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## Hypothesis Paper

The potential link between inherited G6PD deficiency, oxidative stress, and vitamin D deficiency and the racial inequities in mortality associated with COVID-19<sup>☆</sup>Sushil K. Jain<sup>a,b,\*</sup>, Rajesh Parsanathan<sup>a,b</sup>, Steve N. Levine<sup>c</sup>, Joseph A. Bocchini<sup>d</sup>, Michael F. Holick<sup>e</sup>, John A. Vanchiere<sup>a</sup><sup>a</sup> Department of Pediatrics, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130, USA<sup>b</sup> Center for Cardiovascular Diseases and Sciences, Louisiana State University Health Sciences Center, Shreveport, LA 71130, USA<sup>c</sup> School of Medicine, Section of Endocrinology & Metabolism, Louisiana State University Health Sciences Center, Shreveport, LA 71130, USA<sup>d</sup> Department of Pediatrics, Tulane University, 2508 Bert Kouns Industrial Loop, Suite 103, Shreveport, LA 71118, USA<sup>e</sup> Section of Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Vitamin D, Skin, and Bone Research Laboratory, Boston University School of Medicine, Boston, MA, USA

## A B S T R A C T

There is a marked variation in mortality risk associated with COVID-19 infection in the general population. Low socioeconomic status and other social determinants have been discussed as possible causes for the higher burden in African American communities compared with white communities. Beyond the social determinants, the biochemical mechanism that predisposes individual subjects or communities to the development of excess and serious complications associated with COVID-19 infection is not clear. Virus infection triggers massive ROS production and oxidative damage. Glutathione (GSH) is essential and protects the body from the harmful effects of oxidative damage from excess reactive oxygen radicals. GSH is also required to maintain the VD-metabolism genes and circulating levels of 25-hydroxyvitamin D (25(OH)VD). Glucose-6-phosphate dehydrogenase (G6PD) is necessary to prevent the exhaustion and depletion of cellular GSH. X-linked genetic G6PD deficiency is common in the AA population and predominantly in males. Acquired deficiency of G6PD has been widely reported in subjects with conditions of obesity and diabetes. This suggests that individuals with G6PD deficiency are vulnerable to excess oxidative stress and at a higher risk for inadequacy or deficiency of 25(OH)VD, leaving the body unable to protect its 'oxidative immune-metabolic' physiological functions from the insults of COVID-19. An association between subclinical interstitial lung disease with 25(OH)VD deficiencies and GSH deficiencies has been previously reported. We hypothesize that the overproduction of ROS and excess oxidative damage is responsible for the impaired immunity, secretion of the cytokine storm, and onset of pulmonary dysfunction in response to the COVID-19 infection. The co-optimization of impaired glutathione redox status and excess 25(OH)VD deficiencies has the potential to reduce oxidative stress, boost immunity, and reduce the adverse clinical effects of COVID-19 infection in the AA population.

## 1. Introduction

Clinical symptoms in people with SARS-CoV-2 viral infection (COVID-19) infection include cough, shortness of breath, and difficulty breathing. These symptoms are reported to range from mild to severe. While symptoms may appear 2–14 days after exposure to the virus, some people infected with COVID-19 do not display any symptoms—the clinical symptoms and mortality associated with COVID-19 show racial and ethnic disparities. The rates of hospitalization and severity associated with COVID-19 are highest in the AA males [1,2]. Previous reports suggest that AA are more likely to be exposed to COVID-19 due to social determinants, such as low socioeconomic status, employment in jobs

considered essential during the pandemic, and a greater reliance on public transportation, all of which lead to greater potential exposure. In addition, a disproportionately higher percentage of AA has underlying health conditions, such as diabetes and hypertension. The incidence and severity of infection associated with COVID-19 and G6PD deficiency are higher in males, and both are higher in AA.

The reasons why AA have died from the disease at almost three times the rate of whites and have a disproportionately higher rate of severe complications as a result of the coronavirus pandemic is not understood. This paper reviews the literature and discusses the mechanistic evidence-based hypothesis for an interdependent link between G6PD and 25(OH)VD deficiencies with the COVID-19 associated higher risk in

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the AA population. The molecular mechanisms underlie the potential role of the inherited genotypes and co-morbidity-associated phenotypes combined with viral infection-mediated excess oxidative stress in the disproportionately higher mortality rate in AA.

