Original article

COVID-19 and micronutrient deficiency symptoms — is there some overlap?

Sherri L. Lewis*, Lora R. Chizmar, Sydni Liotta

James A. Haley VA Hospital and Clinics, 13000 Bruce B Down BLVD, Tampa, FL, 33612, USA

SUMMARY

Background & aims: COVID-19 is highly inflammatory and when it affects the elderly who have multiple comorbidities, the risk of malnutrition is high. The aim of this review is to highlight the evidence for COVID-19 and risk for malnutrition (macro- and micro-nutrient deficiency) sharing two case reports.
Methods: We report two cases of patients with COVID-19. The first case includes a 75-year-old male with increasing confusion, delirium and malnutrition once he had clinically resolved from his COVID-19 diagnosis. The patient had a number of comorbidities and was treated with diuretics before and after his hospital admission. He was treated with intravenous thiamine and enteral nutrition. The second case includes a 77-year-old male with diabetes who presented with suspected vitamin C deficiency likely due to chronic aspirin use nearly two weeks prior to being diagnosed with pneumonia and COVID-19. The patient recovered from his COVID-19 diagnosis but continued to decline nutritionally and was readmitted sixty days later with failure to thrive.
Results: The first case had significant improvements in his appetite and neurological conditions following thiamine infusion and enteral nutrition and was discharged to home after a 19-day hospital stay. The second case presented with a vitamin C deficiency before testing positive for COVID-19. Although he did recover from COVID-19 he struggled to meet nutritional needs post-COVID and passed away 60 days after his COVID-19 diagnosis with pneumonia and failure to thrive.
Conclusion: Elderly patients with chronic diseases who use nutrient depleting medications are particularly high risk for micronutrient deficiency when they also experience the inflammatory insult of COVID-19. Patients who continue to have poor nutrition intake even after they appear to be clinically resolved from the virus should be closely monitored.

Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism.

1. Introduction

In December 2019, the first cases of a pneumonia of unknown cause were reported in Wuhan, China. The illness came to be known as coronavirus disease 2019 (COVID-19) and was found to be caused by the newly named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 is an RNA beta coronavirus [1]. The virus enters cells that produce receptors for the angiotensin-converting enzyme 2 (ACE2) by binding to these receptors on the cell membranes [1–3]. These cells then replicate the virus, leading to apoptosis and necrosis on a large scale [3]. Cells that express ACE2 receptors are found primarily in the lungs but are also found elsewhere throughout the body, such as in the nasal and intestinal mucosa [1–3]. It is believed that nasal and pulmonary epithelial cells are the main entry sites of the virus [4].

Normally, ACE2 is metabolized after binding to cell receptors, but when the receptors are blocked with SARS-CoV-2, ACE2 accumulates in the body which can lead to hypertension and lung or renal failure [5]. Further, infections with the virus can trigger the release of massive amounts of cytokines, referred to as a cytokine storm. These cytokines can cause a prolonged systemic inflammatory response (SIRS) [2,6–8]. SIRS contributes to the widespread effects of the virus on different organs of the body. It is known that the lungs are greatly affected by the SARS CoV-2 infection with acute respiratory distress syndrome (ARDS) being one of the most common complications. However, it has also been shown that the gastrointestinal tract, heart, liver, kidneys, and brain may all be affected as well [7,9].

COVID-19 has presented with every range of illness, from asymptomatic cases to intensive care unit (ICU) admissions

* Corresponding author. 13000 Bruce B. Downs Blvd. Tampa, FL, 33612, USA.
E-mail address: Sherri.lewis@va.gov (S.L. Lewis).

[10–13]. Reports suggest about 80% of cases are mild enough to be managed at home, with up to 50% of those cases being completely asymptomatic [12,13]. The other approximately 20% of cases have resulted in hospitalization; a quarter being severe enough to require ICU admission [13]. Severe COVID-19 cases are characterized by the cytokine storm and SIRS mentioned above [2,6–8]. Neurological side effects can include encephalopathy, confusion, delirium, seizures, and even the augmentation or development of psychiatric or psychological disorders, such as depression [7,9–11]. Mild symptoms may include anorexia, nausea, abdominal pain, diarrhea, dyspnea, dyssomnia, and dysgeusia which all affect nutrient intake [11].

2. Malnutrition risk and COVID-19

The systemic inflammation and effects of the cytokine storm can last for an undefined period of time after a patient is considered clinically resolved [6]. Individuals who suffer from COVID-19 related effects for at least a month after the acute phase of the illness has passed, are termed COVID long haulers. These continued symptoms last for at least a month and, in some literature, have lasted past three months [14,15]. The condition has also been referred to as chronic COVID, long COVID, or simply post-COVID [14]. The prolonged effects of COVID-19 do not seem to be affected by the severity of the acute case, though those with a greater number of symptoms in their acute phase may be more likely to develop post-COVID symptoms [15]. This prolonged inflammatory state can sustain anorexia and catabolism which, combined with the prolonged gastrointestinal and neurological symptoms, put COVID long haulers at increased risk of malnutrition, physical deconditioning, further prolonged recovery, and even hospital readmission [14,16–18]. COVID long haulers may need targeted nutrition interventions and physical therapy to rehabilitate and regain functional status [11,16] Long-term nutrition support may be necessary to help meet their needs [14].

