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Can Vitamin D and L-Cysteine Co-Supplementation Reduce 25(OH)-Vitamin D Deficiency and the Mortality Associated with COVID-19 in African Americans?

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ABSTRACT

Early reports indicate an association between the severity of the COVID-19 infection and the widespread 25-hydroxy vitamin D deficiency known to exist in populations around the world. Vitamin D deficiency is extremely common among African American (AA) communities, where the COVID-19 infection rate is three-fold higher, and the mortality rate nearly six-fold higher, compared with rates in predominantly white communities. COVID-19 infection primarily affects the lungs and airways. Previous reports have linked 25-hydroxy vitamin D deficiency with subclinical interstitial lung disease. AA are at risk for lower cellular glutathione (GSH) levels, and GSH deficiency epigenetically impairs VD biosynthesis pathway genes. Compared with vitamin D alone, co-supplementation of vitamin D and L-cysteine (a GSH precursor) showed a better efficacy in improving levels of GSH and VD-regulatory genes at the cellular/tissue level, increasing 25(OH) vitamin D levels, and reducing inflammation biomarkers in the blood in mice studies. We propose that randomized clinical trials are needed to examine the potential of co-supplementation with anti-inflammatory antioxidants, vitamin D and L-cysteine in correcting the 25(OH)VD deficiency and preventing the 'cytokine storm,' one of the most severe consequences of infection with COVID-19, thereby preventing the adverse clinical effects of COVID-19 infection in the vulnerable AA population.

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Vitamin D; glutathione; COVID-19; L-cysteine; African American

Introduction

The Centers for Disease Control and Prevention (CDC) has reported that African Americans (AA) have the highest age-adjusted case rate for contracting coronavirus disease (COVID-19), a higher rate of hospitalization, and are more likely to die compared to white Americans (Caucasians) (1, 2). Studies from different parts of the world demonstrate how the association between 25(OH) vitamin D deficiency (3–12) and elevated pro-inflammatory cytokine levels (cytokine storm) (13–18) affects the severity and outcome in subjects infected with COVID-19.

High risk of 25(OH) vitamin D deficiency in AA

Two-thirds of the US population, particularly African Americans (AA), are at risk for inadequate or deficient levels of 25-hydroxy vitamin D (25(OH)D) (5, 19, 20). This is caused in part due to their increased skin pigmentation, which functions not only as a natural sunscreen, but it also significantly reduces the ability of the skin to produce vitamin D from sun exposure. The bioavailability of 25(OH)VD in response to ingesting VD supplements varies significantly among individual subjects and is dependent on the status of the VD-metabolism genes (21–24). Acquired risk factors for vitamin D deficiency include race, higher BMI, winter season, higher geographic latitudes, and inadequate dietary intake (21). 25(OH)VD biosynthesis mainly occurs in the liver by the action of VD-25hydroxylase (CYP2R1, CYP27A1) on cholecalciferol consumed from diet or formed during the skin exposure to Ultraviolet B from sunlight . 25(OH)VD is transported into the circulation bound to VDBP/GC. 25(OH)VD conversion to its active metabolite (1,25(OH)2VD) is catalyzed by CYP27B1 present in both renal (primary site) and non-renal tissues. Catabolic inactivation of 25(OH)VD and 1,25(OH)2D3 by CYP24A1 is thought to limit 1,25(OH)2D3 signaling. The circulating and cellular levels of 1,25(OH)2VD (calcitriol) are regulated by cellular CYP27B1, CYP24A1, and circulating PTH concentrations. The biological actions of 1,25(OH)2 VD are directly related to the status of VDR in target tissues where translocation of 1,25(OH)2VD/VDR to the nucleus regulates transcription of target genes. The incidence of vitamin D deficiency or inadequacy is on the rise because of the increasing prevalence of metabolic syndrome disorders, such as obesity and diabetes, as well as inadequate sensible sun exposure. Circulating 25(OH)VD is considered a comprehensive and stable metabolite to diagnose 25(OH)VD deficiencies and monitor VD consumption. According to the clinical practice guidelines recommended by the Endocrine Society, vitamin D deficiency was defined as 25(OH)D < 50 nmol/l and vitamin D-inadequacy as

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$50 \leq 25(OH)D < 75$ nmol/l. Clinical studies have demonstrated an association between better health outcomes and higher blood levels of 25(OH)D (5, 19, 20, 23, 24).

