Neha D. Shah, MPH, RD, CNSC, CHES, Series Editor
Elizabeth Wall, MS, RDN-AP, CNSC, Series Editor

Exploring the Role of Vitamin C in Gastrointestinal Function and Disorders


Hannah Freid


Mark Shneyderman


Sonia Mehra


Abigail Bacharach


David Kohler


Stephanie Gold

Vitamin C, also known as L-Ascorbic Acid, is a water-soluble vitamin that cannot be synthesized by humans and is commonly found in many fruits and vegetables. Although vitamin C is traditionally known for its role in the immune system, this vitamin also has many other functions in the human body including as a cofactor in enzymatic reactions, supporting catecholamine production, and aiding tissue repair.[1] Of interest, vitamin C plays a role in almost every organ system, including the gastrointestinal tract. From the stomach to the pancreas, small intestine, liver and colon, vitamin C plays a role in the pathophysiology of many common disorders encountered by gastroenterologists. This review will focus on the role of vitamin C in many of these diseases of the gastrointestinal tract, including, but not limited to H. pylori associated peptic ulcer disease, pancreatic cancer, metabolic associated steatotic liver disease (MASLD), constipation and inflammatory bowel disease.

INTRODUCTION

Vitamin C, also known as L-Ascorbic Acid, is a water-soluble vitamin commonly found in many fruits and vegetables.[1] Unlike many other organisms, humans lack the enzymatic ability to synthesize vitamin C endogenously and therefore they must depend on the diet to obtain their daily requirements. Although vitamin C is often highlighted for its role in immune system

Hannah Freid[1] Mark Shneyderman[1] Sonia Mehra MD[2] Abigail Bacharach MD[2] David Kohler MD[3] Stephanie Gold MD[4] [1]Icahn School of Medicine at Mount Sinai Hospital [2]Department of Internal Medicine, Icahn School of Medicine at Mount Sinai Hospital, [3]Department of Pediatrics, Icahn School of Medicine at Mount Sinai Hospital[4] The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

