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Coronavirus Pandemic

The role of high dose vitamin d and glutathione supplementation in COVID-19 treatment: A case series

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Abstract

COVID-19 has been affecting millions of people worldwide and becoming a global public health burden. Therefore, exploring treatment options is essential to help flatten the curve and reduce hospitalization time. This is a case series of ten COVID-19 patients in Jakarta and Tangerang, Indonesia, who received a high dose of vitamin D and glutathione supplementation daily. Within 5-7 days of treatment, all patients were confirmed COVID-19 negative. To date, this is the first report from Indonesia describing the potential benefit of supplementing vitamin D and glutathione concurrently in improving clinical conditions and expediting the recovery time of COVID-19 patients.

Key words: COVID-19; vitamin D; glutathione; renin-angiotensin system; case reports.

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Introduction

Coronavirus Disease 2019 (COVID-19) outbreak has been a global concern. Since 2020, COVID-19 has affected approximately 617 million people and caused more than 6.5 million deaths worldwide [1]. In Indonesia, COVID-19 has affected more than 6 million people and caused the death of nearly 160,000 people [1]. As the cases are still fluctuating and tend to rise in many parts of the world, it is important to flatten the curve and reduce the hospitalization time.

A recent study from Indonesia discovered that vitamin D deficiency is commonly found among COVID-19 patients [2]. Vitamin D is predominantly perceived as a vitamin, but it is in fact a secosteroid hormone that exerts the function-modulating effect at a cellular level through its receptor [3]. Vitamin D receptor is expressed in immune cells and has been known to modulate up to 500 genes regulating immunity [3]. In fact, vitamin D is crucial in preventing cytokine storm which is responsible for severe manifestations of COVID-19. It works by reducing renin expression and thus, balancing the angiotensin converting enzyme (ACE)/angiotensin converting enzyme 2 (ACE2) ratio [4-6]. Furthermore, vitamin D is related to COVID-19 severity and mortality risk [5].

Another nutrient with a significant role in COVID-19 patients is glutathione, an endogenous frontline antioxidant that is present in every cell of the human body. Glutathione is found in the lung's epithelial lining fluid and regulates inflammatory response in lung cells [7]. Low levels of glutathione in the epithelial lining fluid may disrupt the balance of oxidants and antioxidants in the lung, inducing inflammatory responses and potentiating lung damage [7]. Studies also showed that the level of glutathione dropped in SARS-CoV-2 infection [8,9].

To the best of our knowledge, there has not been any publication from Indonesia describing the potential benefit of co-supplementing vitamin D and glutathione in accelerating the recovery time of COVID-19 patients.

Methodology

This is a case series of 10 COVID-19 patients which describes the potential benefit of vitamin D and glutathione supplementation for COVID-19 recovery time. A literature review from recently published studies regarding vitamin D, glutathione, and COVID-19 was also conducted and discussed in this article.

Case inclusion criteria

Ten consecutive cases of COVID-19 patients admitted to two hospitals in Jakarta and Tangerang, Indonesia, during January 2021 were included in this

descriptive study. The inclusion criteria were the confirmation of COVID-19 diagnosis through real-time polymerase chain reaction (PCR) and no history of COVID-19 infection prior to hospital admission. Informed consent was obtained from the patients and available on request. Data on clinical symptoms and laboratory examinations were obtained from electronic medical records. All data in this case series is properly anonymized. Due to the full hospital capacity at the moment, all of the patients received home care treatment and were monitored thoroughly every day.

Laboratory analysis

The serum level of vitamin D was measured using the enzyme immunoassay method. The interpretation of vitamin D serum level was categorized as follows: deficiency (< 10 ng/mL), insufficiency (10–29 ng/mL), and sufficiency (≥ 30 ng/mL). Glutathione serum level was not measured because glutathione testing is not widely available in Indonesia.

