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REVIEW

Vitamin C, Gastritis, and Gastric Disease: A Historical Review and Update

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Abstract The discovery of *Helicobacter pylori* as the cause of gastritis and peptic ulcers ushered in the modern era of research into gastritis and into acid-peptic diseases and rekindled interest in the role of ascorbic acid in the pathophysiology and treatment of gastritis and peptic ulcer disease. Here, we review historic and modern studies on ascorbic acid and gastric diseases with an emphasis on *H. pylori* gastritis and its sequelae. The relationship of ascorbic acid and gastritis and peptic ulcer and its complications was extensively studied during the 1930s through the 1950s. Much of this extensive literature has been effectively "lost." Ascorbic acid deficiency was associated with all forms of gastritis (e.g., autoimmune, chemical, and infectious) due in varying degrees to insufficient intake, increased metabolic requirements, and destruction within the GI tract. Importantly, gastritis-associated abnormalities in gastric ascorbic acid metabolism are reversed by *H. pylori*-eradication and potentially worsened by proton pump inhibitor therapy. Diets rich in naturally occurring ascorbic acid are associated with protection of the gastric corpus from atrophy and a reduction in the incidence of gastric cancer possibly through the ability of ascorbic acid to reduce oxidative damage to the gastric mucosa by scavenging carcinogenic *N*-nitroso compounds and free radicals and attenuating the *H. pylori*-induced inflammatory cascade. Ascorbic acid supplementation was possibly associated with a decreased incidence of bleeding from peptic ulcer disease. Pharmacologic doses of ascorbic acid also may improve the effectiveness of *H. pylori*-eradication therapy. Occasionally, looking back can help plot the way forward.

Keywords *Helicobacter pylori* · Ascorbic acid · Vitamin C · Peptic ulcer · Gastritis · Pernicious anemia · Gastric cancer · Dehydroascorbic acid · Intestinal metaplasia · Gastrointestinal bleeding

Introduction

Vitamin C is a micronutrient essential for human health. Vitamin C deficiency results in scurvy, which for centuries was a major health problem for armies and for blue-water sailors. It was long known that ingestion of various plants (e.g., citrus fruits and scurvy grass) would result in clinical improvement of the disease. In addition, early human experimentation showed that scurvy could be prevented by ingestion of citrus fruits and juice, but despite this evidence the cause remained unknown and the data controversial [1]. In the late 19th and early 20th centuries, animal and human experimentation explored the etiology of pellagra, beriberi, and scurvy, all of which subsequently proved to be vitamin-deficiency diseases [1–3]. During that period, investigators were greatly influenced by the work of Pasteur and the germ theory and although the experimental results often pointed to a relation between a food and a disease, the

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possibility that these diseases were microbial in origin (e.g., a result of infected corn or rice) often appeared to the investigators to be a more likely explanation than a simple deficiency of a specific nutrient [1–3].

The discovery and synthesis of what we now know as vitamins and proof that specific diseases could be rapidly reversed or prevented by administration of the specific dietary ingredients brought that phase of discovery to an end and prompted the still-ongoing investigations into the role of vitamins in health and disease. Here, we explore the associations of vitamin C (ascorbic acid) in gastritis with an emphasis on *Helicobacter pylori*-associated gastritis and the *H. pylori*-associated diseases, peptic ulcer disease and gastric cancer.

Vitamin C in Health and Disease

Humans are unable to synthesize ascorbic acid de novo and must rely on dietary sources for vitamin C and its oxidation product, dehydroascorbic acid [4]. Ascorbic acid is an antioxidant that also plays a critical role in the production of key proteins such as collagen, norepinephrine, and serotonin [4]. The daily recommendation of ascorbic acid is 90 mg for men and 75 mg for women. A wide variety of foods, such as oranges, lemons, cabbage, broccoli, tomatoes, and potatoes are high in ascorbic acid and many prepared foods are now fortified with synthetic vitamin C.