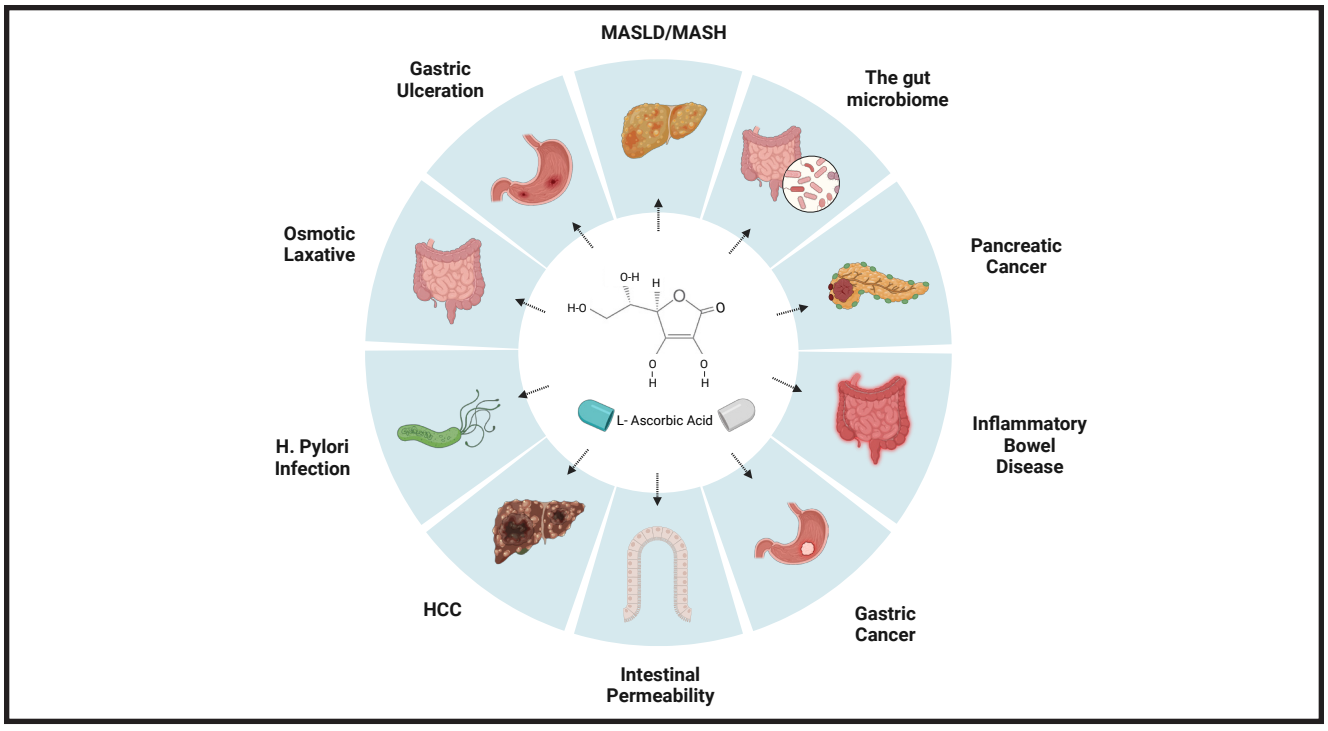

Figure 1. The impact of ascorbic acid (vitamin C) on the gastrointestinal tract, including the stomach, pancreas, liver, small bowel and colon *Figure created with Biorender.com*

function, it also has many other functions in the human body including as a cofactor in enzymatic reactions, supporting catecholamine production, and aiding tissue repair.[1] As a cofactor, vitamin C is involved in numerous enzymatic reactions for the biosynthesis of collagen, L-carnitine and some neurotransmitters.[2] Vitamin C is also a crucial physiologic antioxidant in the human body, donating electrons and scavenging reactive oxygen species, limiting damage by free radicals and oxidative stress.[1,2] With all of these properties, vitamin C is involved in the synthesis of neurotransmitters and hormones in the nervous system. Vitamin C has been shown to affect almost all of the organ systems in the body and may underly many of the pathologic conditions that impact patients today. More specifically, studies have suggested that vitamin C deficiency may play a role in cancer development, diabetes, chronic inflammatory disorders, neurodegenerative disorders and even metal toxicities.[3] In this review, we will focus on the function of vitamin C in the gastrointestinal (GI) tract and its role in major GI illnesses. (**Figure 1**)

Absorption and Bioavailability of Vitamin C

Vitamin C is absorbed in the distal small bowel and this process is regulated by renal excretion. At doses of 100-200 mg, nearly 100% of vitamin C can be absorbed in the small bowel, however, at higher doses (>500 mg), significantly less is absorbed and the excess is excreted in the urine.[4] Vitamin C is absorbed through simple diffusion and active transporters (using sodium dependent vitamin C transporters and hexose transporters). The bioavailability of naturally occurring vitamin C (from food) and synthetic vitamin C (from supplements) is thought to be identical; in a study of 68 healthy men, plasma vitamin C levels rose equally after consumption of broccoli, orange juice, and a synthetic supplement.[4,5]

Vitamin C Sources and Daily Requirements

Given that humans are unable to synthesize vitamin C, dietary consumption is incredibly important to maintain healthy levels. Fruits and vegetables are the major sources of vitamin C in the American diet. While grains are not a natural source of vitamin C, many cereals and flours in the United States are fortified for additional supplementation. Of note, animal proteins contain no vitamin C. Foods highest in vitamin C are listed in **Table 1**. Synthetic vitamin C supplements contain ascorbic

acid in various forms, all of which have similar bioavailability. The majority of supplements contain ascorbic acid or its related sodium salt, sodium ascorbate.[4] The mineral/salt forms of ascorbic acid, including sodium ascorbate and calcium ascorbate are thought to be less acidic and potentially better tolerated (fewer GI side effects).[4]

The recommended dietary allowance (RDA) of vitamin C varies based on age and biologic sex as well as a patient's smoking, pregnancy and lactation status.[2,4] Ideally patients would consume the minimum amount to maintain a steady state neutrophil vitamin C concentration with minimal excess renal excretion.[2] Studies have demonstrated that current and past smokers have consistently lower levels of plasma and neutrophil vitamin C levels as compared to never smokers, likely secondary to the increased oxidative stress associated with nicotine.[2] Therefore, it is recommended to increase the RDA by 35 mg/day in those who are active or prior smokers.[2,4] The RDA for vitamin C is listed in **Table 2**. Vitamin C deficiency is commonly diagnosed based on symptoms and plasma blood testing. Symptoms of vitamin C deficiency include changes in hair and nails, bleeding gums, fatigue and weakness, as well as skin changes.[4]

