory marker include IL6 , CRP and TNFα were measurement for all participant

**Biostatistical analysis:**

Our data were express as mean ± stander devotion, student's T- test was tested to verify differences among healthy and COVID-19 patient and among the subgroup of COVID-19 individual depend on age and sex for all estimated parameters .Significant differences was accept when P-value less than 0.05.

**Result :-**

After analysis the date the results from table two display significant higher level for MDA (4.51± 1.6,p=0.001) , PC (1.81±0.92 ,p= 0.003)and significant low level for GSH(2.89±0.42,p=0.001) in patient group compare with healthy group, while the data in table three exhibit significant higher level for 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 significant low level of D3(19.71±8.72,p=0.001) in patient in compare to healthy group .In table four the data demonstrate the age influencing on disease , it show significant higher level for MDA(4.02 ± 1.12,p=0.004),PC(2.05±0.02,p=0.028) and low level for vit D (18.01±6.89,p=0.004)and GSH(2.01 ±0.33,p=0.001) in aging group(67±12 year) compare with other group having age of (62±14year).In other hand the gender factor display significant higher level for MDA(4.34± 1.81,p=0.03) ,PC(2.15±0.11,p=0.002) and significant low level for GSH(2.36 ±0.53 ,p=0.003) in male compare to female and failure to show significant differences for D3(21.91±6.96,p=0.51) among two subgroup as in table five.

**Table 1 :. The demographic properties for study**

|  |  |  |
| --- | --- | --- |
| **COVID-19 N = 171**  **Case group))** | **Controls N = 166**  **(Healthy group)** | **Parameters** |
| 64 ±14 | 62 ±12 | Mean age (year) |
| (%50.88) 87  (%49.12)84 | 87(52.41%)  (%47.59)79 | Gender  Males  Females |
| 72 (42.11%)  59 (34.5%)59  40 (23.39%) | There is no | Symptoms  Mild case  moderate case  Severe case |
| 167 (97.66%)  1 (0.59%)  3 (1.75%) | There is no | Comorbidities  None  Hypertension  Gall stone |

**Table 2:- Oxidative stress and Antioxidant value among Healthy and COVID 19 patient**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Healthy**  **(Control group)**  **NO =166** | **COVID 19**  **(Case group)**  **NO = 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 3:- Biochemical and inflammatory marker for Healthy and patient**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **Healthy**  **(Control group)**  **NO=166** | **COVID 19 (Case group)**  **NO= 171** | **P-value** |
| Glucose ( mg/dl) | 96.4±8.31 | 141.1±11.32 | 0.001 |
| 25(OH)Vit 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 |
| TNFα (pg/ml) | 1.31±0.93 | 5.32±1.03 | 0.001 |

**Table 4:- Oxidative stress , Antioxidant and Vit D3 value among COVID 19 patient depend on Age**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **COVID 19 patient NO = 64** | **COVID 19 patient NO =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)Vit D (ng/ml) | 21.61±7.11 | 18.01±6.89 | 0.004 |

**Table 5:- Oxidative stress , Antioxidant and Vit D3 value among COVID 19 patient**

**depend on gender**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameters** | **COVID 19 patient Female = NO = 84** | **COVID 19 patient Male = NO =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)Vit D (ng/ml) | 22.68±8.33 | 21.91±6.96 | 0.51 |

**Discussion**

This pandemic is highly spread, appear new generation as alpha, sigma lack of knowledge, absent the information and absent efficient treatment (30).Therefore, it is required to identify certain factors that interact with mechanisms of pathogenicity of this virus to lowering time of hospitalization and mortality rate. The oxidative stress is correlated with disease severity of the specially when there is a decrement in antioxidant level such as GSH, Ascorbic acid, vit D and other. Oxidative stress association with different disease and certain infections as COVID-19 (31).