It has been well established that adequate nutrient status is important for proper immune function. Micronutrients prevent excess damage from daily oxidative stress and adequate macronutrients prevent or minimize catabolism. Malnutrition frequently occurs in the presence of inflammation [18–22]. With such inflammation, COVID-19 may place patients into a hypermetabolic state [6,11,18,23]. Two studies using indirect calorimetry with COVID-19 patients in the ICU found measured resting energy expenditures of up to 200% of predicted needs [6,23]. Increased energy needs will also increase micronutrient needs. Adequate nutrient status is especially important during times of infectious disease so that cells can be replenished when injury has occurred [24]. A prospective, observational study of 68 adults admitted to the hospital under infectious disease care found that 32% of patients had multiple micronutrient deficiencies. The most prevalent micronutrient deficiencies included zinc (66.7%), selenium (46.6%) and thiamine (39.7%) [24]. A more recent study found that 94.4% of adults admitted to the ICU with COVID-19 and who met criteria for ARDS had undetectable vitamin C levels in their blood [25]. The role of micronutrients during times of pandemics has been discussed by experienced ICU researchers who have recommended therapeutic protocols. One protocol consisted of methylprednisolone, ascorbic acid, thiamine, heparin and a number of co-interventions and thus was called "MATH+" [26,27]. These experts recommended high dose vitamin C as an effort to downregulate the cytokine storm experienced by COVID-19 patients. Additionally, vitamin C can help repair tissue damage and can work synergistically with glucocorticosteroids that help with pulmonary function [26]. Thiamine

was selected for use with the MATH + therapeutic protocol for its antioxidant properties and reported evidence of increased needs during other viral diseases [26–29]. Additionally, when used together with vitamin C and glucocorticosteroids, thiamine may help reduce delirium. Delirium is a known symptom experienced during thiamine deficiency, it has also been reported as a symptom of COVID-19 [26]. Thiamine has a half-life of 9–18 days and the body can only store up to 30 mg (mg), making continual dietary intake important [30–32]. The recommended daily allowance for thiamine is 1.1 and 1.2 mg per day for men and women, respectively [33]. Requirements for thiamine proportionately increase with increased energy and carbohydrate needs, presenting yet another risk factor for deficiency [32].

The role of vitamin D in immune function has been well established now. Vitamin D has a role in both innate and adaptive immunity as well as a role in the antiviral response. The important roles vitamin D plays in immunity and infection have led to many studies conducted in COVID-19 patients. Ghelani et al. [34] reviewed 37 studies conducted in 2020 and 2021 worldwide. The authors summarized that most studies found positive outcomes associated with obtaining vitamin D levels within normal limits with or without supplementation. The overall recommendation is to treat all patients with vitamin D deficiency as soon as possible and give preemptive supplementation to at risk populations. Supratherapeutic levels are not recommended [34–36]. This was stated more specifically in another recent review conducted by Borsche et al. [35] in which they merged and compared two diverse databases and determined a mathematical regression value of 50 ng/mL as a vitamin D3 level that prevents excess mortality. The authors also stated that with future variants and breakthrough infections approaching, the entire population should optimize its vitamin D3 level.

COVID-19 patients are at higher risk of malnutrition and weight loss independently of disease severity and hospitalization [20]. Symptoms such as anorexia, dyssomnia, dysgeusia, nausea, dyspnea, and fatigue can all lead to reduced food intake, leading to weight loss and suspected micronutrient deficiencies [14,16,20,37–39]. Further, decreased physical activity or bed rest during illness can contribute to losses in lean body mass, especially in the absence of adequate nutrient intake [11,18,20]. These factors, in addition to the hypermetabolic state promoted by inflammation, can put recovered infected individuals at high risk for malnutrition both in the hospital and at home [20]. There are few studies evaluating micronutrient status of patients who had mild cases of COVID-19 at home and continue to decline nutritionally in the recovery period. Symptoms of early micronutrient deficiencies often overlap with the symptoms of viral illnesses such as poor appetite, nausea, diarrhea, muscle weakness, pain, apathy, and confusion. These micronutrient deficiency symptoms are easily overlooked, and laboratory assessment is often not considered in hospital settings. Taking a proactive approach and treating suspected deficiencies of water-soluble vitamins and monitoring for improvement in signs and symptoms is the most common approach in hospital settings [30].

In addition to poor nutrient intake and increased nutrient needs during viral illness, common medications have also been shown to deplete several micronutrients, further increasing risk for deficiencies. Examples of these interactions include aspirin and vitamin C, diuretics and water-soluble vitamins, and oral contraceptives and B vitamins. This idea is further elaborated in Table 2. Drugs have been found to affect appetite, nutrient absorption, metabolism, and excretion, all affecting the need to either manage food and drug timing or nutrient needs [40]. The impact medications may have on patients presenting with COVID-19 who also have comorbidities will be highlighted in the following case reports.

Table 1
Nutrition-related assessment information for two cases with COVID-19.