Treatment

All patients were treated according to COVID-19 Treatment Guideline in Indonesia (3rd Edition, December 2020), which was used nationally as the treatment reference at the time patients were infected with COVID-19 [10]. Asymptomatic patients were given multivitamins containing vitamins C, B, E, and zinc 1-2 tablets/day. Besides receiving multivitamins, patients with mild and moderate symptoms were given Favipiravir 1,600 mg orally every 12 hours on the first day followed by 600 mg every 12 hours on the second to fifth day; Azithromycin 500 mg orally every 24 hours for 5 days; and other symptomatic treatment, such as Paracetamol 500 mg to reduce fever if necessary. Medications to treat comorbidities such as amlodipine, candesartan, and atorvastatin were also added. According to the guideline, vitamin D, antioxidants, and other supportive medications can be given at the discretion of the physician and considering patients' clinical conditions [10]. In this case series, all patients were given high-dose Vitamin D (Hi-D®) up to 10,000 IU per day and Glutathione (Glubio®) up to 2 grams per day. Hi-D® is a vitamin D chewable tablet that is available in 1,000 IU and 5,000 IU. Glubio® is an L-reduced Glutathione 500 mg capsule. The dose given was determined by age and general clinical examinations. Patients were instructed to bed rest, consume meals with adequate calories and high protein, and maintain good hydration by drinking an adequate amount of water every day.

Results

We report the demographics, clinical characteristics, and laboratory results of the patients in Table 1. All patients are COVID-19 confirmed through real-time PCR testing with mild to moderate severity according to WHO Interim Guidance and COVID-19 Treatment Guideline in Indonesia (3rd Edition) [11] (Table 2). The mean age of all patients was 35.2 years. In this case series, 50% of the patients were male and 50% were female. Symptoms appeared within 5 days since presumed contact with the source of infection through tracing system. Fever was the most frequent symptom (70%), followed by sore throat (30%), myalgia (20%), fatigue (10%), and anosmia (10%). There were 30% asymptomatic patients (Patient 2-4); 60% patients with mild symptoms (Patient 5-10); and 10% patients with moderate symptoms (Patient 1). There were 60% patients without comorbidities. Among all patients, dyslipidemia (40%) was the most common comorbidity, followed by hypertension (20%) and diabetes (20%).

Measurement of vitamin D was conducted as soon as the COVID-19 status was confirmed. There was 1 patient with vitamin D deficiency and 9 patients with vitamin D insufficiency (Table 1). Oxygen saturation was normal for all patients. Computed tomography (CT) scan was conducted for all patients and 20% had mild to moderate peripheral ground-glass opacity (GGO) (Figure 1A).

Table 1. Demographics, clinical characteristics, and laboratory results.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)	54	11	18	45	32	36	22	34	56	44
Gender	Male	Male	Male	Male	Male	Female	Female	Female	Female	Female
Symptoms	Fever, Myalgia	-	-	-	Fever, Sore throat	Fever, Sore throat	Fever, Fatigue	Fever, Anosmia	Fever, Myalgia	Fever, Sore throat
Comorbidities	Hypertension, Dyslipidemia	-	-	Diabetes, Dyslipidemia	-	-	-	-	Hypertension, Dyslipidemia	Diabetes, Dyslipidemia
Vitamin D levels (ng/mL)	9.8	11.6	17.8	21.5	13.4	16.9	14.2	23.2	18.4	18.3
Vitamin D status	Deficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency	Insufficiency
O_2 saturation (%) on admission	96	98	98	96	98	98	97	98	98	98
Day of Diagnosis	3	1	3	5	3	2	1	5	5	4
Day of Recovery	5	7	7	5	7	5	5	7	7	7

Symptoms of all patients were improved within a few days of treatment, therefore, PCR testing was then performed on day 5 and day 7 for all patients. Forty percent of the patients became COVID-19 negative on day 5 while 60% became COVID-19 negative on day 7. The PCR test was conducted twice for each patient to confirm the negative results. The CT scan post-treatment revealed notable improvement in the GGO (Figure 1B).