Different evidence reported that the GSH dearth is most caustic agent for harmful demonstration in addition to the death due to this virus (32). The GSH has antiviral property through inhibit viral replication and this activity lead to prevent increased the massive inflammatory markers liberation into the lung (33). Al so GSH decrement the activity of ACE, reduction ROS synthesis so, GSH keep cytokine storm will be under control (34).

From other hand different studies show prevention role of vit D the against SARS-CoV2- infection(35,36,37).Meltzer et al. during her study, He concluded that there is duplicated

In rate of infective with COVID.19 in human with vit D deficiency (38).So analyze role of vit D in keeping the redox- status of cell become essential, the vit D demonstrate significant rate of reduction in infected cells number lower levels of proinflammatory markers (39,40,41).

The interaction of GSH and Vit D deficiency and overproduction the ROS with pathogenicity of this virus make us to measure intracellular GSH concentrations ,oxidative stress parameter and Vit D in those individuals (42).

Our data in table one exhibit a significant higher level for MDA , PC and significant low level for GSH in case group in compare to healthy group it's not surprising that ,the depletion of GSH able to increasing OxS and more carbonylation of proteins resulting PC (43,44,45,46) and the abnormal production for free radicals will cause lipid cell membranes destroys with MDA formation. It has been show the possible explanation for severity and complication of COVID-19 is GSH deficit (47) ,Different studies were compatible with our output data (48),Karkhanei et al.(49)Muhammad et al.(50). The researchers found elevated levels of oxidative stress and reduced antioxidant status GSH in the patient group (51,52).

The data in table three demonstrate significant higher level for TNF-α, IL-6, , CRP and in patient group compare to healthy group . In COVID‐19 patients the depletion GSH increase OS resulting in increased (TNF-α) and (IL-6) (53,54).

Al so the result show significant higher level for D3 associated with low level of inflammatory marker and oxidative stress in control group in compares to case group, and this explain the role of vit D in down regulate the synthesis these markers and it has role in reducing oxidative stress. (55,56,57). Studies show that the GSH stimulate regulation of vit D gene and elevated concentrations of vit D with in the cell.From other hand vit D influence on the biosynthesis of GSH through increase cellular glutathione formation.(58,59).So there is positive inter action among D3 and GSH in lowering the severity of COVID 19(60).

**COVID-19 and Age**

The age, comorbidities, smoking, and dietary are considers risk agent for COVID-19 infection(61).The age implicated in making such aged-subject highly exposure to stressing factors of environment as infectious virus such SARS-CoV-2.In addition, aging involve in normal immune responses dysfunction and induced dysregulation pathways of inflammation (62).The deterioration of redox homeostasis and oxs come out to be critical biological processes that could account for enhancing human susceptibility to disease in elderly patient (63).The possible causes is depletion of GSH which associated with age advancing.

Our observation are interesting because they exhibit significant GSH deficiency in aged group compare with other group of patient .Our study was agreement with different studies which have reported in (64,65,66).From this point the Age, may considers a factor involve in pathogenesis COVID-19 (67).

Know we discuss the level of Vit D in aged patient and its association with disease severity

The data exhibits significant low level for vit Din aging group (≥67 years compare with other group. Many studies indicated that the aged pupulation are at higher risk towards COVID-19 infection (68,69).Our data agreement with other studies which decided ,the COVID-19 incidence is significantly greater in older patient Specially with vit D deficiency (70,71,72)

The less exposure to sunlight, absence of appetite ,reduction absorption of vit D and other are commonest in old age patient and resulting in deficit of it. Our data indicate significant low level of vit D , GSH in association with significant higher level for oxidative stress(MDA and PC) in aging group. Oxidative stress are neutralize with (GSH) is the most intracellular antioxidant .Older age individual with COVID-19, is high risk of elevated OxS combined with GSH deficiency and vit D deficiency (73,74).

Recently vit D plays significant role in lowering the oxs by activated of many antioxidant cascade and the block certain pathways which make ROS-activating .So there is sincere interrelationship betwixt oxidative stress , vit D and GSH level specially in old age(75).