	Case 1				Case 2			
Age	75 years old				77 years old			
Medical History	- COVID-19, clinically resolved - CVA - COPD - CAD/HTN				- CVA - CHF - CKD stage 3 - DM			
Nutritionally Relevant Medications	- Potassium Chloride - Furosemide				- Aspirin - Furosemide - Insulin (ASPART 70/30)			
Anthropometrics	Height: 181.6 cm Weight: 96.8 kg BMI: 29 Weight Change: 12% loss −1 month				Height: 180.3 cm Weight: 84.78 kg BMI: 26 Weight Change: None			
Biochemical Data Medical Tests	Plasma	Value	Units	Ranges	Plasma	Value	Units	Ranges
	Na	139	mmol/L	136−145	Na	147 H	mmol/L	136−145
	K	3.9	mmol/L	3.5−5.2	K	3.4 L	mmol/L	3.5−5.2
	Cl^-	107	mmol/L	98−109	Cl^-	111 H	mmol/L	98−109
	CO_2	23	mmol/L	22−32	CO_2	22	mmol/L	22−32
	BUN	13	mg/dL	8−23	BUN	16	mg/dL	8−23
	Cr	0.8	mg/dL	0.8−1.3	Cr	0.9	mg/dL	0.8−1.3
	Gluc	156 H	mg/dL	65−110	Gluc	227 H	mg/dL	65−110
	Ca	8.4	mg/dL	8.3−10.2	Ca	8.6	mg/dL	8.3−10.2
	Mg	1.9	mg/dL	1.5−2.6	Mg	−	mg/dL	1.5−2.6
	PO_4	3.0	mg/dL	2.3−4.3	PO_4	−	mg/dL	2.3−4.3
	Albu	3.2 L	g/dL	4.0−4.9	Albu	3.6 L	g/dL	4.0−4.9
	Folate	7.6	ng/mL	≥5.4	Folate	13.1	ng/mL	≥5.4
	B-12	>1000	pg/mL	218−1124	B-12	524	pg/mL	218−1124
	Vit D	24 L	ng/mL	30−100	Vit D	14 L	ng/mL	30−100
	CRP	3.3 H	mg/dL	0−1.0	CRP	4.9 H	mg/dL	0−1.0
Nutrition Focused Physical Findings	- Moderate muscle wasting: temples, clavicle and scapula - Mild orbital fat pad wasting - Handgrip: 21.3 kg (borderline weak)				- Corkscrew hairs: Forearms - Mottled pail toenails - Stage 1 pressure injury: Left heel - Blisters: Top of both feet - Ecchymosis: Left forearm			
General Complaints	- Generalized weakness - Mild anorexia - Depression with new onset suicidal ideation - Hypoactive delirium - Waxing and waning mentation - Irritability				- New onset confusion with possible right sided weakness − admitted for CVA alert			
Additional Results	- CT Thorax − bilateral ground glass opacities - CT Head - encephalomalacia of the left thalamus and basal ganglia				- CT Head − hypodensity in right thalamus - No infectious processes found to explain mental status changes			

3. Case reports

3.1. Case 1

A 75-year-old male with right sided hemiplegia and expressive aphasia from a prior cerebrovascular accident (CVA) 25 years ago and comorbidities including coronary artery disease, atrial fibrillation, hypertension, and chronic obstructive pulmonary disease complained of a dry cough during the COVID-19 pandemic. Six days after initial symptoms, he tested positive for COVID-19. Overall, his symptoms were mild, yet he complained of anorexia and poor nutrient intake. Two weeks from his initial symptoms, he complained of progressive weakness and functional decline, reporting that he could no longer care for himself at home. Symptoms at this point included anorexia, muscle weakness, magnified depression, irritability and agitation, and weight loss of 12% of his usual weight with muscle and fat wasting, resulting in a malnutrition diagnosis. Medication taken prior to admission included amlodipine, atorvastatin calcium, losartan, oxybutynin chloride, potassium chloride, furosemide, and metoprolol tartrate. Head computed tomography showed encephalomalacia involving the left thalamus and basal ganglia likely due to previous CVA. The esophagogastroduodenoscopy revealed normal gastrointestinal findings. Oral nutritional intake continued to be very poor for the first eight days of his hospital stay despite attempts to increase nutrition with oral nutrition supplements, modifications to meal patterns and frequent encouragement. During this time the patient's neurological findings worsened with waxing and waning delirium, encephalopathy and increasing agitation. The interdisciplinary team determined that a nasogastric feeding tube would be placed to provide supplemental nutrition. Registered dietitians on the team determined that the patient was high risk for refeeding syndrome and recommended thiamine supplementation prior to initiating enteral nutrition with a standard enteral formula. Daily 100 mg intravenous thiamine was started and continued for the next seven days. Nutritional needs were met with enteral nutrition within 72 h of feeding tube placement. Within 48 h of nutrition intervention the patient was alert and oriented. Appetite had improved within four days of nutrition intervention and continued to improve over the next seven days with decreasing irritability and resolved delirium. For full nutrition assessment details see Table 1. The enteral feeding tube was removed, and the patient discharged on hospital day 19.

3.2. Discussion

Although the team did not suspect thiamine deficiency initially, it was determined that after sudden improvement in symptoms within days of intravenous thiamine, retrospective review of the patient's symptoms aligned with thiamine deficiency. The overlap of symptoms expected with COVID-19 and malnutrition did not put

Table 2
COVID-19 symptoms that relate to micronutrient deficiencies and associated nutrient depleting medications [50—57].