Discussion

The number of COVID-19 cases has been rising globally, resulting in an increase in the bed occupancy rate. Efforts should be made to reduce hospital burden as treatment access for other diseases became limited. Treatment guideline in Indonesia has been revised and updated several times, adapted to follow the development of science related to COVID-19. During the development of this case series, no definitive treatment for COVID-19 has been decided. However, studies about COVID-19 has been progressing, including the treatment targets for COVID-19 and the management of the disease. The renin-angiotensin system (RAS) is one of the plausible treatment target for COVID-19.

COVID-19 is caused by the SARS-CoV-2 virus, which uses the ACE2 receptor to enter the host cells [6]. ACE2 receptors are expressed nearly in all human organs to various degree and are parts of the RAS [6,12]. ACE2 has a role in lowering blood pressure and works in the opposite of ACE, the other enzyme [6]. When the virus enters the human body, the ratio of ACE/ACE2 is imbalanced and consequently affects the function of many organs [6,12]. It is also known that reactive oxygen species (ROS) are related to the ACE/ACE2 balancing system [6]. The imbalance caused by the SARS-CoV-2 virus upregulates Angiotensin II, triggering the inflammatory pathway

Figure 1. Multiple ground-glass opacity (GGO) seen on lung computed tomography (CT) scan. (**A**) One of the infected patient lung CT scan before the treatment; (**B**) Improvement in the lung bilaterally 7 days after first observation.

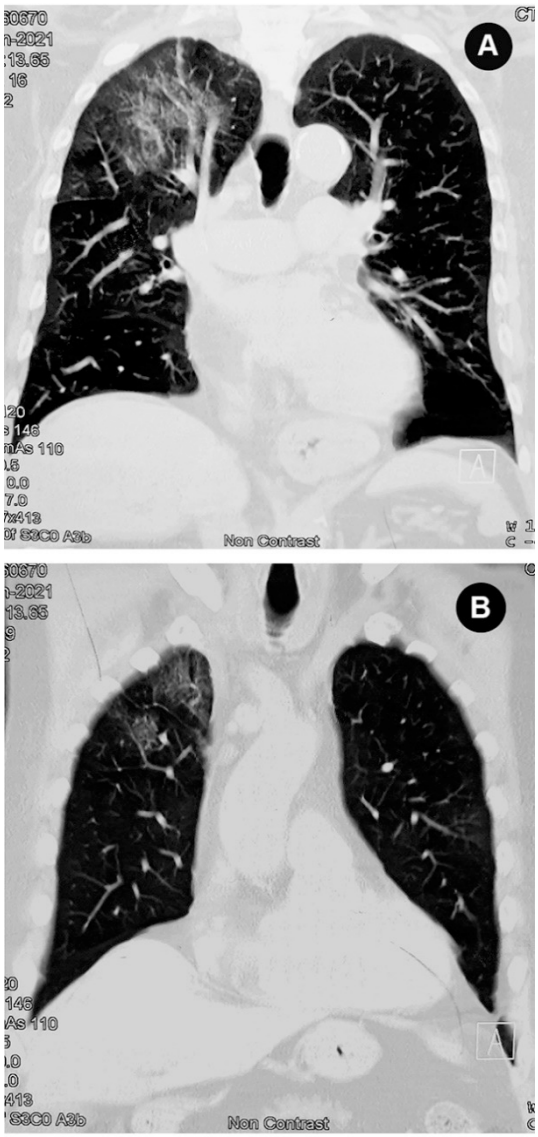

Table 2. Classification of COVID-19 Disease Severity [10,11].