Role of glutathione (GSH) in VD metabolites biosynthesis and metabolism

Human studies from different laboratories have reported the existence of a positive correlation between blood levels of GSH and those of 25(OH)D in adults, children, and diabetic patients and AA subjects (25–27). Consumption of dietary antioxidants plays a beneficial role by increasing serum 25(OH)D (28). Preclinical studies have shown that low levels of GSH negatively affect the vitamin D regulatory and glucose-metabolism genes in the liver and muscle of high fat diet-fed mice and diabetic rats (27, 29–31). Improved GSH status following co-supplementation with vitamin D and L-cysteine (a GSH precursor) demonstrated a significantly greater increase in circulating 25(OH)VD and a significantly greater decrease in the oxidative stress, TNF and insulin resistance levels compared with supplementation with vitamin D alone in a vitamin D deficient mouse model (27). The mechanism may result from the dual action of GSH-mediated reduction in oxidative stress and upregulation of the vitamin D regulatory genes ((VDBP/CYP2R1/CYP27A1/VDR), which are required for the efficient transport and hydroxylation of vitamin D in the liver, as well as the activation of the VDR/PGC-1α/GLUT-4 pathway responsible for the metabolic actions of 1,25(OH)2D in target tissues (27, 29, 30). Indeed, lower levels of GSH, impaired vitamin D responsive genes, and vitamin D deficiency have been reported in obesity and diabetes in general, and in AA subjects in particular (25–27). These preclinical studies provide strong evidence for a previously undiscovered mechanism by which a deficiency or inadequacy in 25-hydroxy vitamin D is linked to lower GSH levels. The combination of vitamin D and L-cysteine has been found effective for improving clinical outcomes in animal studies, and this needs to be examined in human studies. This has not been studied in the clinical setting of COVID-19.

Reduced GSH levels in AA

GSH is formed from L-cysteine (LC), glycine, and glutamate by the enzymatic action of glutamate-cysteine ligase and glutathione synthetase (32). LC is a rate-limiting factor in GSH synthesis (32). GSH is a major antioxidant, and reflects the *in vivo* defense against oxidative stress (32). GSH is oxidized to GSSG during its antioxidative function. Glucose-6-phosphate dehydrogenase (G6PD) catalyzes the production of nicotinamide adenine dinucleotide phosphate reduced form (NADPH). NADPH is needed by glutathione reductase for the recycling of oxidized glutathione (GSSG) to GSH. Blood levels of GSH are lower in African Americans, presumably due to lower consumption of L-cysteine and a deficiency of G6PD. GSH deficiency increases oxidative stress and oxidative modification of endogenous enzymes and proteins, which can result in impaired cell function (27). A link has been established between impaired immunity associations and reduced cellular levels of GSH (33). GSH or its precursor L-cysteine has been used to replenish intracellular GSH levels in anti-viral therapy (34). An imbalance in both GSH homeostasis and oxidative stress is an essential component of the inflammation and respiratory distress common not only to aging, but also to a variety of diseases, such as diabetes, chronic obstructive pulmonary disease, acute respiratory distress syndrome, tuberculosis, neurodegenerative diseases, and several viral infections, including HIV (in humans) and SIV (in rhesus macaques) (33, 35, 36). The incidence of G6PD is nearly 11% in AA, compared with 1% in Caucasians (37–39). Diabetes *per se* results in lower GSH levels in diabetic animals and patients (26, 40, 41). Under stressful situations, such as diabetes, G6PD deficient cells are unable to regenerate enough NADPH. This exacerbates GSH deficiency and oxidative stress (42, 43), and it can contribute to GSH and 25(OH)VD deficiencies in AA.