Table 1. Food Sources of Vitamin C

Food	Serving Size	Vitamin C (mg)
Acerola Cherries	½ cup	825
Bell Peppers	1 cup	152
Kiwi Fruit	1 fruit	132
Guava	1 fruit	125
Grapefruit	¾ cup of fruit	94
Orange Juice, fresh	¾ cup	93
Strawberries	1 cup	85
Orange	1 fruit	65
Broccoli, cooked	½ cup	51
Brussels sprouts, cooked	½ cup	37
Potato, white (with skin)	1 (medium)	22
Tomato	1 (medium)	17
Cheerios	1.5 cups (1 serving)	~8

Information obtained primarily from Oregon State University Linus Pauling Institute Micronutrient Information Center.[4]

Vitamin C and Gastric Disease

The role of vitamin C in the pathophysiology of gastric disease has been a topic of investigation for nearly a century, and vitamin C deficiency has been identified in the most common gastric diseases including gastritis, peptic ulcer disease, and gastric cancer.[6-8] Gastric cytoprotection relies on both endogenous and ingested antioxidants, including vitamin C, so the well-established association between vitamin C deficiency and gastric disease is not suprising.[8] The prevalence of vitamin C deficiency in gastric diseases is currently attributed to four mechanisms: insufficient vitamin C intake, decreased vitamin C absorption, increased metabolic requirement for ascorbic acid in gastric diseases, and increased destruction of vitamin C in the diseased stomach.[6]

H. Pylori Infection and Gastric Ulceration

Reduced plasma and gastric vitamin C levels are seen in H. pylori (HP) infection. Henry et al.[9] and Woodward et al.[10] noted decreased dietary vitamin C in H. pylori-positive subjects relative to uninfected individuals. After correcting for the reduced dietary intake, vitamin C levels were still significantly lower in infected patients relative to controls, suggesting that HP infection impairs the bioavailability of dietary vitamin C.[9-12] The correlation between low vitamin C levels and HP infection could also be explained by vitamin C's crucial role in collagen synthesis. Vitamin C is a cofactor in the synthesis of type IV collagen, which is a component of the lamina propria within the stomach. In this way, vitamin C helps strengthen the stomach's connective tissue, making it difficult for HP to infiltrate the gastric epithelial cells.[13,14] Finally, vitamin C inactivates the HP urease enzyme, inhibiting the bacteria's ability to survive in the stomach's acidic environment.[8]

Despite our understanding of how vitamin C may impede HP's infiltration and survival in the stomach, randomized trials have yielded inconsistent data on the effects of vitamin C supplementation on HP eradication.[14,15] Many studies have demonstrated that HP eradication is improved by supplementing triple therapy with vitamin C and some even argue that vitamin

Table 2. Recommended Dietary Allowances for Vitamin C Across the Lifespan

	Vitamin C Recommended Dietary Allowances				
Age	**Male (mg)**	**Female (mg)**	**Pregnancy (mg)**	**Lactation (mg)**	**Smoking (mg)**
0-6 months	40*	40*			
7-12 months	50*	50*			
1-3 years	15	15			
4-8 years	25	25			
9-13 years	45	45			
14-18 years	75	65	80	115	110
19+ years	90	75	85	120	125

**AI: Adequate intake values Information obtained primarily from the National Institute of Health Vitamin C Fact Sheet[2]*

C intake for extended duration after HP triple therapy is beneficial in preventing re-infection in susceptible individuals.[16-21] However, other studies have found no significant therapeutic effect of vitamin C intake, suggesting that further research is needed to better understand this relationship.[22]

Vitamin C supplementation may also be beneficial in preventing gastric ulcers and their complications, such as upper gastrointestinal bleeds (UGIB). Clinical trials have shown that Vitamin C is gastroprotective and attenuates non-steroidal anti-inflammatory-drug-induced gastric damage.[23-28] Additionally, vitamin C deficiency is highly prevalent among patients with UGIB and is associated with worse outcomes, greater mortality risk, and longer hospital stay after UGIB.[29]