Disease Severity	Definition
Mild	Patients with COVID-19 symptoms: fever, cough, fatigue, anorexia, shortness of breath, myalgia, headache, nasal congestion, sore throat, diarrhea, nausea, vomiting, anosmia, and ageusia without evidence of viral pneumonia or hypoxia.
Moderate	In adults and adolescents: presence of pneumonia symptoms (fever, cough, dyspnea, fast breathing) without signs of severe pneumonia, including SpO2 ≥ 90% on room air. In children: presence of non-severe pneumonia symptoms (cough or difficulty breathing + fast breathing and/or chest indrawing) and without signs of severe pneumonia.
Severe	In adults and adolescents: the presence of pneumonia symptoms (fever, cough, dyspnea, fast breathing) with one of the following: respiratory rate > 30 breaths/minute, severe respiratory distress, or SpO_2 < 90% in room air. In children: the presence of pneumonia (cough or difficulty breathing), with at least one of the following: • Central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, severe chest indrawing); • General danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions Fast breathing is defined as ≥ 60 breaths/minute (2 months); ≥ 50 breaths/minute (2–11 months); ≥ 40 breaths/minute (1–5 years).

and provoking more oxidative stress events in the infection parts [6,12]. Therefore, balance in RAS could be an important target for COVID-19 treatment. We explored possible nutrients that may manage and improve the imbalance of RAS. Vitamin D and glutathione are found in most human cells, including the lungs [5,7]. They are normally available in healthy people, however, many studies discovered that vitamin D and glutathione deficiency in COVID-19 patients were frequently found [2,5,8].

Vitamin D suppresses ACE2 hypomethylation caused by the SARS-CoV-2 virus and hence, provides better overall conditions for the body to fight the virus and decrease the viral load [4]. In addition, vitamin D itself plays a direct significant role in modulating the immune system both innate and adaptive immunity avoiding excessive production of cytokine [3]. Moreover, vitamin D inhibits the pro-inflammatory cytokines by blocking the TNF-induced NFkB1 signaling pathway; and initiates the antiviral defense program by prompting the IFN-α induced Jak-STAT signaling pathway [13]. A recent study discovered that lower levels of vitamin D had a 54% positivity rate of COVID-19 [14]. In other words, if vitamin D level is higher, the risk of acquiring COVID-19 is lower [14]. Additionally, another study also revealed that a higher concentration of vitamin D is associated with lower mortality and morbidity in COVID-19 cases [15].

All of the patients in this case series had low levels of vitamin D. Specifically, 10% had deficiency status and the other 90% had insufficiency status. In addition, 40% had comorbidities such as hypertension, diabetes, and dyslipidemia. These comorbidities are associated with RAS overactivation, and thus, these patients were prone to a higher risk of COVID-19 severity and mortality. Persistent deficiency in vitamin D levels may activate RAS further, leading to chronic cardiovascular disease dan decreased lung function. Moreover, vitamin D deficiency is proportional to many comorbidities [16]. This is in line with the finding that COVID-19 patients with comorbidities have lower vitamin D levels, contributing to the higher proportion of COVID-19 severe illness. COVID-19 infection, coinciding with excessive activation of RAS, will create a perfect storm which can lead to lethal respiratory syndrome.

Furthermore, vitamin D deficiency can decrease glutathione levels in cells, mediated by the enzyme c-glutamyl-transpeptidase [17]. Glutathione is a primary antioxidant in the form of tripeptide (cysteine, glycine, and glutamate), found in high concentrations in cells (2-5 millimolar) [18]. Glutathione is crucial in various processes in the human body, such as detoxification, antiviral defense, and immune response [18]. Glutathione exists in 2 states, reduced (GSH) and oxidized (GSSG) form. The ratio of GSH to GSSG determines cell redox status, in which healthy cells should have a ratio of more than 100. If the ratio is below 100, it indicates ongoing oxidative stress in the cells [18,19]. A review in 2020 revealed that the GSH levels in COVID-19 patients is below 1 micromolar/L with a low GSH/GSSG ratio [8].