Ascorbic acid and dehydroascorbic acid have equal bioavailability. Both are absorbed from the stomach and along the entire length of the small intestine via specific uptake mechanisms involving a number of trans-membrane proteins that facilitate the transport of ascorbic acid at the intestinal brush border. Ascorbic acid is absorbed across cellular membranes via two saturable transporters: the Sodium dependent Vitamin C Transporters 1 (SVCT1) and Sodium-dependent Vitamin C Transporter 2 (SVCT2) [5]. Both transporters exhibit significantly higher affinities for L-ascorbic acid compared to D-ascorbic acid or dehydroascorbic acid and depend on the co-transport of two Na+ ions; however, the transporters differ in their protein kinetics and tissue distribution. SVCT1 has consistently been found to have a higher capacity to transport ascorbate (i.e., higher V_m), whereas SVCT2 has a slightly higher affinity for ascorbate, with a $K_{0.5}$ of 10–70 μM versus 20–100 μM for SVCT1. Consistent with its enzyme kinetics, SVCT1 is found largely in the bulk transporting epithelium of the small intestine, renal proximal tubule, and the liver while SVCT2 is more widely expressed. SVCT2 is located in the gastric mucosa from the base of the stomach to the isthmus and is suspected to mediate basolateral uptake of L-ascorbic acid by gastric glands against a concentration gradient [6]. Studies of ascorbate absorption have shown that both SVCT1 and SVCT2 mRNA are expressed in human intestinal epithelium. Ascorbate transport measurement and imaging analysis using the human intestinal epithelial cell line, Caco-2, revealed that SVCT1 has a predilection for localization in apical membranes [7]. Further study revealed that a region in the carboxyl-terminal portion of SVCT1 targets the protein to the apical membrane of polarized intestinal epithelial cells [7]. As in the stomach, SVCT2 is localized to the basolateral membrane of intestinal cells.

Dehydroascorbic acid absorption occurs along the entire small intestine via facilitated diffusion through sodium-independent carriers; dehydroascorbic acid competes with glucose for uptake through the mammalian glucose transporters GLUT1, GLUT3, and GLUT4 [8]. Human enterocytes contain reductases that convert dehydroascorbic acid to ascorbate, which maintains a low intracellular concentration of dehydroascorbic acid and forms a gradient for continued dehydroascorbic acid uptake [4].

In plasma, ascorbic acid exists mainly in the form of ascorbate ion and reaches a concentration of 30–60 μM, with a maximal concentration of 90 μM, the renal threshold for complete ascorbate reabsorption [4]. Gastric gland ascorbate concentrations are three to ten times higher than plasma levels, suggesting active transport of ascorbic acid into gastric tissue and kinetic analysis of ascorbic acid accumulation in KATO III and AGS gastric epithelial cells revealed the presence of a high affinity saturable transport system with a K_m of 3–11 μmol/l [6].

Normal Ascorbic Acid Levels

Using modern methods, the normal concentration of ascorbic acid in the serum ranges between 30 and 90 μmol/l (0.5 and 1.6 mg/dl). Plasma values between 11 and 23 μmol/l indicate marginal deficiency and values below 11 μmol/l (~0.18 mg/dl) indicate deficiency [9]. These modern values are strikingly similar to those published by Theodore H. Ingalls in 1937 (Table 1) [10].

Measurement of Ascorbic Acid

The early 1900s was a time of great interest in ascorbic acid, which culminated in 1928 when Albert von Szent-Györgyi Nagyrápolt isolated hexuronic acid from the bovine adrenal cortex [11]. By 1933, research from the University of Pittsburgh confirmed that hexuronic acid, which had been renamed ascorbic acid, had anti-scorbutic properties [8, 12, 13]. In 1933, von Szent-Györgyi Nagyrápolt isolated large amounts of ascorbic acid from

Table 1 Plasma ascorbic acid levels as established in 1937

State of nutrition	Category	Plasma ascorbic acid (mg/dl)
Optimum	Saturation	1.00–2.00
	Normal	0.70–1.00
	Low normal	0.50–0.70
Suboptimum		0.30–0.50
Deficiency	Asymptomatic scurvy	0.15–0.30
	Scurvy	0.00–0.15

Adapted from [10]

Hungarian paprika and in 1937 was awarded the Nobel Prize in Physiology or Medicine.