### 1.1. The link between infection, excess oxidative stress, and inflammation

Current studies in the literature report excess vitamin D deficiency [3–12] and elevated levels of proinflammatory cytokines such as IL6, IL1b, and TNF (cytokine storm) in the blood [13–18] and its link with the outcome in COVID-19 patients. There are limited data available in the literature concerning the biochemical mechanisms by which COVID-19 infection causes cellular dysfunction. The activation of a macrophage respiratory burst in response to infection with COVID-19 can induce the onset of ROS production and inflict oxidative damage to the host's tissues. ROS contribute to the oxidative damage that persists at the chronic stage of infection and is involved in functional impairment of the various tissues [19]. ROS is considered to be involved in eliminating pathogens, but recent studies suggest that viral growth is stimulated in an oxidative environment. ROS may facilitate viral entry and thereby promote viral infectivity. Oxidative stress helps viral growth during the acute stage, and at the chronic stage, it participates in tissue damage [20–22]. Viral infection triggers massive ROS production. Suppose ROS production increases to levels that cannot be neutralized by the body's defense mechanisms, including innate immunity and antioxidant defenses. In that case the ROS will damage biological molecules, alter their functions, leading to a spectrum of pathologies.

It has been shown that systemic oxidation (redox potentials Eh Cys/CySS) correlated with decreased lung function in subjects with chronic obstructive pulmonary disease (COPD) with HIV infection compared with subjects with healthy lung function [23]. Viral infections such as HIV, influenza A, respiratory syncytial virus (RSV), and enterovirus 71 induce oxidative stress and are more frequently inhibited by antioxidants such as NAC [21]. Ebselen, a leading compound used in COVID-19 therapy, is a glutathione peroxidase and peroxiredoxin enzyme mimetic compound with pleiotropic effects of an antiviral, antibacterial, and anti-inflammatory nature [24]. Specialized cells such as neutrophils and macrophages produce superoxide free radicals and H<sub>2</sub>O<sub>2</sub> as a physiological defense against invading viruses to help destroy them and halt the virus's replication and its harmful effects on tissues. Overproduction and ROS failure to discriminate between exogenous pathogens such as

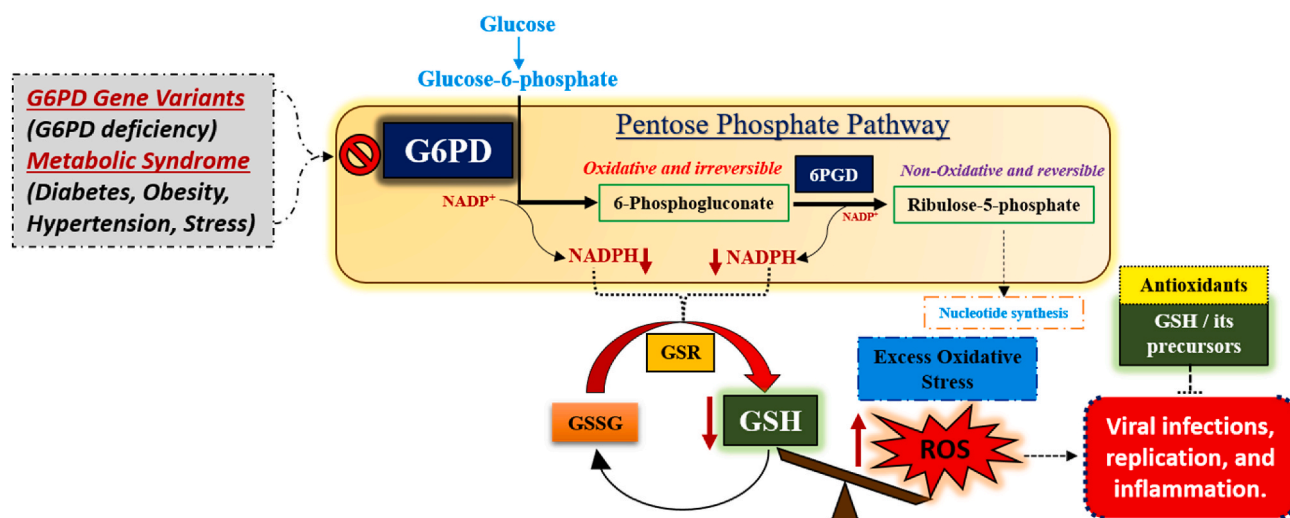
SARS-CoV-2 and endogenous host tissue may result in the tissue damage following SARS-CoV-2 infection.

### 1.2. Inherited G6PD deficiency in African Americans induces glutathione (GSH) depletion and excess oxidative stress

G6PD catalyzes the rate-limiting step in the pentose phosphate pathway, which provides nicotinamide adenine dinucleotide phosphate reduced form (NADPH). NADPH catalyzes the recycling of oxidized glutathione (GSSG) to glutathione (GSH), a potent physiological antioxidant. G6PD catalyzes the production of NADPH essential to fuel glutathione recycling [25]. GSH is paramount to an oxidant defense, and G6PD deficient cells do not cope well with oxidative stress (Fig. 1).