**COVID-19 and gender**

The sex associated COVID-19 infection will disuse in our study as one of the commonest caustic agent responsible for disease .It notice that, the male is more significantly to suffer from COVID-19 infection compare to women (76). In addition, our data show significant lower plasma levels of (GSH) which associated with lower but non-significant vit D level in men in relation to women.(77).So men more susceptible to oxs and inflammation (78 )which observed through significant elevation the MDA (4.34± 1.81,p=0.03) and, PC (2.15±0.11,p= 0.002 )level in man compare to data MDA( 3.88 ± 0.81,p=0.03),( PC 1.91 ± 0.71,p=0.002 )in women.

Several studies was exhibit lower value for GSH in man due to rapid utilization of it compare to woman and the reasons may be due to implicate testosterone hormone in male in exacerbation free radicals and stimulation peroxidation of lipid (79). From other hand it was found the Estrogens female hormone could inhibition synthesis ROS so women has less probability to depilation of GSH (80).

From above data and ample evidence we hypothesis that vit D supplementation and glutathione or its precursor advise to use decrement COVID-19 severity (81).

**Limitation**

Small sample size ,the data obtain from only one hospital ,the recommendation for future study should consider these limitation by increase the sample size and measure other antioxidant  **Conclusion:**

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

**References :**

1.Wu Z, Mc Googan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention, JAMA, 2020, 323(13): 1239-1242.

2.Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target, Intensive Care Med., 3, 2020.

3.Tisoncik J.R, Korth M.J, Simmons C.P, Farrar J, Martin T.R, Katze M.G, Into the eye of the cytokine storm, Microbiol Mol Biol Rev., 2012, 76: 16-32. https://doi: 10.1128/MMBR.05015-11.

4.Polonikov A, Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in COVID-19 patients, ACS Infectious Diseases, 2020, 6(7): 1558-1562.

5.Dobrakowski, M.; Pawlas, N.; Hudziec, E.; Kozłowska, A.; Mikołajczyk, A.; Birkner, E.; Kasperczyk, S.Glutathione, glutathione-related enzymes, and oxidative stress in individuals with subacute occupational exposure to lead. Environ. Toxicol. Pharmacol. 2016, 45, 235–240.

6.Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of Infection and Public Health, 2020, 13(10): 1373-1380.

7. Aarón J, Méndez R, Ester R, Puc M. N-acetylcysteine as a potential treatment for novel coronavirus disease 2019,Future Microbiol., 2020, 15: 959-962.

8. Horowitz RI, Freeman PR, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases Respiratory Medicine Case Reports, 2020, 30: 101063.

9. Choudhuri SK. Glutathione Enrichment as a Possible Prevention and Treatment for COVID-19, Int. J. of Pharma Sci. and Scientific Res., 2020, 6(4): 65-66.

10. Spitalization, and Death by Age Group. Available online: (accessed on 1 December 2021).

11.Sastre J, Federico VP, Viña J. Glutathione, oxidative stress and aging, AGE 19, 1996, 129-139.

12. Berridge, M.J. (2015) Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun. 460 (1): 53–71.

13. Alvarez, J. A., Chowdhury, R., Jones, D. P., Martin, G. S.,Brigham, K. L., Binongo, J. N., Ziegler, T. R., and Tangpricha, V.(2014) Vitamin D status is independently associated with plasmaglutathione and cysteine thiol/disulphide redox status in adults. Clin.Endocrinol. (Oxford, U. K.) 81, 458−466.

14. Jain, S. K., Micinski, D., Huning, L., Kahlon, G., Bass, P. F., and Levine, S. N. (2014) Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels in the blood of type 2 diabetic patients. Eur. J. Clin. Nutr. 68, 1148−1153.

