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What Stone-formers Should Know About Vitamin C and D Supplementation in the COVID-19 Era

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Abstract

Coronavirus disease 2019 (COVID-19) remains without a well-defined management strategy. Some patients have initiated supplementation with vitamins C and D on the basis of circumstantial evidence. We lack crucially needed double-blind controlled studies on the use of these vitamins for COVID-19. Vitamin C is metabolized to oxalate, and vitamin D regulates calcium homeostasis. Thus, these vitamins are potentially lithogenic. Nephrolithiasis is a highly prevalent urologic illness. Here we highlight relevant literature regarding vitamins C and D and their relationship to respiratory infections and nephrolithiasis. We conclude that vitamin C should be used with caution, particularly doses of ≥1000 mg/day and in men. Stone-formers receiving vitamin C should be monitored for hyperoxaluria. Vitamin D appears to be safe at doses up to 4000 IU/d, although patients should be monitored for hypercalciuria. Studies on the impact of vitamin C and D use for COVID-19 on nephrolithiasis risk are critically needed.

***Patient summary*:** We discuss the relationship of vitamins C and D to respiratory infections, such as COVID-19, and kidney stones. We conclude that vitamin C may increase kidney stone risk, particularly in men, while vitamin D appears to be safe for at least 1 yr. Evidence supporting vitamin C and D supplementation for COVID-19 is indirect and requires further research.

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Keywords

COVID-19; Kidney stones; Dietary supplementation; Urology

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Coronavirus disease 2019 (COVID-19) has rapidly evolved into a pandemic but remains without a well-defined treatment or prevention strategy. Research efforts have focused on the use of existing medications, such as azithromycin, hydroxychloroquine, remdesivir, and famotidine. The use of vitamin supplements, particularly vitamins C and D has also garnered great interest. Prior research on respiratory infections suggests that vitamin C and D supplementation may be beneficial [1–4]. However, crucially needed data from double-blind controlled studies are lacking.

Vitamin C is metabolized to oxalate and vitamin D regulates calcium homeostasis. Thus, these supplements are potentially lithogenic. Nephrolithiasis is a common urologic pathology and it is critical for practitioners to counsel stone-forming patients on the safety of vitamin C and D supplementation in the COVID-19 era, particularly given that universal facemask precautions may limit routine oral hydration. Here we highlight relevant literature regarding vitamins C and D and their relationship to respiratory infections and nephrolithiasis to guide practitioners during the COVID-19 pandemic (Table 1).

Vitamin C is an antioxidant critical for immune system function [5]. A large meta-analysis found that vitamin C supplementation at doses of ≥200 mg/d was associated with shorter duration of the common cold [4]. Furthermore, high-dose intravenous vitamin C improved outcomes in critically ill patients with sepsis and acute respiratory distress syndrome [1]. Studies on the role of vitamin C in COVID-19 management are ongoing.

Although generally well tolerated, vitamin C is associated with adverse effects at higher doses. Of urological interest, vitamin C is metabolized to oxalate and excess consumption may lead to hyperoxaluria [5]. Daily supplementation with 2000 mg/d of vitamin C was associated with increased urinary oxalate [6]. Furthermore, stone-formers treated with 1000 mg/d had an increase in 24-h urinary oxalate from 31 mg to 50 mg [6]. Literature on the impact of lower vitamin C doses on hyperoxaluria is limited but suggests a dose-dependent linear relationship [7]. Notably, oxalate excretion is significantly higher for vitamin C doses of 1000 mg/d compared to ≤200 mg/d [7]. Although the data available are limited, a linear relationship is intuitive given that oxalate is a metabolic byproduct of vitamin C [5].

Large population-based studies on vitamin C intake and nephrolithiasis suggest an increase in risk for men but not women [8]. Among men, vitamin C supplementation at doses ≥1000 mg/d was associated with a higher risk of developing incident kidney stones, whereas there was no such association for women [8]. It is unclear whether gender differences are due to metabolic or behavioral differences. However, given the evidence linking vitamin C to hyperoxaluria, it is reasonable for female stone-formers to use caution with supplementation as well. Accordingly, we recommend advising stone-forming patients, particularly men, to avoid vitamin C supplementation at doses ≥1000 mg/d. Patients who initiate vitamin C supplementation should be monitored with 24-h urine oxalate levels.

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Vitamin D helps in regulating calcium and phosphate stores in the body and is required for proper immune system function. A large meta-analysis found that vitamin D supplementation reduced the risk of acute respiratory infections [3]. The overall number needed to treat was 33, but was only four in the group with existing vitamin D deficiency. Interestingly, the protective effect was not dose-dependent. The underlying mechanism is unknown but may relate to calcium homeostasis, as viruses alter cellular calcium levels to facilitate survival and reproduction [9]. A recent analysis of European nations also found that lower vitamin D levels were associated with higher COVID-19 caseload and mortality [2].

The relationship between vitamin D and nephrolithiasis has generated significant interest as the majority of kidney stones are calcium stones. A meta-analysis assessing the general risks of vitamin D supplementation identified an increase in nephrolithiasis risk [10]. However, in the majority of the studies included, co-administration of calcium was not standardized in the experimental and control groups. Thus, the study findings were not reflective of isolated vitamin D supplementation and may be secondary to calcium co-administration.