An estimated 400 million people worldwide are affected by G6PD deficiency, which is more prevalent on the African continent, in the Middle East, and Southeast Asia [26–29]. G6PD deficiency is the most common X-linked inherited trait and affects ~7% of the global population [26]. Both male hemizygotes and female homozygotes with G6PD gene deficiency had significantly lower G6PD enzyme activity, while 80% of female heterozygotes had intermediate G6PD enzyme activity [26–30]. Out of five classes of G6PD, deficiency based on enzyme activity levels, the G6PD A<sup>-</sup> variant is associated with mild-to-moderate enzyme deficiency (class III) with residual enzyme activity (10–60%) and is recognized predominately in AA. G6PD deficiency G6PD A<sup>-</sup> variant (class III) incidence with 10–60% residual enzyme activity is nearly 14% in AA compared with only 1% in whites [28,29]. AA males (12.2%) and females (4.1%), along with Asian males (4.3%), have the highest rates of G6PD deficiency [27]. Cellular respiration in an oxygen-rich environment leads to the generation of reactive oxygen species (ROS). These reactive oxygen species can readily react with biological molecules, often modifying their normal biological functions. Antioxidant enzyme mechanisms have evolved to eliminate ROS and minimize oxidative damage. Inherited or acquired deficiencies of crucial antioxidant enzymes lead to a dysregulated redox environment, promoting pathobiology.

G6PD deficiency may have evolved as a form of protection from infection by the malaria parasite *Plasmodium vivax* [30], but it has many adverse effects. Although G6PD deficient subjects are generally asymptomatic throughout their lives, this genetic condition's clinical burdens includes a range of hematological conditions, such as neonatal jaundice and hemolytic anemia [31]. Hemolysis in patients using



**Fig. 1.** Genetic variations of G6PD or metabolic syndrome (diabetes, obesity, hypertension, stress) reduce G6PD activity and cause G6PD deficiency. G6PD deficiency causes NADPH depletion, leading to decreased glutathione (GSH) recycling, which induces reactive oxygen species (ROS). Excess oxidative stress may favor viral infection, replication, and inflammation. Conversely, viral infections, replications, and inflammation are more frequently inhibited by antioxidants (GSH or its precursors, such as N-acetyl cysteine and l-cysteine).

primaquine is thought to be a significant clinical manifestation of G6PD deficiency and contributes to the *Plasmodium vivax* infection [31]. G6PD-deficient mice are more susceptible to ventricular dilation in response to myocardial infarction or pressure overload-induced heart failure. G6PD-deficient heart tissue, which does not recover and healthy heart tissue from ischemia-reperfusion injury, is susceptible to cardiac hypertrophy. The adverse effects of G6PD deficiency may outweigh the potential protective effects of G6PD, particularly in the case of cardiac stress [32].

G6PD-deficient AA subjects showed excess oxidative stress and lower levels of glutathione (GSH) [33]. G6PD deficiency reduces the amount of NADPH required for the formation of nitric oxide (NO) [34,35]. G6PD-deficient endothelial cells demonstrate reduced expression of endothelial nitric oxide synthase and NO levels along with reduced GSH [35]. Decreased NO and increased oxidative stress (OS) impairs endothelial [34,35] and macrophage function [36] and increases inflammatory cytokines, such as tumor necrosis factor (TNF) and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells and monocytes [34,35]. G6PD deficiency alters macrophage polarization and the expression of inflammatory cytokines in human monocytes [29]. Subjects with G6PD deficiency have an increased risk for elevated systolic blood pressure, cardiovascular disease, fibrosis, autoimmune diseases, infections, and metabolic disorders [28,29,37,38].

### 1.3. Acquired impairment of G6PD under psychological stress (aldosterone) and other co-morbidity conditions

Psychosocial stress experienced by AA may account for the observed racial differences in the disease outcome [39–41]. Psychological stress activates both the HPA axis and the sympathetic adrenomedullary system, and aldosterone may be released in response to psychological stress. Pathological consequences of excess mineralocorticoid activity in stress include high blood pressure [42]. Activation of the mineralocorticoid receptor by aldosterone stimulates the inflammatory phenotype in adipocytes and contributes to IR by increasing oxidative stress [43]. Overactivation of aldosterone is associated with hyperglycemia, dyslipidemia, higher insulin resistance, and lower HDL. *In vitro* and *in vivo* infusion of aldosterone decreases vascular G6PD expression and impairs vascular reactivity [44]. Aldosterone increases oxidative stress, decreases G6PD activity, and impairs vascular reactivity [44]. Aldosterone induces a G6PD-deficient phenotype, impairs endothelial function; gene transfer of G6PD improves vascular reactivity by restringing G6PD [44]. Thus, excess psychological stress and increased aldosterone levels can further lower the G6PD activity in those with the genetic G6PD variant phenotype. Hyperglycemia levels and diabetes are independent predictors of mortality and morbidity in patients with SARS-CoV-2 infection [45,46]. Hyperglycemia, diabetes, oxidative stress favors glycosylation of proteins, which can further diminishes G6PD activity and its protective mechanisms particularly in those who has inherited G6PD-deficiency [47–49]. In addition, a recent study shows that high induces von Hippel–Lindau (VHL) protein, an E3 ubiquitin ligase subunit, directly bound to G6PD and degraded G6PD through ubiquitylating G6PD on Lysine 366 and 403 residues [50]. Potential role of GSH or G6PD-deficiency has been discussed in coronavirus infection [38,51,52]. The increase in oxidative stress and deficiency of GSH and G6PD increases protein glycation Fig. 1 summarizes that the presence of obesity, oxidative stress, hyperglycemia and diabetes further decreases G6PD and GSH. This indicates that the psychosocial stress, a high incidence of inherited G6PD deficiency (nearly 14% in AA versus 1% in whites), along with obesity and diabetes, is a triple burden and magnify the increases in oxidative stress, impairment in immune defense mechanisms, and increases the risk of COVID-19 infection in AA. This can result in the intensification of cytokine storm and impaired immunity, making the AA population more susceptible to infection and the mortality associated with COVID-19.