Symptoms	Associated Nutrient Deficiencies	Medications that may deplete associated nutrients
Anxiety	Vitamin C	- Aspirin
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC
Apathy	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Niacin	- Antipsychotics
	Zinc	- Diuretics/ACE inhibitors
Ataxia	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Cobalamin	- OHA/Acid-suppressants
Confusion	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Niacin	- Antipsychotics
Depression/Mood Change	Vitamin C	- Aspirin
	Niacin	- Antipsychotics
	Pyridoxine	- Oral Contraceptives
	Biotin	- Anticonvulsants/Antibiotics
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC
	Cobalamin	- OHA/Acid-suppressants
	Zinc	- Diuretics/ACE Inhibitors
	Magnesium	- Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
Dizziness	Magnesium	- Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
Encephalopathy	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Niacin	- Antipsychotics
Headache	Pantothenic Acid	- Aspirin/Antibiotics
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC
Irritability	Vitamin C	- Aspirin
	Pantothenic Acid	- Aspirin/Antibiotics
	Pyridoxine	- Oral Contraceptives
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC
	Cobalamin	- OHA/Acid-suppressants
Loss of Appetite	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Niacin	- Antipsychotics
	Pantothenic Acid	- Aspirin/Antibiotics
	Magnesium	Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
Changes in ability to concentrate	Niacin	- Antipsychotics
	Cobalamin	- OHA/Acid-suppressants
	Magnesium	- Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
Muscle Cramps	Magnesium	- Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
Muscle Pain	Vitamin C	- Aspirin
/Tenderness	Thiamine	- Diuretics/Digoxin/Anticonvulsants
Paresthesia of Extremities	Pantothenic Acid Pyridoxine	- Aspirin/Antibiotics
	Biotin	- Oral Contraceptives
	Cobalamin	- Anticonvulsants/Antibiotics
		- OHA/Acid-suppressants
Sleep Disturbances	Pantothenic Acid	- Aspirin/Antibiotics
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC
Shortness of Breath	Vitamin C	- Aspirin
	Vitamin D	- Cholesterol Lowering Meds
	Iron	- Acid-Suppressants
	Thiamine	- Diuretics/Digoxin/Anticonvulsants
	Folate	- OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC OHA/Acid-suppressants
	Cobalamin	- OHA/Acid-suppressants
Weakness/Fatigue	Vitamin C	- Aspirin
	Vitamin D	- Cholesterol Lowering Meds
	Iron	- Acid-Suppressants
	Magnesium	- Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT
	Zinc	- Diuretics/ACE Inhibitors
	All B Vitamins	

OHA — oral hyperglycemic agents HRT — hormone replacement therapies OC — oral contraceptives

thiamine deficiency as a differential diagnosis and therefore no laboratory assessment was completed. This patient was also on furosemide which may have further put him at risk for thiamine deficiency. One study conducted on 149 hospitalized patients who were 50 years or older, found that the sole predictor of low thiamine status was the use of diuretics [41]. In a recent report of three COVID-19 patients with Wernicke Encephalopathy, all three patients received diuretic therapy and responded to thiamine infusions [42]. The authors reported that another 15 patients they were treating with COVID-19 related encephalopathy also responded to thiamine infusion with improved neurological symptoms [42]. The current case demonstrates that not only do ICU patients with COVID-19 need to be closely evaluated for thiamine deficiency but those with less acute hospitalization may also benefit.

3.3. Case 2

A 77-year-old male with a history of congestive heart failure, chronic kidney disease and type 2 diabetes was admitted to the hospital for a suspected CVA. Nutrition specific findings included no reported weight loss, fair to good appetite, and long-term use of the following medications: atorvastatin calcium and aspirin. A nutrition-focused physical exam completed by the dietitian was positive for impaired skin integrity including a stage 1 pressure injury on left heel and ecchymosis on patients left forearm, mottled pale nails, and corkscrew hairs found on patient's forearms. Suspected vitamin C deficiency was identified by the nutrition team, and nutrition interventions included vitamin C 500 mg tab daily and high calorie high protein oral nutrition supplements twice

daily. CVA was ruled out and patient was discharged with vitamin C supplementation. There were no other significant findings during this admission and the diagnosis was undetermined encephalopathy. Full nutrition assessment findings for this initial hospital stay are found in Table 1. However, 8 days later the patient experienced a sudden onset of hypoxia and was admitted for low oxygen saturations, pneumonia and COVID-19 positive status. Supportive care was provided to this patient, and the patient was discharged after five days in the hospital. Patient continued to take vitamin C supplements. Unfortunately, over the course of the next month the patient developed anorexia that resulted in poor nutritional intake and weight loss. Sixty days following his COVID-19 diagnosis he was admitted to the hospital with failure to thrive, and a 33-pound weight loss (16.5% of usual weight) with worsened skin integrity, leukocytosis, left lower lung infiltrate and likely aspiration pneumonia, and a complicated urinary tract infection. Patient was also diagnosed with vitamin D deficiency and macrocytic anemia due to folate deficiency related to his severe malnutrition. Head computed tomography showed tiny focus of hypodensity in right thalamus. The patient continued to decline throughout admission with worsening mental status. The family declined enteral nutrition and requested hospice care, and the patient passed 4 days after admission and 10 weeks after his COVID-19 diagnosis.