A subsequent meta-analysis focused on the impact of long-term vitamin D supplementation on calcium metabolism and nephrolithiasis risk; calcium supplementation did not differ between the control and experimental groups in the studies included [11]. The authors concluded that ≥24 wk of supplementation was associated with an increase in the risk of hypercalciuria but not in the risk of nephrolithiasis. Since many of the studies had follow-up of <1 yr, it is unclear if this hypercalciuria associated with vitamin D is transitory or whether longer follow-up would have identified differences in nephrolithiasis risk.

Another meta-analysis by the same team found that patients receiving ≥2800 IU/d of vitamin D for at least 1 yr had a borderline increase in the risk of hypercalciuria but no increase in the risk of nephrolithiasis events [12]. In the studies analyzed for nephrolithiasis risk, doses ranged from 20 000 IU/wk (~2850 IU/d) to 40 000 IU/wk (~5700 IU/d) and none identified a higher risk of nephrolithiasis events. This suggests that vitamin D supplementation up to the reported upper tolerable dose (4000 IU/d) does not confer an increase in the risk of nephrolithiasis, although it may increase the risk of hypercalciuria. Thus, stone-formers initiating vitamin D supplementation should be monitored with 24-h urine studies for the development and subsequent resolution of hypercalciuria.

Circumstantial evidence suggests that vitamin C and D supplementation may be beneficial in the management of COVID-19. However, supplementation with these vitamins is not without risk. Vitamin C supplementation at doses ≥1000 mg/d should be used with caution, particularly in men, and patients should be monitored with 24-h urine studies for hyperoxaluria. Vitamin D supplementation at doses ≤4000 IU/d appears to be safe for at least 1 yr, although patients should be monitored with 24-h urine studies for the development and subsequent resolution of hypercalciuria. Given the rapid spread and morbidity of COVID-19, all health care practitioners are responsible for understanding how potential treatments for the virus impact common pathologies within their scope of practice. Accordingly, double-blind controlled studies on the benefits of vitamins C and D for COVID-19 and potential sequelae of their use for this indication, such as nephrolithiasis, are critically needed.

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Conflicts of interest: Mantu Gupta is compensated for educational training for Cook Urological, Boston Scientific, Olympus, Lumenis, and Retrophin outside the scope of the current study. The remaining authors have nothing to disclose.

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Table 1 – Summary of the key studies discussed

Study	Study type	Population	Study arms	Relevant outcom
Vitamin C and respiratory illness/COVID-19				
Hemila [4]	SRMA	Participants in controlled studies on VCS and the common cold	VCS ≥0.2 mg/d vs placebo	VCS had no effe the general comr risk of developir skiers, and soldi VCS reduced th children
Fowler [1]	Double-blind placebo-controlled study	Adult ICU patients with sepsis and acute respiratory distress syndrome	50 mg/kg IVVC every 6 h for 96 h vs placebo	Lower mortality Shorter ICU stay Shorter hospital
Vitamin D and respiratory illness/COVID-19				
Illie [2]	Observational study	Europeans	European nation of residence	There was a sign mean national vi national COVID
Martineau [3]	SRMA	Participants in controlled studies on VDS and acute respiratory infections	VDS vs placebo	VDS was associ respiratory tract The association vitamin D defici The effect was d administered in
Vitamin C and hyperoxaluria/nephrolithiasis				
Baxman [6]	Prospective partially randomized interventional study	A cohort of adults with a history of calcium stones and a cohort of NSFs	Stone-formers randomized to VCS of 500 mg BID for 3 d vs stone-formers randomized to VCS of 1000 mg BID for 3 d vs NSFs receiving VCS of 1000 mg BID for 3 d	24-hr urinary ox increased in all t
Levine [7]	In-hospital depletion-repletion study	Healthy adult men aged 20–26 yr	Patients were admitted to hospital and started a very low vitamin C diet (<5 mg/d). They were then given increasing VCS doses starting at 30 mg/d progressively increasing to 2500 mg/d. The total study duration was 4–6 mo	Urinary oxalate 1000 mg/d vs ≤2 Urinary oxalate mg/d and less vs did not reach sta
Ferraro [8]	Prospective large cohort study via surveys	Female nurses aged 22–55 yr and male health care workers aged 40–75 yr	Patients who developed incident kidney stones vs those who did not	VCS >1000 mg kidney stones fo VCS was not ass stones for wome
Vitamin D and hypercalciuria/nephrolithiasis				
Bjelakovic [10]	SRMA	Adults enrolled in trials comparing VDS to placebo or no intervention	VDS vs placebo or no intervention	Combined VDS developing kidn In the majority o standardized in t making it unclea or calcium
Malihi [11]	SRMA	Adults enrolled in randomized controlled trials of ≥24 wk of VDS in which CCS was consistent between the control and experimental arms	VDS vs placebo	Patients receivin of hypercalciuria

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Malihi [12]	SRMA	Adults enrolled in randomized controlled trials of ≥1 yr of high-dose (≥2800 IU/day) VDS in which CCS was consistent between the control and experimental arms	VDS vs placebo	Patients receivin at higher risk of borderline highe

BID = twice daily; CCS = calcium co-supplementation; ICU = intensive care unit; IVVC = intravenous vitamin C; NSFs = non–stone-formers; SRMA = systematic review and meta-analysis; VCS = vitamin C supplementation; VDS = vitamin D supplementation.

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