### 1.4. Impairment in glutathione (GSH) biosynthesis and excess oxidative stress in chronic diseases

GSH is formed from L-cysteine (LC), glycine, and glutamate by the enzymatic action of glutamate-cysteine ligase and glutathione synthetase [53–55]. LC is a rate-limiting factor in GSH synthesis [53]. GSH is a major antioxidant and reflects the *in vivo* defense against oxidative stress [53]. Glucose-6-phosphate dehydrogenase (G6PD) catalyzes the production of nicotinamide adenine dinucleotide phosphate reduced form (NADPH). Glutathione reductase requires NADPH to recycle oxidized glutathione (GSSG) to GSH. Lower GSH levels can occur because LC is not available in the food consumed, or it can result from the consumption of an energy-rich diet, which increases ROS and oxidative stress. GSH depletion increases oxidative stress and extensive carbonylation of proteins and modifies endogenous enzymes and proteins, resulting in impaired cellular function [56]. [56–58].

Blood levels of GSH are lower in AA, presumably due to lower consumption of L-cysteine and a deficiency of G6PD (Fig. 1). The incidence of G6PD is nearly 11% in AA, compared with 1% in whites [28,29,59]. Diabetes *per se* results in lower GSH levels in diabetic animals and patients [60–62]. Under stressful situations, such as diabetes, G6PD-deficient cells cannot regenerate enough NADPH, which exacerbates GSH deficiency and oxidative stress [63,64] and can contribute to GSH and 25(OH)VD deficiencies in AA. G6PD deficiency conditions also influence the polarization and the expression of inflammatory cytokines in human monocyte and macrophage cells that play vital roles in the innate immune defense against invading pathogens and in support of adaptive immunity. The presence of diabetes and hyperglycemia tends to shift monocytes towards a functionally proinflammatory phenotype, which induces chronic inflammation and insufficient M2 functional profibrotic TGF- $\beta$  signaling [29] similar to that seen in G6PD-deficient subjects.

*In vitro* studies showed that partial depletion of the intracellular GSH pool could negatively impair T cells' immune regulatory potential [65]. The intracellular glutathione redox status is also linked to the production of proinflammatory cytokines, such as IFN and IL-4, which regulate IL-12 and T-cell differentiation [66]. GSH or its precursor L-cysteine has been used to replenish intracellular GSH levels in antiviral therapy. Deficiency of G6PD or GSH has been implicated in increasing the inflammation and respiratory distress common to various diseases, such as diabetes, chronic obstructive pulmonary disease, and several viral infections, including HIV [55,67–70].

### 1.5. Effect of glutathione (GSH) status on circulating 25(OH)VD levels

The blood levels of 25(OH)VD show a positive correlation with glutathione and redox status in healthy adults, children, diabetic patients, and AA subjects [5,56,62,71–76]. Similarly, a correlation exists between serum 25(OH)VD and total antioxidant capacity in adult diabetics and obese adolescents [77,78]. Dietary antioxidant consumption increases serum 25(OH) D [79]. Circulating 25(OH)VD is considered a stable metabolite with which to monitor VD consumption and diagnose 25(OH)VD deficiencies [80].