4. Discussion

This unfortunate case calls providers to reflect on the relationship between nutrition status and immune function during this pandemic. This case is unique in that the patient presented as generally well-nourished but had two risk factors for vitamin C deficiency: type 2 diabetes mellitus and long-term use of aspirin. This patient had an uneventful hospital admission first for undetermined encephalopathy and then quickly followed with another short stay admission for COVID-19. During the months that followed, despite resolution of clinical COVID-19 symptoms, this patient developed decreasing nutrition intake that resulted in malnutrition and eventual death.

Tissue saturation of vitamin C is equal to 1500 mg, and the level at which clinical deficiency symptoms occur is 300—400 mg [43]. The body tightly controls tissue and plasma concentrations of vitamin C; with a moderate intake of 30—180 mg per day, 70—90% is absorbed [44]. Subclinical deficiencies of vitamin C are more common than once thought [45]. It takes 8—12 weeks of inadequate intake for vitamin C deficiency to begin showing symptoms [45]. Initial symptoms of vitamin C depletion include fatigue and inflammation of the gums [44]. As it progresses, symptoms such as petechiae, ecchymoses, purpura, joint pain, anemia, depression, poor wound healing, hyperkeratosis, and corkscrew hairs [44]. If the disease continues to progress, the deficiency may be life threatening with anasarca, hemolysis, jaundice, and convulsions [45].

Repletion of vitamin C can be administered orally or intravenously. These different routes will produce different vitamin C concentration in the body when administering the same dose [46]. It was found in a study that vitamin C concentrations were consistently higher when given the same dose intravenously versus orally. In this case, the patient was given an oral administration of vitamin C, which produces more tightly controlled plasma values [46]. All aspects of the case should be considered such as severity of illness and ability to swallow when determining which route to administer vitamin C. Individuals with diabetes are reported to have lower vitamin C status [47,48]. This phenomenon of lower vitamin C status in individuals with diabetes was explained by three proposed reasons: decreased renal reabsorption of vitamin C, ascorbic acid uptake competition with glucose, and an increase in oxidative stress in individuals with type 2 diabetes mellitus [47].

The relationship between aspirin and vitamin C has been studied in human subjects and Guinea pigs as neither can endogenously produce vitamin C [40,49]. Aspirin is thought to impact the storage of vitamin C in the leukocytes by inhibiting uptake into these specific cells [40]. Interestingly, high doses of vitamin C may also lead to the body retaining more of the drug [50]. The short-term effect aspirin has on vitamin C depletion is well recognized, yet the long-term effects of aspirin on vitamin C status are not fully clear [40].

Vitamin C affects immune function in a number of ways: modulation of T cell expression of genes, supporting natural killer cell activity providing protection against viral attacks, supporting response of neutrophils, protecting against oxidative stress, and supporting humoral thymus immune antibodies and delayed hypersensitivity responses [51—53]. There have been cases of vitamin C deficiency following infectious epidemics which suggests infections may deplete vitamin C [43]. Patients with pneumonia and acute respiratory distress had significantly lower vitamin C levels when compared to controls; vitamin C status decreased as severity of the condition increased [43]. The same has been found with vitamin D deficiency. Based on the study conducted by Borsche and colleague [35] there is a strong inverse relationship with vitamin D3 levels and mortality when controlling for other factors. Case 2 had extremely low vitamin D3 levels.

Vitamin C has been shown to have preventative benefits considering infections. One study showed for COVID-19 prevention, the recommended daily dosage of oral vitamin C is 2000—3000 mgs per day [54]. This however conflicts with the United States tolerable upper limit of vitamin C in adults which is 2 g per day [54]. As for the therapeutic effects of vitamin C, a study showed that an oral dose of vitamin C, 2000—8000 mgs per day may be beneficial in reducing the incidence and duration of respiratory infections [55]. This same study also found that intravenous vitamin C of 6000—24,000 mgs per day produced lower mortality, intensive care unit, and hospital stays for patients with severe respiratory infections [55].

Unfortunately, in the current case example, the patient had three episodes of pneumonia in the last year of his life. It is unclear in this case example if the patient's vitamin C or D deficiency had any impact on his immune system's ability to recover from the illness. This question will remain unanswered but exploring the role of micronutrients and malnutrition in immunity may heighten provider awareness of how important nutrition may be for elderly patients with COVID-19.

Micronutrient deficiencies rarely occur in isolation. Clinical manifestations occur late in the course of micronutrient deficiency, and routine vitamin and mineral laboratory measurements are infrequent in many hospital settings. Many symptoms of deficiencies overlap with symptoms of other medical conditions. Table 2 outlines common clinical complaints that align with both micronutrient deficiencies and COVID-19. Medications commonly prescribed are also listed in Table 2.