Role of 25(OH)D in boosting immunity and lung functions

Vitamin D supplementation upregulates and induces innate antimicrobial and anti-viral defense mechanisms and it reduces the insult caused by both viral and bacterial stimuli (44, 45). The benefits of vitamin D supplementation in lowering the risk of viral infection and providing protection against acute respiratory tract infections have been reviewed previously (46). Improvement in vitamin D status reduces the incidence and infectivity of influenza A, retrovirus, and dengue virus infection (45, 47). The potential mechanisms by which vitamin D reduces the risk of viral infection and respiratory illness include induction of the antimicrobial peptide cathelicidin and IL-17 and suppression of the CD26 cell receptors that facilitate virus entry into the host (45, 47). Vitamin D upregulates glutamate-cysteine ligase, increases GSH, lowers oxidative stress, and pro-inflammatory cytokines levels and hereby can prevent built up of so-called cytokine storm (48–50). Low levels of serum 25(OH)D have been independently associated with subclinical interstitial lung disease and COPD. Alpha-1-antitrypsin (AAT) is a protease inhibitor. The primary function of AAT is to inhibit neutrophil elastase and prevent elastin degradation in the lungs. AAT deficiency and excess elastin degradation impair the recoiling of elastin and make breathing difficult, as observed in chronic obstructive pulmonary disease (COPD). Vitamin D deficiency has been shown to result in significantly lower AAT expression in the lungs and emphysema in mice exposed to cigarette smoke (35, 51). ATT synthesis by the CD4+ T cells is required in mediating the immune regulatory system controlled by vitamin D (52). Both vitamin D deficiency/insufficiency and AATD are extensively linked to decreased lung function. A positive correlation between low blood levels of 25(OH)D and lower AAT levels has been observed in type 2 diabetic patients (53).

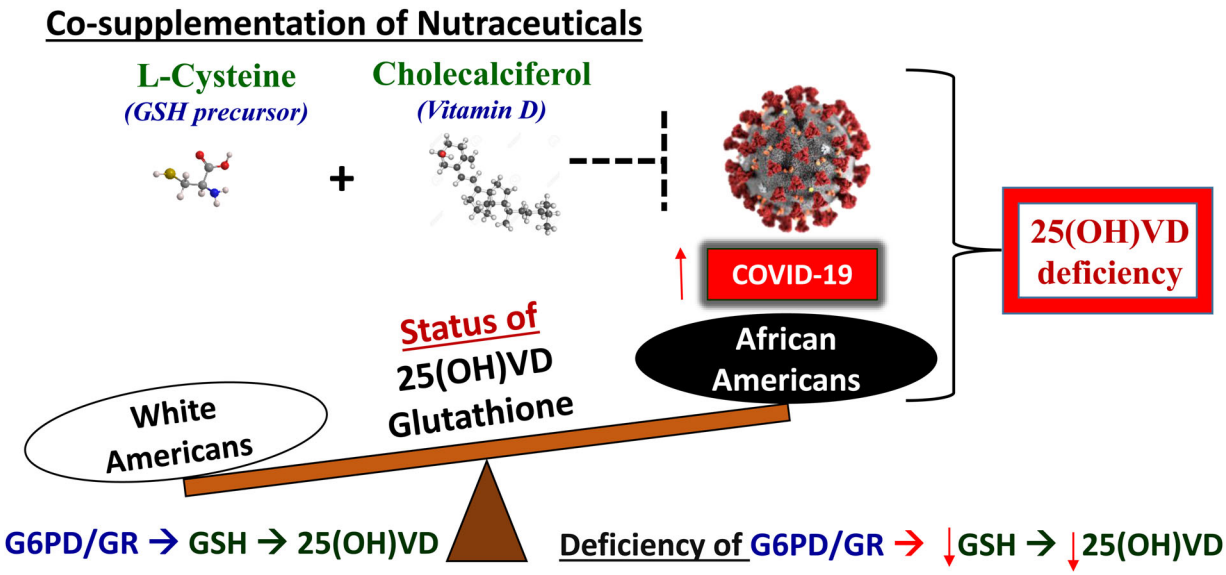

Figure 1. Potential of L-cysteine and vitamin D co-supplementation to reduce vitamin D deficiency and mortality associated with COVID-19 in African Americans.