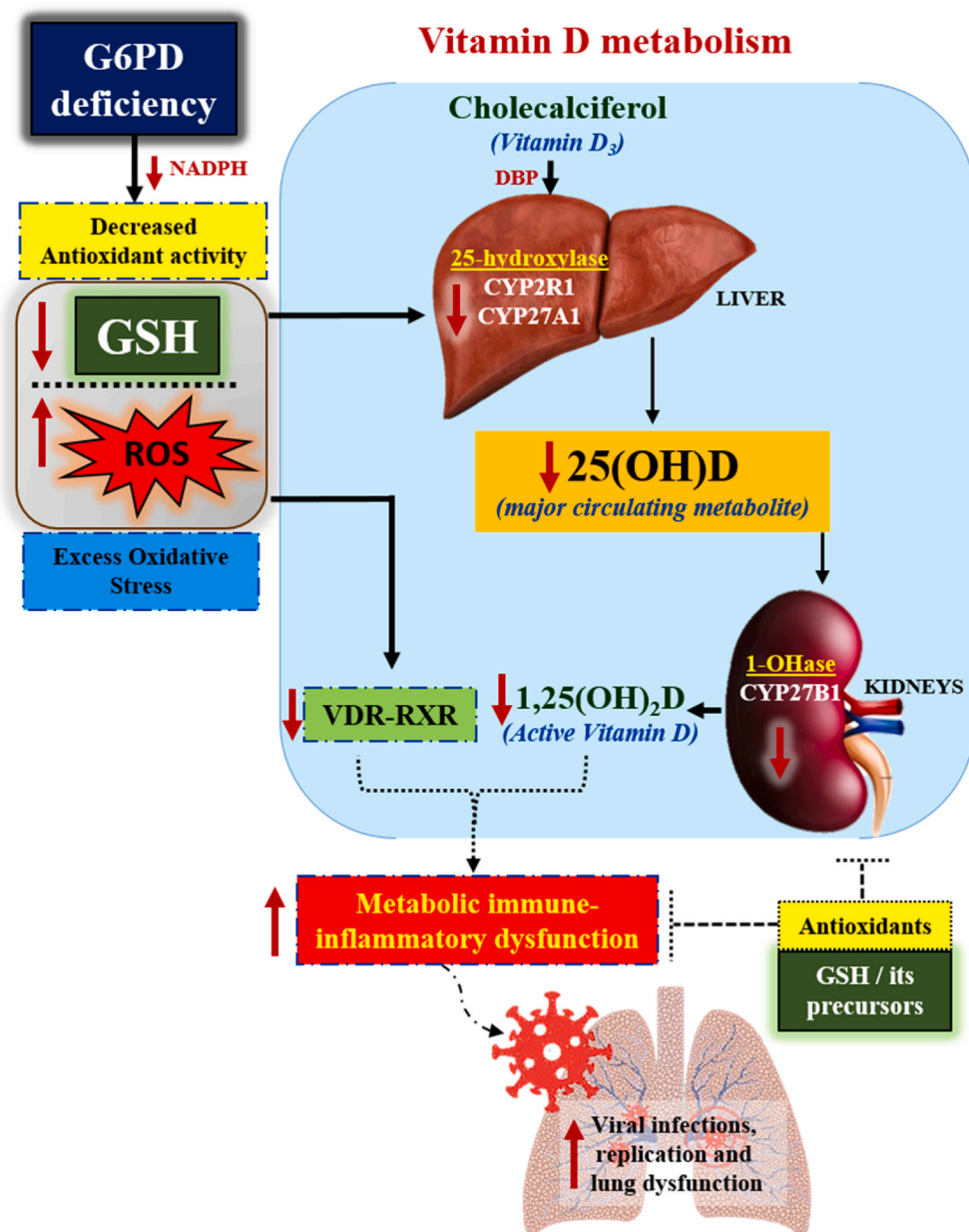
Animal studies have shown that low levels of GSH downregulate the VD-regulatory (VDBP/VD-25-hydroxylase/VDR) and glucose-metabolism (PGC-1 $\alpha$ /VDR/GLUT-4) genes in the liver, kidney, and muscle of HFD-fed mice and diabetic rats [56,58,73,81]. Co-supplementation with VD and L-cysteine (a GSH precursor) had significant positive results on increasing GSH compared with supplementation with VD alone in ZDF rats and a mouse model of 25(OH)VD deficiency [56,73]. These included upregulated VD-regulatory genes in the liver and glucose-metabolism genes in muscle, increased levels of 25(OH)VD, reduced lipid peroxidation, and lower levels of protein carbonyl and TNF in the blood [56].

Cell culture studies showed that GSH deficiency induced *in vitro* caused increased oxidative stress, downregulation of VDBP/VD-25-

hydroxylase/VDR, upregulation of CYP24A1 in hepatocytes, and downregulation of PGC-1 $\alpha$ /VDR/GLUT-4 in myotubes [56]. We recently showed that GSH deficiency epigenetically alters VD-biosynthesis pathway genes in HFD-fed obese mice. Replenishment of GSH beneficially altered epigenetic enzymes and VD-metabolism genes in hepatocytes [57]. These studies suggest a significant role of GSH deficiency in the molecular mechanisms contributing to the VD deficiency and the potential benefits of GSH optimization in reducing 25(OH)VD deficiency (Fig. 2). Further obesity and diabetes conditions accelerate the rate of GSH utilization and depletion, which alters redox homeostasis [56–58, 82–84]. Conversely, VD supplementation also suppresses oxidative stress by ameliorating the Nrf2–Keap1–GSH biosynthesis pathway. Studies have indicated an association between vitamin D deficiency and reduced antioxidant capacity or increased oxidative stress [62,85–90]. These studies indicate that lower GSH levels are linked to 25(OH)VD deficiency/inadequacy. The simultaneous co-optimization of GSH is required for the success of the VD supplements widely consumed by the public for better health (Fig. 2).