Case 1 and Case 2 both had encephalopathy. Case 1's encephalopathy resolved after thiamine infusion. Case 2 initially presented with a suspected CVA and was discharged with an undetermined reason for the encephalopathy. In hindsight, the authors suspect that other nutrient deficiencies may have been present and not yet diagnosed, as Case 2 had been on diuretics which placed him at risk of this deficiency. The signs and symptoms of encephalopathy may easily be mistaken for signs and symptoms of a stroke; indeed, ischemic strokes can result in encephalopathy [56]. Altered mental status, lethargy, muscle weakness, dysphagia, dysarthria, and nystagmus are symptoms common to both strokes and encephalopathy [56—58].

Both patients highlighted here experienced protein-calorie malnutrition shortly after a COVID-19 diagnosis. Although the

cases were mild and considered clinically resolved, their nutrition status worsened. The mutual relationship between protein-calorie malnutrition and immunity has been well-established in literature [59—62]. Protein-calorie malnutrition is believed the be the primary cause of immune deficiency worldwide [59]. Protein-calorie malnutrition can result in a decreased effectiveness of both innate and acquired immunity [61]. The gut-associated lymphoid tissue is the primary defensive barrier between the body and pathogens present in the gastrointestinal tract [62]. Protein-calorie malnutrition can lead to deterioration of the epithelial layer in the intestines, weakening the protection of the gut-associated lymphoid tissue [59—62] and possibly leading to bacterial translocation [60—62]. Moreover, when activated by an infection, the immune system requires supplies of protein and energy beyond the normal metabolic demands. A triggered immune response leads to immune cell proliferation, necessitating the multiplication of cellular components from protein-based nucleotides and organelles to lipid-based structural components. Protein is further demanded for the creation of Ig proteins, acute-phase proteins, and cytokines and their receptors [62]. In the presence of protein-calorie malnutrition, there may not be adequate provision of the substrates needed to meet these demands, resulting in a diminished response [59,60,62]. There may even be atrophy of lymphoid tissues when protein and energy supplies are scarce [61].

Similarly, an impaired immune system can cause or exacerbate protein-calorie malnutrition, resulting in a vicious cycle [59—62]. Infections can lead to nutrient malabsorption and loss, such as in the incidence of diarrhea or emesis. An infection may result in anorexia which can in turn cause decreased nutrient intake, as was seen in Case 1. Infections can also have a catabolic effect, resulting in the loss of muscle and fat tissues as nutrients are directed towards the immune response [62]. The compounding effects of protein-calorie malnutrition, infection, and a weakened immune system cannot be overlooked in the discussion of these two cases of predicted micronutrient malnutrition.

5. Conclusion

Malnutrition, including micro- and macronutrient deficiencies, are common in elderly patients who have multiple comorbidities. The comorbidities themselves may deplete tissues of valuable nutrients, and the medications used to manage the comorbidities may increase urinary excretion or decrease absorption of the nutrients needed to weather an upcoming cytokine storm. While there are no definitive recommendations for micronutrient supplementation in the post-COVID period at this time, it is recommended that patients with COVID-19 be monitored in the post-COVID period to assess risk factors for nutrient depletion such as inadequate intake and nutrient-depleting medications. Provider education on the overlapping symptoms and a lower threshold for laboratory monitoring of micronutrients may be warranted.

Authorship

All authors developed the manuscript concept. S. Lewis conducted the analysis. S. Lewis wrote the first draft of the manuscript with input from Lora Chizmar and Sydni Liotta.

All authors reviewed and commented on subsequent drafts of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This

material is the result of work supported with resources and the use of facilities at the James A. Haley Veterans' Hospital yet do not represent the views of the Department of Veterans' Affairs or the United States Government.

Declaration of competing interest

No potential conflict of interest is reported by any of the authors.

Acknowledgements

We would like to acknowledge Islena Keyes, RD and Kathleen Sanders, MS, RD for their expertise and consultation while working with the two cases.