In 1930, Tillmans took advantage of the reducing property of vitamin C to measure plasma and tissue ascorbic acid concentration by titration of study samples with the redox-dye 2,6 dichlorophenol indophenols [14]. Van Eekelen and Harris subsequently showed that it was possible to estimate body stores of ascorbic acid measuring the urinary excretion of ascorbic acid by administration of sufficient vitamin C to saturate body stores during the saturation process [15]. They showed that it was possible to give repeated doses of ascorbic acid to subjects with depleted body stores without a concomitant increase in urinary excretion. However, when the deficiency was corrected, urinary ascorbic acid excretion would increase. The point where this occurred was defined as the saturation point. They found that the dose necessary to produce saturation was associated with a plasma level of 1.4 mg/dl and was inversely proportional to the level of depletion of vitamin C stores in the body [15]. This approach provided a simple, practical test to assess the degree of hypovitaminosis and was subsequently used by many investigators as a clinical test to examine the role of ascorbic acid deficiency in disease [16].

Ascorbic Acid Deficiency in Peptic Ulcer and Gastritis

Using the ascorbic acid saturation test in control patients who ingested the "minimal optimal" daily dose of ascorbic acid of 25 mg/day, Harris et al. [16] identified the daily urinary excretion of the minimal optimal stores to be 13 mg/day. In 1936, Harris et al. [16] measured vitamin C stores in 74 hospitalized patients including 19 with gastric ulceration or dyspepsia. They found that the average daily excretion of ascorbic acid among hospitalized patients was lower than the minimal optimal stores (8.9 vs. 13 mg/day). Furthermore, the 19 gastric ulceration and dyspepsia patients had an average excretion of only 5.6 mg/day. That same year Archer and Graham studied the body saturation of ascorbic acid in 9 patients with gastric or duodenal ulcer and found 6 (66.6 %) to have urinary excretion less then 13 mg/day (Fig. 1) [17].

In 1937, Ingalls studied the urinary excretion of ascorbic acid in children and concurrently measured plasma levels to establish the plasma values for ascorbic acid deficiency (Table 1) [18]. Later that year, Ingalls and Warren compared ascorbic acid levels in 20 peptic ulcer patients with two healthy hospital workers. The ulcer patients had an average plasma ascorbic acid approximately 15 % of controls (0.19 mg/dl compared to 1.25 mg/dl) [10]. In 1940, Field et al. [19] reported that 39 of 58 ulcer patients had blood ascorbic acid levels below 0.5 mg/dl, which is considered a borderline scorbutic level. Twelve (31 %) of these patients suffered gastrointestinal bleeding during the study and ten of these had plasma ascorbic acid levels of less than 0.4 mg/dl [19]. In 1941, Riggs et al. [20] reported that the average plasma ascorbic acid level among 53 ulcer patients was 0.24 mg/dl compared to 0.52 mg/dl for 15 controls.

In 1938, Portnoy and Wilkinson evaluated the effect of oral and intravenous administration of 1,000 mg of ascorbic acid on total body ascorbic acid stores [21]. They studied 107 subjects including 26 normal controls, 25 hospitalized patient controls, 25 ulcer patients without a GI bleed, and 31 ulcer patients with a GI bleed. The plasma ascorbic acid levels of the control groups ranged from 0.60 to 1.85 mg/dl compared to 0.14–0.59 mg/dl in those with peptic ulcer. Oral administration of 1,000 mg of ascorbic acid to the controls resulted in a rapid increase in plasma ascorbic acid in the first 2 h with peaks between 1.80 and 3.5 mg/dl and the urinary concentration of ascorbic acid showed "a maximal increase." In contrast, ulcer patients with initial low ascorbic acid values showed increases to plasma levels of only 0.48–0.60 mg/dl with little or no increases in urinary levels. Using the urinary excretion ascorbic acid saturation test (the excretion rate for patients with "minimal optimal" stores being 13 mg/day) they reported that the urinary ascorbic acid

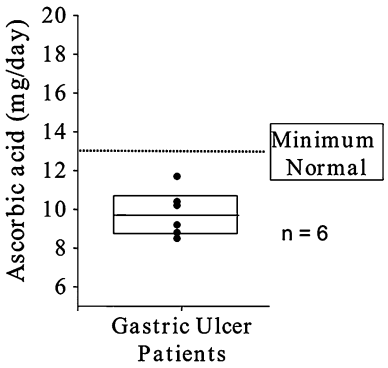

Fig. 1 Urinary ascorbic acid excretion in six subjects with gastric ulcers compared to minimal normal excretion of 13 mg/day. Adapted from [17]

Table 2 Plasma ascorbic acid concentration, urinary excretion, and dose required for saturation amongst peptic ulcer disease and control subjects