Gastric Malignancy

Finally, an inverse relationship has been observed between vitamin C and gastric cancer incidence.[7,15,30-32] Many studies have demonstrated that increased vitamin C intake reduces the risk of gastric cancer development.[7,33] This may be due to vitamin C's ability to reduce oxidative stress, preventing cellular and DNA damage that may be associated with the development of gastric cancer.[33,34] Antineoplastic effects of ascorbic acid may also be related to its inhibition of the formation of certain carcinogens such as N-nitroso compounds.[35,36] Kong et al. provides a specific dose needed to achieve vitamin C's risk reduction effect, suggesting that 100 mg of vitamin C intake per day, a dose well under the tolerable upper intake level for vitamin C, significantly reduces the risk of gastric cancer.[37] Vitamin C's protective effects against gastric cancer may also be mediated by its interaction with HP infection, as HP is a leading cause of gastric cancer worldwide.[33,38] Of interest, Kim et al. found that HP infection was a significant risk factor for gastric cancer in patients with low vitamin C intake, but not in patients with high vitamin C intake, implying that vitamin C consumption modifies the relationship between H. pylori and gastric cancer.[39]

Vitamin C and Pancreatic Disease

Pancreatitis

Given vitamin C's role as an important antioxidant in human blood, it has been studied as a potential mediator for acute and chronic pancreatitis. In a study comparing patients with acute pancreatitis on admission to the hospital with healthy controls, those with pancreatitis had a significantly lower plasma vitamin C level (15 μg/mL vs. 2.8 μg/mL).[40] The authors suggested that in patients with acute pancreatitis, significant oxidative stress from the underlying insult denatures the vitamin C that is available and results in a significant drop in plasma vitamin C levels.[40] A systematic review showed that a combined antioxidant including vitamin C, selenium, beta carotene, vitamin E and methionine improved pain in patients admitted with chronic pancreatitis.[41] Similarly, a study of 84 patients with acute pancreatitis demonstrated that those who received high dose intravenous vitamin C supplementation (10 grams/day) had a shorter hospital duration and lower mortality compared to those in the standard of care group.[42]

Pancreatic Cancer

Vitamin C has similarly been studied to assess its role in the pathogenesis and treatment of pancreatic malignancies. Numerous observational studies have suggested that there is an inverse relationship between vitamin C intake and the risk of developing pancreatic cancer. Given this, a meta-analysis was performed including 20 studies and roughly 5,000 cases of incident pancreatic cancer; in this study, the relative risk for developing pancreatic cancer in the highest and lowest consumption of vitamin C was 0.58 vs. 0.66.[43] The authors of this study concluded that there was insufficient evidence to suggest that vitamin C consumption reduced the risk of pancreatic cancer.[43] This finding was supported by a subsequent systematic review including 12 European and North American studies with 2 randomized controlled trials (RCTs) and 3 Mendelian randomization studies.[44] The authors of this review concluded that there was no evidence to support an association between vitamin C intake and the development of pancreatic cancer.[44]

However, there is stronger evidence on the use of vitamin C in the treatment of pancreatic cancer. Numerous studies to date have demonstrated the antitumor effect of vitamin C in a variety of malignancies.[45] Specifically in patients with pancreatic cancer, high doses of vitamin C have been shown to impede the growth of pancreatic ductal adenocarcinoma cells through reduction in glucose metabolism, trigger apoptosis, and suppress invasion and metastasis of pancreatic adenocarcinoma cells.[45] Vitamin C is of particular interest as a treatment modality in pancreatic cancer, as it has been shown in high doses (intravenously) to selectively induce cytotoxicity in pancreatic cells while sparing normal cells.[46] Research is currently being done in humans to understand the impact of high dose vitamin C on specific pancreatic cancer mutations in order to offer more personalized oncologic treatments.

Vitamin C and Liver Disease

Metabolic Dysfunction-Associated Steatotic Liver Disease & Metabolic Dysfunction-Associated Steatohepatitis

The incidence and prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) is increasing exponentially in the United States.[47,48] Oxidative stress and gut derived lipopolysaccharides (LPS) have been shown to contribute towards the progression of MASLD to MASH.[49,50] As such, the anti-inflammatory and antioxidant effects of vitamin C have been suggested to play an important role in the development of MASLD.[51,52] In addition, vitamin C has been shown to activate the adiponectin pathway, a hormone that can reduce the accumulation of triglyceride levels in the liver, potentially reducing the risk of MASLD.[53-55] Studying the relationship between serum vitamin C levels and the risk of MASLD, Wu et al.[56] performed a cross sectional study of 5,578 participants in a large national survey study (National Health and Nutrition Examination Survey [NHANES]) and found that higher serum vitamin C levels were protective against the development of MASLD in both men and women. However, with inverse variance weighted Mendelian randomization, no causal relationship between serum vitamin C levels and MASLD risk was observed (OR = 0.82, p = 0.502).[56] Two subsequent studies demonstrated that there was no difference in the vitamin C serum and plasma concentrations between those patients with MASLD and healthy controls.[57,58] Looking forward, large prospective studies are necessary to better elucidate this relationship.