References

[1] Aguila EJT, Cua IHY, Fontanilla JAC, Yabut VLM, Causing MFP. Gastrointestinal manifestations of COVID-19: impact on nutrition practices. Nutr Clin Pract 2020 Oct;35(5):800—5.
[2] Aguila EJT, Cua IHY, Dumagpi JEL, Francisco CPD, Raymundo NTV, Sy-Janairo MLL, et al. COVID-19 and its effects on the digestive system and endoscopy practice. JGH open 2020 Jun;4(3):324—31.
[3] Nägele MP, Haubner B, Tanner FC, Ruschitzka F, Flammer AJ. Endothelial dysfunction in COVID-19: current findings and therapeutic implications. Atherosclerosis 2020 Dec;314:58—62.
[4] Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. Crit Rev Clin Lab Sci 2020;58(5):12—21.
[5] Almeida Joana Ferro Machado de, Chehter EZ. COVID-19 and the gastrointestinal tract: what do we already know? Einstein (Sao Paulo, Brazil) 2020;18: eRW5909.
[6] Whittle J, Molinger J, Macleod D, Haines K, Wischmeyer PE, Whittle J, et al. Persistent hypermetabolism and longitudinal energy expenditure in critically ill patients with COVID-19. Crit Care 2020;24(1):9—28.
[7] Pero A, Ng S, Cai D. COVID-19: a perspective from clinical neurology and neuroscience. Neuroscientist 2020 Oct-Dec;26(5—6):387—91.
[8] Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020 12 May;5(7):667—78.
[9] Mudatsir M, Fajar JK, Wulandari L, Soegiarto G, Ilmawan M, Purnamasari Y, et al. Predictors of COVID-19 severity: a systematic review and meta-analysis. F1000Res 2020 9 Sep;9:1107.
[10] Pergolizzi JV, Raffa RB, Varrassi G, Magnusson P, LeQuang JA, Paladini A, et al. Potential neurological manifestations of COVID-19: a narrative review. Postgrad Med 2020 Oct 22:1—11.
[11] Thibault R, Coëffier M, Joly F, Bohé J, Schneider SM, Déchelotte P. How the Covid-19 epidemic is challenging our practice in clinical nutrition-feedback from the field. Eur J Clin Nutr 2021 Mar;75(3):407—16.
[12] Patel JJ, Martindale RG, McClave SA. Relevant nutrition therapy in COVID-19 and the constraints on its delivery by a unique disease process. Nutr Clin Pract 2020 Oct;35(5):792—9.
[13] Ochoa JB, Cárdenas D, Goiburu ME, Bermúdez C, Carrasco F, Correia M. Lessons learned in nutrition therapy in patients with severe COVID-19. JPEN - J Parenter Enter Nutr 2020 Nov;44(8):1369—75.
[14] Mechanick JI, Carbone S, Dickerson RN, Hernandez BJD, Hurt RT, Irving SY, et al. Clinical nutrition research and the covid-19 pandemic: a scoping review of the ASPEN COVID-19 task force on nutrition research. JPEN - J Parenter Enter Nutr 2021 Jan;45(1):13—31.
[15] Mendelson M, Nel J, Blumberg L, Madhi SA, Dryden M, Stevens W, et al. Long-COVID: an evolving problem with an extensive impact. S Afr Med J 2020 23 Nov;111(1):10—2.
[16] Fernández-Quintela A, Milton-Laskibar I, Trepiana J, Gómez-Zorita S, Kajarabille N, Léniz A, et al. Key aspects in nutritional management of COVID-19 patients. J Clin Med 2020 Aug 10;9(8).
[17] Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the Covid Symptoms Study App. 2020 21 Oct.
[18] Pironi L, Sasdelli AS, Ravaioli F, Baracco B, Battaiola C, Bocedi G, et al. Malnutrition and nutritional therapy in patients with SARS-CoV-2 disease. Clin Nutr 2021 Mar;40(3):1330—7.
[19] Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr 2020 Jun;39(6): 1631—8.
[20] Di Filippo L, De Lorenzo R, D'Amico M, Sofia V, Roveri L, Mele R, et al. COVID-19 is associated with clinically significant weight loss and risk of malnutrition, independent of hospitalisation: a post-hoc analysis of a prospective cohort study. Clin Nutr 2021 Apr;40(4):2420—6.

[21] Anker MS, Landmesser U, Haehling S, Butler J, Coats AJS, Anker SD. Weight loss, malnutrition, and cachexia in COVID-19: facts and numbers. J Cachexia Sarcopenia Muscle 2021 Feb;12(1):9–13.

[22] White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement: academy of nutrition and dietetics and American society for parenteral and enteral nutrition. JPEN - J Parenter Enter Nutr 2012;36(3):275–83.

[23] Yu P, Cassiere H, DeRosa S, Bocchieri K, Yar S, Hartman A. Hypermetabolism and coronavirus disease 2019. JPEN - J Parenter Enter Nutr 2020 Sep;44(7):1234–6.

[24] Dizdar OS, Baspınar O, Kocer D, Dursun ZB, Avcı D, Karakükcü C, et al. Nutritional risk, micronutrient status and clinical outcomes: a prospective observational study in an infectious disease clinic. Nutrients 2016 29 Feb;8(3):124.

[25] Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. Crit Care 2020;24(1):8–26.

[26] Marik PE, Kory P, Varon J, Iglesias J, Meduri GU. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. Expert Rev Anti Infect Ther 2021;19(2).

[27] Kory P, Meduri GU, Iglesias J, Varon J, Marik PE. Clinical and scientific rationale for the "MATH+" hospital treatment protocol for COVID-19. J Intensive Care Med 2021;36(2):135–56.

[28] Larsen TR, Dragu D, Williams M. Wernicke's encephalopathy: an unusual consequence of the acquired immune deficiency syndrome-case report and literature review. Case Rep Med 2013 Dec 01;2013. 709474–4.

[29] Heye N, Terstegge K, Sirtl C, McMonagle U, Schreiber K, Meyer-Gessner M. Wernicke's encephalopathy — causes to consider. Intensive Care Med 1994;20(4):282–6.

[30] Frank LL. Thiamin in clinical practice. JPEN - J Parenter Enter Nutr 2015 Jul;39(5):503–20.

[31] Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6(5). 05.

[32] Dhir S, Tarasenko M, Napoli E, Giulivi C. Neurological, psychiatric, and biochemical aspects of thiamine deficiency in children and adults. Front Psychiatr 2019;10. -04.

[33] Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. 1998.

[34] Ghelani D, Alesi S, Mousa A. Vitamin D and COVID-19: an overview of recent evidence. Int J Mol Sci 2021 29 Sep;22(19).