### 1.6. The epidemic of vitamin D deficiency and inadequacies

Vitamin D (where D represents vitamin D<sub>2</sub> and vitamin D<sub>3</sub>) ingested in the diet or produced in the skin from sun exposure is transported by the vitamin D binding protein (DBP) to the liver, where it is metabolized by vitamin D-25-hydroxylase(s) (CYP2R1, CYP27A1) to 25-hydroxyvitamin D [25(OH)VD] (45,46). 25(OH)VD, the major circulating form of vitamin D, has a half-life of approximately 2–3 weeks and is the clinical marker used to determine a person's vitamin D status [91–94]. 25(OH)VD enters the circulation and is bound to DBP. This complex binds to megalin in the renal tubules and is internalized, releasing 25(OH)VD for its conversion by 25-hydroxy-vitamin D-1 alpha-hydroxylase (CYP27B1) to biologically active form 1,25-dihydroxy vitamin D [1,25(OH)<sub>2</sub>D]. 1,25(OH)<sub>2</sub>D interacts with its nuclear vitamin D receptor (VDR) in the intestine to increase the efficiency of intestinal calcium absorption [91–94]. The skeleton interacts with VDR in osteoblasts, resulting in the production of the receptor activator of NF kappa B ligand (RANKL). This protein interacts with the receptor activator of NF kappa B (RANK) on monocytes, inducing them to become osteoclasts, which releases



**Fig. 2.** G6PD deficiency causes NADPH depletion, leading to decreased glutathione (GSH) recycling, which induces reactive oxygen species (ROS). Cholecalciferol (free vitamin D) is transported in the blood and liver by a specific vitamin D-binding protein (DBP). Decreased antioxidant activity and excess oxidative stress (GSH deficient) decreases vitamin D (VD) metabolism genes in the liver (25-hydroxylases: CYP2R1, CYP27A1) and the kidneys (1- $\alpha$ -hydroxylase: CYP27B1), which contributes to reduced circulating levels of 25(OH)VD (major circulating metabolite) and a decline in levels of 1,25(OH)<sub>2</sub>D (active vitamin D form). GSH depletion can contribute to metabolic immune-inflammatory dysfunction, which may favor excess viral infection and lung dysfunction. Antioxidants (GSH or its precursors, such as N-acetyl cysteine and L-cysteine) may act as an adjuvant therapeutic target for normalizing the VD status in disease vulnerable populations.

skeletal calcium into the circulation to maintain calcium homeostasis. The renal production of 1,25(OH)<sub>2</sub>D is tightly regulated by a variety of factors including parathyroid hormone, fibroblast growth factor 23, 1, 25(OH)<sub>2</sub>D, and phosphate [91–94]. Besides, once 1,25(OH)<sub>2</sub>D enters the cell and interacts with the VDR to initiate its biological response, it simultaneously induces 25-hydroxyvitamin D-24-hydroxylase (CYP24A1). This enzyme hydroxylates 1,25(OH)<sub>2</sub>D on carbons 24 and 23, followed by oxidation, forming a water-soluble, biologically inactive carboxylic acid metabolite, calcitriol, which is eliminated in the bile. Many other tissues in the body, including immune cells, also have VDR and can locally produce 1,25(OH)<sub>2</sub>D [93,94]. The circulating and cellular levels of 1,25(OH)<sub>2</sub>D (calcitriol) are regulated by cellular CYP27B1, CYP24A1, and circulating PTH concentrations. The biological actions of 1,25(OH)<sub>2</sub>D are directly related to the status of VDR in target tissues where translocation of 1,25(OH)<sub>2</sub>D/VDR to the nucleus regulates transcription of target genes.

Risk factors for vitamin D deficiency include race, higher BMI, winter season, higher geographic latitudes, and inadequate dietary intake [95]. Darker skin pigmentation can potentially reduce the skin's ability to produce vitamin D from sun exposure in AA [91,92,96]. The increasing prevalence of metabolic syndrome disorders, such as obesity and diabetes, inadequate sun exposure, and food habits, has contributed to the epidemic of vitamin D deficiency or inadequacy in populations worldwide, particularly in the darker skin people.