Dietary intake of vitamin C has been shown to have protective effects in patients with MASLD and MASH.[59] An RCT in adults with MASLD showed that high vitamin C intake in diet was associated with improved liver biomarkers including lower levels of ferritin and increased albumin.[60] Another RCT including adults with MASLD found that a twelve-week course of vitamin C supplementation led to higher serum adiponectin levels as well as increased intestinal microbiota diversity, both of which may improve liver function recovery in patients with MASLD.[61] Given the potential impact of vitamin C supplementation on liver disease, further studies are necessary to identify the dose and formulation of vitamin C that is most effective. A cross-sectional study of 4500 participants found that serum vitamin C levels of 50.5-67.0 µmol/L were associated with reduced liver disease risk whereas serum levels greater than 67 µmol/L were associated with a higher risk of MASLD, liver

fibrosis and cirrhosis.[62] Which patients would benefit from supplementation and at what doses, formulations, etc. is an area of future research.

Hepatocellular Carcinoma

Given the antioxidant properties of vitamin C and the impact on MASLD and MASH, researchers have studied the use of vitamin C in patients with hepatocellular carcinoma (HCC). Going back to the 1970s, Pauling and Cameron demonstrated that intravenous injections of vitamin C were effective at prolonging survival in patients with advanced malignancies.[63] This same effect was not demonstrated from oral vitamin C supplementation in subsequent malignancy studies. In 2018, Lu et al.[64] demonstrated that intravenous vitamin C supplementation had a significant effect on prolonging tumor free survival in patients with HCC. In a subsequent in vitro study, the effect of combined vitamin C and Lenvatinib was studied in HCC cells; in this study, vitamin C alone significantly reduced the proliferation, migration and invasion of HCC cells while vitamin C in combination with Lenvatinib showed a synergistic relationship in inhibiting cancer cell proliferation.[63] This study suggested that vitamin C may have a beneficial role in the treatment of HCC; however, once again, the correct dose and method of delivery needs to be identified.[63]

Vitamin C and the Small and Large Intestine

Intestinal Permeability and Injury

Over the last decade, there has been variability in the findings from the literature evaluating the impact of vitamin C on intestinal permeability, which may be secondary to significant heterogeneity in study design (vitamin C dose, definition of gut permeability etc.). In a recent study assessing the impact of vitamin C on intestinal permeability and absorption, Sequeira et al.[65] compared the effects of oral aspirin and ascorbic acid on excretion in healthy adults, demonstrating that in the 3 hours following intake, lactulose excretion was significantly greater following ascorbic acid administration alone as compared to aspirin administration alone ($p<0.05$). Of interest, the authors identified that aspirin and ascorbic acid have an additive effect, with the combined administration of these two substances leading to the greatest increase in intestinal permeability.[65] This study suggested that vitamin C may be useful in increasing paracellular nutrient absorption, which is a route of many nutrients, such as calcium and oxalate. [66,67]

Looking at intestinal injury, McAlindon et al.[68] investigated the impact of vitamin C on gastric mucosal reactive oxygen metabolites and gastroduodenal injury as assessed on endoscopy in healthy volunteers. In this study, vitamin C administration significantly reduced duodenal injury and therefore the authors proposed that vitamin C may have a protective effect against aspirin induced duodenal injury.[68-70] There are few other studies in humans assessing this effect; however, in a study assessing the protective effect of vitamin C in rats who undergo ethanol induced duodenal injury, a combination of vitamin C, vitamin E and selenium was found to be protective against duodenal damage.[71]