Group (*n*)	Plasma AA (mg/dl)	Urinary excretion (mg/day)	Dose needed to reach saturation (mg)
Control [26]	0.6–1.85	29	500–1,000
Hospital control [25]	0.6–1.85	17	1,252
PUD w/o bleed [25]	0.42	7	3,691
PUD w/bleed [31]	0.34	7	4,543

Adapted from [21]

excretion was normal for non-hospitalized controls (29 mg/day) and for hospitalized controls (17 mg/day). In contrast, ulcer patients had daily ascorbic acid urinary excretion of only 7 mg/day. The amount of ascorbic acid needed to saturate body stores was between 500 and 1,000 mg for non-hospitalized controls, 1,252 mg for hospitalized controls, 3,691 mg for ulcer patients without bleeding and 4,543 mg for ulcer patients who had bled (Table 2) [21].

In 1947, Crescenzo and Cayer studied ascorbic acid loading in ulcer patients and controls [22]. They obtained fasting plasma ascorbic acid levels and subsequently provided a 1,000-mg loading dose of ascorbic acid. The plasma ascorbic acid concentration was assessed hourly for 3 h after ascorbic acid loading; the results confirmed the prior observations that patients with peptic ulcer, especially those with ulcer hemorrhage, typically had ascorbic acid deficiency (Table 3) [22].

In 1957, Freeman and Hafkesbring compared the plasma and gastric fluid ascorbic acid concentrations (which were known to reliably represent the total body stores of ascorbic acid) of 108 patients with gastric disease and 113 controls [23]. They showed that mean plasma and mean gastric ascorbic acid level were 50 and 42 %, respectively, lower in those with gastritis, peptic ulcer disease, pernicious anemia, and gastric cancer compared to controls (Fig. 2) [23]. Importantly, as will be emphasized below, low ascorbic acid levels were shown to be present in pernicious anemia, a non-*H. pylori* form of gastritis.

Mechanisms of Ascorbic Acid Deficiency in Gastric Diseases

Increasing evidence of a high prevalence of ascorbic acid deficiency amongst peptic ulcer patients led to investigations into the role of vitamin C in the pathogenesis and the course of peptic ulcer disease. Researchers studied whether ascorbic acid deficiency played a role in the pathogenesis of the ulcer or its complications as well as whether ascorbic acid therapy would treat the ulcer or prevent ulcer complications. Ludden et al. [24] proposed four factors that could be responsible for ascorbic acid deficiency in gastrointestinal disease including: (1) decreased absorption, (2) insufficient intake, (3) increased metabolic requirement, and (4) rapid destruction in the GI tract.

Decreased Absorption

Ludden et al. [24] reported no differences in ascorbic acid absorption between controls and patients with superficial gastritis, chronic hypertrophic gastritis, or peptic ulcer disease. These findings are in accordance with current knowledge that ascorbic acid can be absorbed along the entire small intestine (i.e., at sites distant from the gastric inflammation present in peptic ulcer disease). The authors did however note that patients with chronic atrophic gastritis had diminished absorption and suggested this was likely due to destruction of ascorbic acid in the gastric mucosa, possibly by elevated pH and bacterial overgrowth.

Insufficient Intake

Until recently, foods were not fortified with vitamins and adequate vitamin intake relied solely on the diet. In many regions, maintaining adequate levels was particularly difficult, especially where winters were severe and ascorbic acid-containing foods often became scarce or unavailable. In addition, previously physicians relied heavily on diets

Table 3 Plasma ascorbic acid levels (fasting and hourly after a 1,000-mg ascorbic acid oral challenge) in ulcer patients and hospital controls

Group (*n*)	Fasting (mg/dl)	Hours post infusion (mg/dl) 1	Hours post infusion (mg/dl) 2	Hours post infusion (mg/dl) 3
Bleeding ulcer [7]	0.07	0.25	0.44	0.63
Active ulcer [13]	0.22	0.53	0.90	1.0
Hx of ulcer [10]	0.34	0.70	1.4	1.7
Control [25]	0.64	1.0	1.63	1.83

Adapted from [22]