### 1.7. The link between vitamin D deficiency and impaired immunity and lung disease

Low serum 25(OH)-vitamin D have been independently linked to the higher incidences of subclinical interstitial lung disease and chronic obstructive pulmonary disease. Boosting circulating 25(OH)-vitamin D levels has lowered the incidence and infectivity of influenza A, retrovirus, and dengue virus infection [97]. Vitamin D supplementation upregulates and induces innate anti-microbial and antiviral defense mechanisms, including induction of the anti-microbial peptide cathelicidin and interleukin-17 and downregulation of the lymphocyte membrane receptors that promote virus infectivity thereby reducing the adverse clinical effects of infection [98]. Alpha-1-antitrypsin is critical for optimal lung functions because it prevents elastin degradation by inhibiting neutrophil elastase. Excess elastin degradation caused by alpha-1-antitrypsin-deficiency impairs elastin's recoiling and causes breathing complications and chronic obstructive pulmonary disease. The deficiency of 25(OH)VD has been shown to cause down-regulation of alpha-1-antitrypsin expression in the lungs and emphysema in animals exposed to cigarette smoke [99]. Type 2 diabetic patients have reduced circulating 25(OH)VD and alpha-1-antitrypsin, as well as a significant positive correlation between 25(OH)VD and alpha-1-antitrypsin levels [100]. Various human studies have observed an association of a decrease in lung function with higher incidences of deficiency and insufficiency in circulating levels of 25(OH)VD and that of alpha-1-antitrypsin [101,102]. 1,25(OH)<sub>2</sub>D interacts with the macrophage's VDR to induce the production of defensin proteins, including cathelicidin, which can fight infectious agents. The anti-microbial, antiviral, and anti-inflammatory actions of vitamin D metabolites may be severely diminished or missing altogether in the vulnerable vitamin D-deficient AA population. Vitamin D optimization has the potential to increase immunity and prevent or reduce inflammatory responses and the risk of acute respiratory tract infections in subjects infected with COVID-19.

### 1.8. Co-optimization of vitamin D and glutathione levels

The most promising strategies to alleviate symptoms and potentially prevent Covid-19 associated morbidity and mortality are antiviral drugs and the development of strain-specific vaccines. The disease's worst effects are attributed to an over-exuberant immune response and

subsequent cytokine storm that cause localized tissue damage and systemic illness. In the absence of strain-specific vaccines, strategies to modulate or prime an appropriate immune response irrespective of the infecting strain could provide protection and reduce the adverse clinical impact of COVID-19 viral infection. Vitamin D and GSH natural products have tremendous potential to scavenge superoxide and other ROS generated in response to infection, boost immune defensive pathways, and protect against the excessive oxidative damage and pathology associated with respiratory infections and COVID-19. Improvement in the cellular redox status will prevent the inflammation, cytokine storm, and viral replication. Vitamin D and L-cysteine co-supplementation provide an alternate strategy to boost bodily defenses in fighting COVID-19 and accelerating the clearance of viral infection in the absence of a COVID-19 vaccine.

The disconnect between the convincing association of low levels of 25(OH)VD and poor health with VD supplementation therapy's limited success in clinical trials is puzzling [103–106]. We believe that the co-optimization approach using vitamin D and L-cysteine is likely to be successful and superior to supplementation with vitamin D alone. An improvement in cellular GSH status will be beneficial and is required for the bioavailability and efficacy of consumed VD. Evidence supporting this argument can be derived from various direct and indirect studies in the literature. Human studies report a significant correlation among the levels of 25(OH)VD and that of the glutathione in the blood of healthy subjects, diabetic patients, and in African Americans [5,56,62,71–76]. Glutathione upregulates the VD-metabolism genes required for the efficient transport and hydroxylation of cholecalciferol to 25(OH)VD and the biosynthesis and the metabolic actions of 1,25(OH)<sub>2</sub>VD at the cellular level in target tissues [56–58,73]. GSH deficiency epigenetically alters VD biosynthesis pathway genes in HFD-fed obese mice [57]. GSH beneficially alters epigenetic enzymes and VD-metabolism genes in hepatocytes [57]. GSH precursor L-cysteine and vitamin D are antioxidants. Vitamin D is lipophilic, and LC is hydrophilic; acting together, they are more likely to effectively neutralize oxidative injury and provide more reliable antioxidative and anti-inflammatory protection. Animal studies also demonstrate the significant benefit of optimizing the levels of both GSH and VD-regulatory genes at the cellular/tissue level, in increasing 25(OH)-vitamin D levels and in reducing oxidative stress, TNF, and inflammation biomarkers in the circulation following co-supplementation with vitamin D and L-cysteine compared with vitamin D alone supplementation.

Clinical studies demonstrate an association of excess 25-hydroxyvitamin D deficiency with the severity and outcome of patients infected with COVID-19 [3,107–111]. We believe there is potential for co-optimization of 25-hydroxy-vitamin D and L-cysteine in boosting the body's immunity and defenses to fight the excess oxidative stress and adverse clinical effects of COVID-19 infection.