15. Banerjee K, Biswas MK, Choudhuri SK. A newly synthesized Nickel chelate can selectively target and overcome multidrug resistance in cancer through redox imbalance both in vivo and in vitro, J. Biol. Inorg. Chem., 2017, 22(8): 1223-1249.

16. Banerjee K, Ganguly A, Chakraborty P, Sarkar A, Singh S, Chatterjee M, Bhattacharya S, Choudhuri SK. ROS and RNS induced apoptosis through p53 and iNOS mediated pathway by a dibasic hydroxamic acid molecule in leukemia cells, European Journal of Pharmaceutical Sciences, 2014, 52: 146-164.

17. Basu S, Ganguly A, Chakraborty P, Sen R, Banerjee K, Chatterjee M, Efferth T, Choudhuri SK. Targeting the mitochondrial pathway to induce apoptosis/necrosis through ROS by a newly developed Schiff’s base to overcome MDR in cancer, Biochimie, 2012, 94: 166-183.

18. Townsend DM, Tew KD, Tapiero H. The importance of glutathione in human disease, Biomed. Pharmacology, 2003, 57: 145-155.

19. Silvagno F, Vernone A, Pescarmona GP. The role of glutathione in protecting against the severe inflammatory response triggered by COVID-19. Antioxidants (Basel), 2020, 9(7): 624.

20. McGuinness AJ, Sapey E. Oxidative stress in COPD: Sources, markers, and potential mechanisms, J. Clin. Med., 2017, 6(2): 21.

21. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention, Reviews in Endocrine and Metabolic Disorders, 2017, 18(2): 153-165.

22. Nobrega A. IMPORTÂNCIA DA VITAMINA D EM COVID-19, Revista Ibero-Americana de Humanidades,Ciências e Educação, 2021, 7(7): 1060-1081

23. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1, 25 (OH) 2D regulation of T cells, Nutrients, 2015, 7(4): 3011-3021.

24. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections, Reviews in Medical Virology, 2017, 27(1): e1909.

25. Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, Xue X. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system, Scientific Reports, 2017, 7(1): 1-10.

26. Yoshihara E, Masaki S, Matsuo Y, Chen Z, Tian H, Yodoi J.Thioredoxin/Txnip: Redoxisome, as a redox switch for the pathogenesis of diseases. Front in Immunol. 2014;4:514.

27. Jain SK, Kahlon G, Bass P, Levine SN, Warden C. Can L-cysteine and vitamin D rescue vitamin D and vitamin D binding protein levels in blood plasma of African American type 2 diabetic patients? 2015, 23(8): 688-693.

28 Jain SK, Marie PK, Warden C, Micinski D. L‐cysteine supplementation upregulates glutathione (GSH) and vitamin D binding protein (VDBP) in hepatocytes cultured in high glucose and in vivo in liver, and increases blood levels of GSH, VDBP, and 25‐hydroxy‐vitamin D in Zucker diabetic fatty rats, Molecular Nutrition & Food Research, 2016, 60(5): 1090-1098. https://doi.org/10.1002/mnfr.201500667.

29. Parsanathan R, Jain SK. Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice, Scientific Reports, 2019, 9(1): 1-11

30. Valencia DN. Brief review on COVID-19: the 2020 pandemic caused by SARS-CoV-2. Cureus 2020;12(3).

31. Ntyonga-Pono MP. COVID-19 infection and oxidative stress: anunder-explored approach for prevention and treatment? Pan Afr Med J2020;35(Suppl. 2):12.

32. Droge W, Schulze-Osthoff K, Mihm S, Galter D, Schenk H, Eck HP, Roth S, Gmunder H. Functions of glutathione and glutathione disulfide in immunology and immunopathology. FASEB J.1994;8(14):1131–8. doi:10.1096/fasebj.8.14.7958618.

33. Wu, Z., and McGoogan, J. M. (2020) Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 323, 1239.

34. Hayes, J.D., & Dinkova-Kostova, A.T. (2014) The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci. 39 (4): 199–218.