In addition, glutathione suppresses oxidative stress by balancing the ratio between ACE/ACE2 which is also key in managing COVID-19 cases as discussed above [18]. Hence, maintaining glutathione levels is important to avoid the cytokine storm in COVID-19. Horowitz reported that the use of glutathione supplementation up to 2 gram/day is helpful to relieve dyspnea in COVID-19 cases [9]. In this case series, we also used the same dose of glutathione and resulted in good response. Use of glutathione supplementation for other pulmonary diseases is a common practice, as low levels of glutathione significantly affects chronic obstructive pulmonary disease, asthma, and acute respiratory distress syndrome [7].

Glutathione increases the expression of Vitamin D Binding Protein (VDBP) [8]. Therefore, glutathione is closely related to vitamin D and has a role in maintaining the biosynthesis of vitamin D. On the other hand, vitamin D increases the rise of GSH levels by engendering the expression of glutamate-cysteine ligase and glutathione reductase genes, which are the catalysts for GSH [18]. Since vitamin D and glutathione work synergistically to enhance each other's levels in circulation, co-administration of vitamin D and glutathione can be beneficial, particularly in preventing cytokine and bradykinin storms.

This case series supports the idea of the benefit of vitamin D and glutathione co-supplementation. Early treatment with supplementation of aggressively high dose vitamin D and glutathione in this case series showed good response to medication, prevented progression to severe stage, and alleviated symptoms within a few days. A 2020 study showed the acceleration of SARS-CoV-2 negative conversion along with significant improvement of the inflammation markers with a high dose of Vitamin D supplementation (60,000 IU/day) [20]. In this case series, all of the patients tested negative for PCR evaluation in 7 days or less with up to 10,000 IU vitamin D per day and up to 2 grams glutathione per day. In contrast, the average conversion from positive SARS-CoV-2 to negative was 17 days [20]. Another study stated 10 days as the median of hospitalization

time for COVID-19 patients with comorbidities [15]. The findings in this case series align with our notion that vitamin D works as a RAS regulator by transcriptional suppression of renin expression to prevent cytokine and bradykinin storm, [5,6] and glutathione can help to prevent cytokine storm by balancing the ratio between ACE and ACE2 [18].

SARS-CoV-2 virus activates the human innate immune system upon entering cells. This system will release some pro-inflammatory factors, leading to cytokine storm and injury to the lung's epithelial and endothelial cells [6,12]. As a result, interstitial thickening may occur, and lung alveoli may collapse or be partially filled by fluid [21]. This event manifests as the GGO appearance in COVID-19 patients [21]. GGO is seen on computed tomography (CT) and X-Ray as an opacification of the lung without obliteration of bronchial or vascular markings [21]. GGO is found in more than 80% of COVID-19 patients and is the earliest sign of lung manifestation in COVID-19 [21]. However, another study revealed that up to 50% of COVID-19 patients had a normal lung CT scan in the first two days of infection [22]. This statement supports the finding in this case series, in which only 2 of 10 COVID-19 patients had mild to moderate GGO as seen in Figure 1A. It also aligns with the fact that 60% of our patients in this case series were diagnosed with COVID-19 within the first three days of infection. The repeat CT scan in Figure 1B after treatment revealed an improvement rather than a deterioration. This finding strengthens the presumption that vitamin D and glutathione work synergistically to suppress pro-inflammatory level and prevent cytokine storm.

This case series has some limitations. First, this was an observational study with a small sample size. Second, baseline glutathione levels could not be measured due to their unavailability in Indonesia. Last, the subjects in this case series were only the asymptomatic, mild, and moderate COVID-19 patients. Nonetheless, this case series gives a consideration of adding high doses of vitamin D and glutathione supplements as a strategy to combat COVID-19. Further studies are needed to confirm the efficacy of vitamin D and glutathione supplementation in preventing and treating COVID-19. This case series also extends the possibility of using vitamin D and glutathione as prophylaxis for COVID-19 and may encourage more studies on this matter.

Conclusions

This case series suggests combining Vitamin D and glutathione in improving clinical conditions, reducing the length of stay, and accelerating the recovery time of COVID-19 patients.

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