## 2. Summary and conclusions

COVID-19 associated higher incidence of morbidity and mortality reported in minority populations; excess oxidative stress and vitamin D deficiencies are also more present in racial minorities along with comorbid conditions such as obesity and diabetes [1,72–76,112–115]. Fig. 3 summarizes the proposed effects of the inherited glucose-6-phosphate-dehydrogenase (G6PD) gene variant and vitamin D deficiency on increased coronavirus (COVID-19) associated morbidity and mortality and the potential benefits of GSH + vitamin D supplementation in lowering inflammation and boosting immunity and thereby protection from COVID-19 [116]. Compared with whites, the incidences of inherited G6PD deficiency and 25(OH)VD deficiency are markedly higher in the AA population. This increases the risk of excess oxidative stress and impairment in the activities of specialized immune cells and, thus, the body's ability to fight infection. Upregulation of the intracellular glutathione redox status may provide a new therapeutic option for influencing the Th1/Th2 balance and preventing

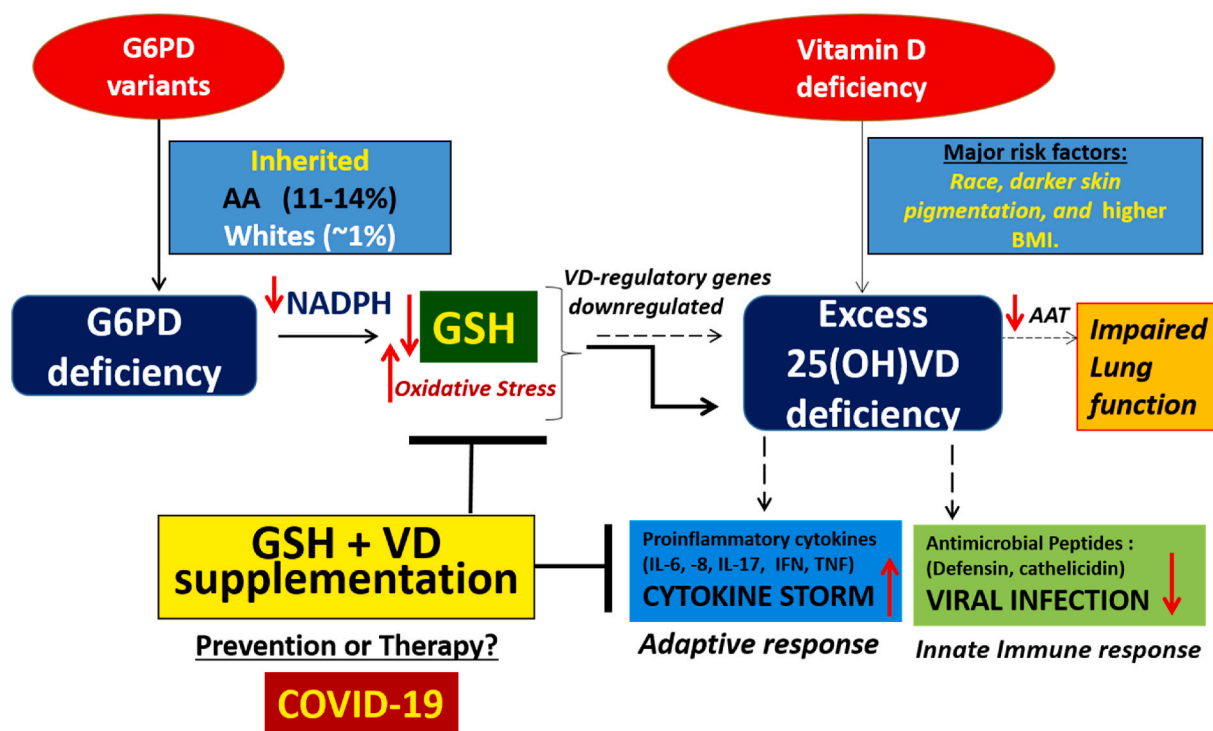


Fig. 3. Proposed effects of excess inherited G6PD gene variant and 25(OH)VD deficiency on the coronavirus infection (COVID-19) and mortality and the benefits of combined GSH + Vitamin D supplementation.

inflammation and impaired immunity in subjects exposed to COVID-19. The body's immune function is the main factor determining how an individual patient responds to the coronavirus infection. We hypothesize that the overproduction of ROS is responsible for the oxidative damage, secretion of a cytokine storm, and onset of pulmonary dysfunction in response to the COVID-19 infection. We believe that combined supplementation using vitamin D along with the GSH precursor L-cysteine could potentially correct the status of GSH, vitamin D metabolism genes, and the biologic action of vitamin D [56,57]. Recent studies have shown that vitamin D deficiency is linked to the hospitalization length of COVID-19 infected subjects [3,107–111]. Whether there is an association between G6PD deficiency and excess oxidative stress with the severity of COVID-19 in AA needs investigation.

Vaccination, which is not yet available, or previous exposure to the virus, is expected to provide immunity to infection with COVID-19. The degree of protection from a vaccine and how long that protection might last is unknown. The available literature suggests the potential benefits of enhancing immunity and reducing inflammation can help prevent or reduce the adverse effects of COVID-19 infection in the AA population by increasing circulating levels of 25(OH)VD using oral supplementation with vitamin D and a GSH precursor, L-cysteine.

#### Declaration of competing interest

The authors declare no competing interests. MFH is a former consultant for Quest Diagnostics, a consultant for Ontometrics, Inc. and is on the speaker's bureau for Abbott.

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