35. Lee, D.H., Gold, R., & Linker, R.A. (2012) Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters. Int J Mol Sci. 13 (9): 11783–11803.

36 Tsai, C.W., Lin, C.Y., & Wang, Y.J. (2011) Carnosic acid induces the NAD (P) H: Quinone Oxidoreductase 1 expression in rat clone 9 cells through the p38/Nuclear Factor Erythroid-2 Related Factor 2 Pathway. J Nutr. 141 (12): 2119–2125.

37. Mitsuishi, Y., Motohashi, H., & Yamamoto, M. (2012) The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism. Front Oncol. 2200.

38. Urakawa, I., Yamazaki, Y., Shimada, T., Iijima, K., Hasegawa,H., & Okawa, K., et al. (2006) Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 444 (7120): 770.

39. Puerta-Guardo H, de la Cruz Hern\_andez SI, Rosales VH,Ludert JE, del Angel RM. The 1α,25-dihydroxy-vitamin D3 reduces dengue virus infection in human myelomonocyte (U937) and hepatic (Huh-7) cell lines and cytokine production in the infected monocytes. Antiviral Res. 2012;94:57–61.

40. Gruber-Bzura BM. Vitamin d and influenza-prevention or therapy?Int J Mol Sci. 2018;19(8):2419.

41. Beard JA, Bearden A, Striker R. Vitamin d and the anti-viral state.J Clin Virol. 2011;50(3):194–200. doi:10.1016/j.jcv.2010.12.006.

42. Bassey OA, Lowry OH, Brook MJ, et al. The determination of vitamin A and carotene in small quantities of blood serum. *J Biol Chem* 1964; 3: 166–170.

43. Derouiche S. Oxidative stress associated with SARS-Cov-2 (COVID-19) increases the severity of the lung disease—a systematic review. *J Infect Dis Epidemol* 2020; 6(3): 1–6.

44. Curtis JM, Hahn WS, Long EK, Burrill JS, Arriaga EA, and Bernlohr DA. Protein carbonylation and metabolic control systems. Trends Endocrinol Metab 23: 399–406, 2012.

45. Dalle-Donne I, Rossi R, Giustarini D, Milzani A, and Colombo R. Protein carbonyl groups as biomarkers of oxi-dative stress. Clin Chim Acta 329: 23–38, 2003.

46. Bloch-Damti A and Bashan N. Proposed mechanisms for the induction of insulin resistance by oxidative stress. Antioxid Redox Signal 7: 1553–1567, 2005

47. Lee, D.H., Gold, R., & Linker, R.A. (2012) Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters. Int J Mol Sci. 13 (9): 11783–11803

48 Alves, M., Bastos, M., Leitão, F., Marques, G., Ribeiro, G., & Carrilho, F. (2013) Vitamina D – importância da avaliação laboratorial. Rev Port Endocrinol, Diabetes Metab. 8 (1): 32–39.

49. Karkhanei B, Talebi Ghane E, Mehri F. Evaluation of oxidative stress

level: total antioxidant capacity, total oxidant status and glutathione activity in patients with COVID‐19. New Microbe New Infect. 2021;42:100897.

50. Muhammad Y, Kani YA, Iliya S, et al. Deficiency of antioxidants and increased oxidative stress in COVID‐19 patients: a cross‐sectional comparative study in Jigawa, Northwestern Nigeria. SAGE Open Med. 2021;9:2050312121991246.

51. Golnaz Vaseghi MM, Karimi R, Heshmat‐Ghahdarijani K, Rouhi P,Shariati M, Javanmard SH. Inflammatory markers in Covid‐19 Patients:a systematic review and meta‐analysis. medRxiv, 2020.

52. Mancˇek-Keber M, Hafner-Bratkovicˇ I, Lainšcˇek D, et al. Disruptionof disulfides within RBD of SARS-CoV-2 spike protein prevents fusion and represents a target for viral entry inhibition by registered drugs. FASEB J. 2021;35:e21651.