Microbial Diversity

Many studies have demonstrated that vitamin C supplementation has the ability to shift the intestinal microbiome and potentially increase diversity.[72,73] More specifically, these studies have demonstrated an increase in the family *Lachnospiraceae* in the stool with vitamin C supplementation, which may result in decreased systemic inflammation through the production of anti-inflammatory short chain fatty acids.[74] In a small study of 14 individuals given 1000 mg daily vitamin C supplementation for 2 weeks, Otten et al.[72] found increases in Lachnospiraceae ($p< 0.05$) and decreases in other species, such as Bacteroidetes ($p<0.01$) and Enterococci ($p < 0.01$), when analyzing stool samples. Similarly, in a randomized control trial, Pham et al.[75] found vitamin C supplementation to significantly increase population size of a specific species of Lachnospiraceae and to also increase alpha diversity, a measure of biodiversity, across 12 participants given 500 mg/day vitamin C. In a study looking at individuals already taking vitamin C supplementations for various reasons, Hazan et al.[76] noted shifts in bacterial populations as well, however, the authors did not find an overall increase in microbiome diversity. The authors suggest that this variability may be secondary to differences in vitamin C dosing, route of administration and duration of supplementation.[76]

Ultimately, it remains unclear whether these shifts in the microbiome's composition provide clinically meaningful health benefits.

Osmotic Laxative

Vitamin C has been noted to be an excellent osmotic laxative. In fact, studies have evaluated the use of vitamin C in combination with polyethylene glycol (PEG) solutions for colonic cleansing prior to colonoscopy.[77] Due to the hexose structure of vitamin C, a portion of orally consumed vitamin C is absorbed in the proximal small bowel and the unabsorbed fraction can act as an osmotic agent, drawing water into the bowel. In a small pilot study of 6 healthy volunteers who were undergoing screening colonoscopy, patients who received PEG in addition to 10 grams of vitamin C had 35% greater stool volume compared to those who had the standard of care PEG alone (2.2 L vs. 1.4 L; $P < 0.01$).[2,77] However, a subsequent study from Mouly et al.[77] compared 6 colon cleansing solutions with varying amounts of PEG and vitamin C; in this study, all of the solutions had similar tolerability and no significant statistical difference in stool volume, suggesting that the presence of vitamin C did not increase the effectiveness of the bowel preparation. Future studies are needed to better understand whether added vitamin C can improve the effectiveness of bowel preparations for colonoscopy.

Given that the unabsorbed fraction of vitamin C is not absorbed and can act as an osmotic laxative in the bowel, researchers have evaluated whether vitamin C rich foods or supplementation can be used for slow transit constipation. In a study looking at the impact of dietary factors on constipation in generally healthy adults, there was a significant positive correlation between intake of vitamin C and constipation.[78] Moreover, in a community-based study assessing the prevalence of constipation in young children, the authors suggested that children with constipation had significantly lower intakes of vitamin C ($p=0.041$) compared to those children who did not have constipation.[79]

Inflammatory Bowel Disease

Vitamin C plays a significant role in inflammatory bowel disease (IBD), and its importance has started to come into focus over the past several years. One small study of Crohn's patients found that administration of vitamin C had a beneficial effect on T-cell function.[80] In addition, as mentioned above, vitamin C plays a role in modulation of the microbiome, which is incredibly important in patients with IBD.[81] Additionally, vitamin C is a strong antioxidant that can modulate gut inflammation and may be associated with improved bone mineral density; vitamin C is crucial for wound healing in IBD patients who have had courses of steroids.[81-86] Finally, vitamin C consumption is known to increase iron absorption in the small bowel, which is important for patients with IBD who are prone to iron deficiency anemia due to luminal bleeding and decreased iron absorption.

Patients with IBD are prone to micronutrient deficiencies for a myriad of reasons, including decreased food intake, malabsorption, increased GI losses, and increased nutritional needs in the setting of systemic inflammation.[86] Traditional guidance for patients with strictures, ileostomies, and those with active IBD symptoms has included restriction of fresh fruits and vegetables. However, this recommendation has changed and we now understand that modification of these foods, including peeling, cooking and pureeing is far superior to restriction, as restriction leads to a myriad of nutritional deficiencies. Unfortunately, vitamin C deficiency often goes undiagnosed in patients with IBD and the clinical implications have not been extensively studied. In one study evaluating the prevalence of vitamin C deficiency in IBD patients, 21.6% of patients in the study had a vitamin C deficiency (24.4% of Crohn's disease patients and 16% of ulcerative colitis patients).[84] In a subsequent case series of patients with IBD and vitamin C deficiency, 16 (80%) of patients had symptoms consistent with clinical scurvy including arthralgias, rash, gingivitis, and brittle hair/nails and the majority of these patients (56%) reported fruit and vegetable avoidance.[83] While restriction of fruits and vegetables certainly plays a role in vitamin C deficiency, patients with IBD have been found to have polymorphisms in vitamin C transporter genes and tumor necrosis factor alpha (TNFa), an important inflammatory cytokine in IBD, which downregulates the transcription of vitamin C transporters, further reducing the