[35] Borsche L, Glauner B, von Mendel J. COVID-19 mortality risk correlates inversely with vitamin D3 status, and a mortality rate close to zero could theoretically Be achieved at 50 ng/mL 25(OH)D3: results of a systematic review and meta-analysis. Nutrients 2021 Oct 14;13(10).

[36] Skrobot A, Demkow U, Wachowska M. Immunomodulatory role of vitamin D: a review. Curr Trend Immun Respir Infect: Springer Int Publ 2018:13–23.

[37] Liu G, Zhang S, Mao Z, Wang W, Hu H. Clinical significance of nutritional risk screening for older adult patients with COVID-19. Eur J Clin Nutr 2020 Jun;74(6):876–83.

[38] Allard L, Ouedraogo E, Molleville J, Bihan H, Giroux-Leprieur B, Sutton A, et al. Malnutrition: percentage and association with prognosis in patients hospitalized for coronavirus disease 2019. Nutrients 2020;12(12).

[39] Del Giorno R, Quarenghi M, Stefanelli K, Capelli S, Giagulli A, Quarleri L, et al. Nutritional risk screening and body composition in covid-19 patients hospitalized in an internal medicine ward. Int J Graph Multimed 2020;12:13.

[40] Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of drug–nutrient interactions with chronic use of commonly prescribed medications: an update. Pharmaceutics 2018 20 Mar;10(1).

[41] Suter PM, Haller J, Hany A, Vetter W. Diuretic use: a risk for subclinical thiamine deficiency in elderly patients. J Nutr Health Aging 2000;4(2):69–71.

[42] Oliveira Branco de, Vinicius Marcus, Bernabé DG, Irikura S, Irikura RB, Fontanelli AM, Gonçalves MVM. . Wernicke encephalopathy in COVID-19 patients: report of three cases. Front Neurol 2021;12.

[43] Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. Crit Rev Food Sci Nutr 2021 9 Mar;61(5):742–55.

[44] Vitamin C. Available at: https://ods.od.nih.gov/factsheets/VitaminC-Health Professional/. [Accessed 22 February 2021].

[45] Maxfield L, Crane JS. Vitamin C deficiency. Available at: https://www.ncbi.nlm.nih.gov/books/NBK493187/. [Accessed 28 February 2021].

[46] Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, et al. Vitamin C pharmacokinetics: implications for oral and intravenous use. Ann Intern Med 2004 6 Apr;140(7):533–7.

[47] Will JC, Byers T. Does diabetes mellitus increase the requirement for vitamin C? Nutr Rev 1996;54(7):193–202. -07-193.

[48] Wilson R, Willis J, Gearry R, Skidmore P, Fleming E, Frampton C, et al. Inadequate vitamin C status in prediabetes and type 2 diabetes mellitus: associations with glycaemic control, obesity, and smoking. Nutrients 2017 9 Sep;9(9).

[49] Basu TK. Vitamin C-aspirin interactions. Int J Vitam Nutr Res Suppl 1982 01 Jan;23:83–90.

[50] Vitamin C. (Ascorbic acid). Available at: https://www.mountsinai.org/health-library/supplement/vitamin-c-ascorbic-acid. [Accessed 28 February 2021].

[51] Li YR, Trush MA. Defining ROS in biology and medicine. ROS 2016;1(1). 01–01.

[52] Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev 2017 27 Jul;2017:8416763.

[53] Sanchez-Moreno C, Dashe JF, Scott T, Thaler D, Folstein MF, Martin A. Decreased levels of plasma vitamin C and increased concentrations of inflammatory and oxidative stress markers after stroke. Stroke 2004 1 Jan;35(1):163–8.

[54] Ajdžanovic V, Filipovic B, Šošic-Jurjevic B, Miler M, Miloševic V. Margins of beneficial daily dosage of supplements in prevention of COVID-19. EXCLI J 2021 1 Jan;20:828–34.

[55] Holford P, Carr AC, Jovic TH, Ali SR, Whitaker IS, Marik PE, et al. Vitamin C—an adjunctive therapy for respiratory infection, sepsis and COVID-19. Nutrients 2020 7 Dec;12(12).

[56] Erkkinen MG, Berkowitz AL. A clinical approach to diagnosing encephalopathy. Am J Med 2019 Oct;132(10):1142–7.

[57] Yew Kenneth S, Cheng Eric M. Diagnosis of acute stroke. Am Fam Physician 2015;91(8):528–36.

[58] Encephalopathy Information Page. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Encephalopathy-Information-Page. [Accessed 24 August 2021].

[59] Katona P, Katona-Apte J. The interaction between nutrition and infection. Clin Infect Dis 2008 15 May;46(10):1582–8.

[60] James PT, Ali Z, Armitage AE, Bonell A, Cerami C, Drakesmith H, et al. The role of nutrition in COVID-19 susceptibility and severity of disease: a systematic review. J Nutr 2021 12 May;151(7):1854–78.

[61] Bourke CD, Berkley JA, Prendergast AJ. Immune dysfunction as a cause and consequence of malnutrition. Trends Immunol 2016;37(6):386–98.

[62] Calder PC. Feeding the immune system. Proc Nutr Soc 2013 Aug;72(3):299–309.