53. Ansari MGA, Sabico S, Clerici M, et al. Vitamin D supplementation is associated with increased glutathione peroxidase-1 levels in Arab adults with prediabetes. Antioxidants. 2020;9:118

54. Ma Q. Role of Nrf2 in oxidative stress and toxicity. Ann Rev Pharmacol Toxicol. 2013;53:401–426.

55. Wimalawansa SJ. Vitamin D deficiency: Effects on oxidative stress, epigenetics, gene regulation, and aging. Biology. 2019;8:30.

56. Sepidarkish M, Farsi F, Akbari-Fakhrabadi M, et al. The effect of vitamin D supplementation on oxidative stress parameters:A systematic review and meta-analysis of clinical trials. Pharma Res. 2019;139:141–152.

57. Chen L, Yang R, Qiao W, et al. 1,25-Dihydroxy vitamin D prevents tumorigenesis by inhibiting oxidative stress and inducing tumor cellular senescence in mice. Intl J Cancer. 2018; 143:368–382.

58. Jain SK, Parsanathan R, Achari AE, Kanikarla-Marie P, Bocchini JA. Glutathione stimulates vitamin D regulatory and glucose-metabolism genes, lowers oxidative stress and inflammation, and increases 25-hydroxy-vitamin D levels in blood:

A novel approach to treat 25-hydroxyvitamin D deficiency.Antioxid Redox Signal. 2018;29:1792–1807.

59. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF,Levine SN. Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels

in the blood of type 2 diabetic patients. Eur J Clin Nutr. 2014;68:1148–1153.

60.Mobeen Abdrabbo , Cole M. Birch ,Michael Brandt et.alVitamin D and COVID-19: A review on the role of vitamin D in preventing and reducing the severity of COVID-19 infection, Protein Science. 2021;30:2206–2220.

61. Kirkham, P.A.; Barnes, P.J. Oxidative stress in COPD. Chest 2013, 144, 266–273.

62. Polonikov A (2020) Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death in COVID-19 patients. ACS Infect Dis 6(7):1558–1562

63. Oh S-J, Lee JK, Shin OS. Aging and the Immune System: the Impact of

Immunosenescence on Viral Infection, Immunity and Vaccine Immunogenicity.

Immune Network [Internet] 2019 [cited 2020 Apr 26

64. Hekimi, S., Lapointe, J., and Wen, Y. (2011) Taking a ″good″ look at free radicals in the aging process. Trends Cell Biol. 21, 569−576.

65. Erden-Inal, M.; Sunal, E.; Kanbak, G. Age-related changes in the glutathione redox system. Cell Biochem. Funct. 2002, 20, 61–66.

66. Nguyen, D.; Samson, S.L.; Reddy, V.T.; Gonzalez, E.V.; Sekhar, R.V. Impaired mitochondrial fatty acid oxidation and insulin resistance in aging: Novel protective role of glutathione. Aging Cell. 2013, 12, 415–425.

67. Kumar, P.; Liu, C.; Hsu, J.W.; Chacko, S.; Minard, C.; Jahoor, F.; Sekhar, R.V. Glycine and N-acetylcysteine (GlyNAC) supplementation in older adults improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, and cognition: Results of a pilot clinical trial. Clin. Transl. Med. 2021, 11, e372.

68. Brenner, H.; Holleczek, B.; Schottker, B. Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic? Nutrients 2020,12, 2488.

69. Giustina, A.; Adler, R.A.; Binkley, N.; Bollerslev, J.; Bouillon, R.; Dawson-Hughes, B.; Ebeling, P.R.; Feldman, D.; Formenti, A.M.;Lazaretti-Castro, M.; et al. Consensus statement from 2(nd) International Conference on Controversies in Vitamin D. Rev. Endocr.Metab. Disord. 2020, 21, 89–116

70. V. Baktash, T. Hosack, N. Patel, S. Shah, P. Kandiah, K. Van Den Abbeele, A.K.

J. Mandal, C.G. Missouris, Vitamin D status and outcomes for hospitalised older

patients with COVID-19, Postgrad. Med. J. (2020).