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capacity for vitamin C uptake.[84] Furthermore, vitamin C is absorbed in the jejunum and ileum, which are commonly affected areas in Crohn's disease.[84,86]

Studies have demonstrated that vitamin C deficiency has been linked with worsened clinical outcomes and disease progression. In the aforementioned study evaluating the prevalence and impact of vitamin C deficiency in patients with IBD, patients with active disease (defined by an elevated C-reactive protein or calprotectin) were significantly more likely to have an abnormal vitamin C level ([CRP: 39.1% vs. 16.9%, $P < 0.001$], [Calprotectin: 50.0% vs. 20.0%, $P = 0.009$]).[84] While this could be secondary to dietary changes in those with active disease (reduced fruits and vegetable intake for example), univariate analysis demonstrated that penetrating disease (p=0.03), obesity (p=0.02) and need for a biologic (p=0.006) were also associated with vitamin C deficiency in this study.[84] Vitamin C deficiency has also been associated with sarcopenia, which is itself associated with worse clinical outcomes in IBD.[86]

Too Much of a Good Thing? Toxicity of Vitamin C

Vitamin C has very low toxicity and has not been associated with significant health concerns in the general population. Given the vitamin's water-soluble nature, excess vitamin C is excreted in the urine without complications.[87] The upper intake level of vitamin C is 2 grams per day; at doses similar to this, vitamin C is poorly absorbed in the gastrointestinal tract and the unabsorbed vitamin C can cause an osmotic effect, leading to diarrhea and abdominal pain.[87] Intravenous vitamin C can cause migraine headaches, flushing and nausea/vomiting when given at very high doses (above the safe upper limit).[87] Of note, supplementation with more than 250 mg of vitamin C daily can interfere with fecal occult blood testing, resulting in a false negative result. In addition, vitamin C supplementation should be avoided in patients with iron overload; in those specifically with cardiac hemochromatosis, large doses of vitamin C supplementation can lead to rapid mobilization of iron from the heart, leading to potentially fatal cardiac arrythmias.[88] Similarly, in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, vitamin C supplementation can lead to hemolysis and a subsequent renal injury. Finally, vitamin C plays a role in oxalate metabolism, and therefore, may increase the risk of calcium oxalate stones.[89] The Nurses' Health Studies identified that intake of over 1000 mg of vitamin C per day was associated with a 41% increased risk for developing a kidney stone.[89] However, this has been an area of controversy, as other studies have not shown this relationship. A recent systematic review with meta-analysis demonstrated that supplementation with ascorbic acid was associated with a higher risk of kidney stone formation in men, but not in women.[90] Future, prospective studies are needed to better delineate this risk. ■

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Answers to this month's crossword puzzle:

1 M	A	2 C	R	3 O	P	4 H	A	5 G	E	■	6 S	7 O	8 Y	9 S
E	■	L	■	I	■	O	■	E	■	10 A	■	11 X	I	I
12 T	C	E	L	L	■	13 R	14 E	L	A	P	S	I	N	G
A	■	F	■	■	15 E	M	G	■	■	P	■	M	■	N
16 P	A	T	17 H	O	L	O	G	Y	■	18 E	N	E	M	A
L	■	■	P	■	■	N	■	■	■	T	■	T	■	L
19 A	G	20 O	■	21 L	I	E	■	22 G	R	I	23 P	E	24 S	■
S	■	F	■	E	■	25 S	26 P	A	■	27 T	I	R	E	■
28 I	N	F	L	U	X	■	29 I	S	L	E	T	■	30 A	31 U
A	■	■	■	K	■	32 G	E	T	■	■	■	33 C	■	R
■	34 F	35 U	C	O	S	E	■	36 R	U	37 P	T	U	38 R	E
■	■	L	■	C	■	M	■	I	■	A	■	■	39 U	T
40 D	41 E	C	A	Y	■	42 I	N	T	E	S	T	43 I	N	E
44 O	N	E	■	45 T	A	R	■	I	■	T	■	I	■	R
46 N	E	R	V	E	■	47 S	Y	S	T	E	M	I	C	■