Justification for co-supplementation with vitamin D and L-cysteine

VD is essential for the regulation of many vital genes (54). Epidemiological studies demonstrate an association between better health outcomes and higher blood levels of 25(OH)VD (55–58). Randomized controlled clinical trials have shown that, while supraphysiological doses of VD are needed to achieve adequate blood levels of 25(OH)VD, not all subjects respond to them (59–62). Recent clinical trials have also questioned the therapeutic effects of high-dose VD supplementation (61, 63, 64). The disconnect between the limited success of VD supplementation therapy in clinical trials, despite the convincing association between low 25(OH)VD levels and the poor health outcomes associated with chronic diseases, is puzzling. The co-supplementation approach using vitamin D and L-cysteine is superior to supplementation with vitamin D alone because an improvement in cellular GSH status due to added LC will be beneficial in several important ways. First, it will upregulate VD-metabolism genes (VDBP/CYP2R1/CYP27A1/VDR), which are required for the efficient transport and hydroxylation of cholecalciferol, and activation of the VDR/PGC-1α/GLUT-4 pathway responsible for the metabolic actions of $1,25(OH)_2VD$ (27). Second, both lipids and proteins are integral constituents of the membrane bilayer and are essential in the maintenance of the structure and specialized physiological functions of various organs in the body. These two micronutrients are complementary: VD is lipophilic, and LC is hydrophilic. Thus, co-supplementation with VD and L-cysteine/GSH will be more effective in neutralizing oxidative injury at both lipid and protein sites and provide stronger antioxidative and anti-inflammatory protection from the oxidative stress induced by the COVID-19 infection. Thus, combined consumption of GSH precursors and VD, rather than solely using high-dose VD, is both novel and a potentially effective strategy to achieve a more efficient bioavailability in response to cholecalciferol alone consumption. Animal studies have shown that, compared with vitamin D alone, co-supplementation of vitamin D and L-cysteine (a GSH precursor) in deed showed a greater benefit in increasing both the levels of GSH and VD-regulatory genes at the cellular/tissue level, increasing 25(OH) vitamin D levels, and in reducing oxidative stress, TNF and inflammation biomarkers in the circulation. Clinical trials are needed to investigate whether co-supplementation of vitamin D and L-cysteine can provide a low-cost strategy to optimize circulating levels of 25(OH)VD and boost body's immunity and defense in protecting from the adverse clinical effects of COVID-19 infection in our population.

Summary

An association between a high incidence of 25(OH) vitamin D deficiency and the severity of COVID-19 infection has been reported. Both GSH and 25(OH) vitamin D deficiencies and insufficiencies are prevalent in people of color, especially African Americans (5, 25–27, 31, 65–68). GSH or its precursor L-cysteine has been shown to stimulate and correct levels of GSH, improve VD-regulatory genes at the cellular/tissue level, increase 25(OH) vitamin D levels, and reduce inflammation biomarkers in the blood. GSH deficiency increases the risk of various diseases, including impairment of the activities of Specialized immune cells and thus the body's ability to fight infection. As a group, African Americans have a higher incidence of 25(OH) vitamin D deficiency or inadequacy. We believe that combined supplementation using vitamin D with the GSH precursor L-cysteine could potentially correct the status of the vitamin D metabolism genes by increasing GSH and the antioxidant capacity. Upregulation of the intracellular glutathione redox status and 25(OH)D may provide a new therapeutic option for preventing inflammation and impaired immunity in subjects exposed to COVID-19. Figure 1 illustrates that both excess vitamin D deficiency and excess adverse clinical effects of COVID-19 occur in African American communities. The treatment of widespread 25(OH) vitamin D deficiency or

inadequacy with co-supplementation using a combination of vitamin D and a GSH precursor (L-cysteine) has the potential to help prevent or reduce the adverse effects of COVID-19 infection, particularly in the AA population.

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Disclosure statement

The authors declare no competing interests.

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