71. C. Annweiler, Z. Cao, J.-M. Sabatier, Point of view: should COVID-19 patients be supplemented with vitamin D? Maturitas (2020).

72. H. Shakoor, J. Feehan, A.S. Al Dhaheri, H.I. Ali, C. Platat, L.C. Ismail,V. Apostolopoulos, L. Stojanovska, Immune-boosting role of vitamins D, C, E, zinc,

selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas

(2020).

73. Teskey, G.; Abrahem, R.; Cao, R.; Gyurjian, K.; Islamoglu, H.; Lucero, M.; Martinez, A.; Paredes, E.; Salaiz, O.; Robinson, B.; et al.Glutathione as a Marker for Human Disease. Adv. Clin. Chem. 2018, 87, 141–159.

74. Nanda, A.; Vura, N.V.R.K.; Gravenstein, S. COVID-19 in older adults. Aging Clin. Exp. Res. 2020, 32, 1199–1202.

75. Jain SK, Parsanathan R, Levine SN, Bocchini JA, Holick MF,Vanchiere JA. The potential link between inherited G6PD deficiency, oxidative stress, and vitamin D deficiency and the racial inequities in mortality associated with COVID-19. Free

Radic Biol Med. 2020;161:84–91.

76. Borges do Nascimento, I. J., Cacic, N., Abdulazeem, H. M., von Groote, T. C., Jayarajah, U., et al. (2020) Novel Coronavirus Infection (COVID-19) in Humans: A Scoping Review and Meta-Analysis. J. Clin. Med. 9, 941.

77.Gender differences in the prevalence of vitamin D deficiency in a southern Latin American country: a pilot study [M. S. Vallejo](https://www.tandfonline.com/author/Vallejo%2C+M+S) ,[J. E. Blümel](https://www.tandfonline.com/author/Bl%C3%BCmel%2C+J+E),[E. Arteaga](https://www.tandfonline.com/author/Arteaga%2C+E),[S. Aedo](https://www.tandfonline.com/author/Aedo%2C+S) ,[V. Tapia](https://www.tandfonline.com/author/Tapia%2C+V),[A. Araos](https://www.tandfonline.com/author/Araos%2C+A) ,[show all](https://www.tandfonline.com/doi/abs/10.1080/13697137.2020.1752171) Pages 410-416 | Received 14 Aug 2019, Accepted 01 Apr 2020, Published online: 05 May 2020

78..Lee, D.H., Gold, R., & Linker, R.A. (2012) Mechanisms of oxidative damage in multiple sclerosis and neurodegenerative diseases: therapeutic modulation via fumaric acid esters. Int J Mol Sci. 13 (9): 11783–11803.

79. Dincer, Y.; Ozen, E.; Kadioglu, P.; Hatemi, H.; Akçay, T. E\_ect of sex hormones on lipid peroxidation in women with polycystic ovary syndrome, healthy women, and men. Endocr. Res. 2001, 27, 309–316.

80. Bukowska, A.; Spiller, L.; Wolke, C.; Lendeckel, U.; Weinert, S.; Ho\_mann, J.; Bornfleth, P.; Kutschka, I.;

Gardemann, A.; Isermann, B.; et al. Protective regulation of the ACE2/ACE gene expression by estrogen in

human atrial tissue from elderly men. Exp. Biol. Med. 2017, 242, 1412–1423. [

81. Annweiler, C.; Hanotte, B.; Grandin de l’Eprevier, C.; Sabatier, J.M.; Lafaie, L.; Celarier, T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J. Steroid Biochem. Mol. Biol. 2020, 204, 105771.