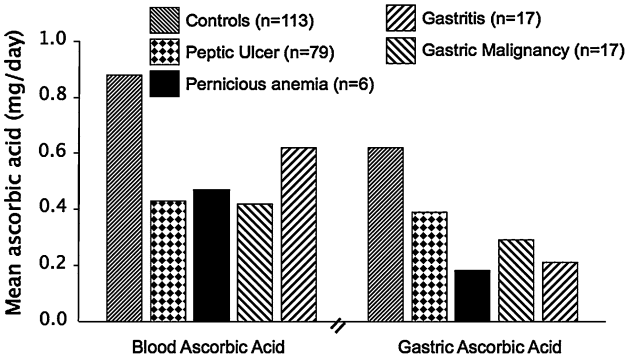

Fig. 2 Plasma and gastric ascorbic acid levels in controls versus subjects with gastric pathology. Adapted from [23]

for the treatment of gastrointestinal diseases and many authors during that period suggested that insufficient intake was likely a major cause or a contributor to ascorbic acid deficiency in peptic ulcer patients. The Sippy diet in particular, which consisted of milk, cream, cereal and eggs, was severely deficient in ascorbic acid [25]. For example, Ebbesen and Rasmussen assessed the plasma ascorbic acid level of 60 ulcer patients on the day of admission to the hospital [26]. All were started on the standard ulcer diet and their plasma ascorbic acid levels were reassessed at 3 to 6-day intervals. By the 12th to 16th day, plasma ascorbic acid levels had dropped by an average of 75 % [26]. Of interest, in 1928 Davidson presented three cases of severe scurvy secondary to adherence to ulcer diets [27] and in 1936 Platt presented three additional cases showing that lessons in medicine are often learned slowly [28].

A recent study suggested that a significant difference in vitamin C intake might exist among *H. pylori*-positive and -negative patients in that the average amount ingested in 14 *H. pylori*-positive subjects was 35.9 mg daily compared to 130.9 mg among 15 *H. pylori*-negative subjects ($p < 0.01$) [29].

Increased Metabolic Requirement

Heinemann, in 1938, suggested that patients with peptic ulcer disease had an increased metabolic requirement for ascorbic acid [30]. He based this hypothesis on use of the ascorbic acid saturation test in four patients with peptic ulcer disease. He found that their requirement was 1.25 mg/kg/day, which was 60 % higher than the 0.7–0.84 mg/kg/day required by controls [30]. These results were rapidly confirmed by Warren et al. [31] in five patients with peptic ulcer disease. In 1953, Breidenbach and Ray fed ten guinea pigs 1 % eugenol to induce gastritis; the control group of 11 received only water [32]. After 7 days, gastric tissue ascorbic acid content in the gastritis group was 44 % lower than the control group, and the authors hypothesized that the decrease was secondary to increased utilization of vitamin C at the site of regeneration in the stomach [32]. This is the second example of reduced ascorbic acid in the stomach related to a non-*H. pylori* form of gastritis (i.e., a chemical gastritis).

Destruction of Ascorbic Acid in the GI Tract

In 1938, Kendall and Chinn suggested that bacterial overgrowth due to achlorhydria caused destruction of ascorbic acid [33]. The following year, Alt et al. [34] compared the plasma ascorbic acid levels among 44 patients with achlorhydria associated with iron deficiency anemia or pernicious anemia with controls. They stratified the results by the amount of ascorbic acid in their diets. The plasma ascorbic acid levels in pernicious anemia subjects with adequate dietary intake was 0.57 mg/dl compared 0.73 mg/dl for iron deficiency anemia and 0.87 mg/dl for controls. The pernicious anemia group that had inadequate dietary ascorbic acid had plasma levels of 0.47 mg/dl compared to 0.64 mg/dl for controls. They also evaluated the effect of pH on ascorbic acid stability in vitro and incubation for 3 h at pH 7.95 resulted in destruction of 65 % of the ascorbic acid versus only 14 % at pH 1.45 [34]. More recent studies have suggested a similar method for destruction of ascorbic acid related to hypochlorhydria induced by potent acid suppression [29, 35]. These recent studies have also highlighted the potential for PPI-associated malabsorption of non-heme iron and vitamin B12 due to reduced release of heme and B12 from ingested food [36–38].

Vitamin C Deficiency and Ulcer Bleeding

Vitamin C is critical for wound repair and several studies have suggested that vitamin C deficiency is associated with an increased risk for peptic ulcer hemorrhage. This hypothesis is consistent with the data shown earlier that bleeding ulcer patients typically had the lower vitamin C levels than ulcer patients who did not bleed [19, 21, 22]. Morris suggested that a diet rich in the vitamin C could play a role in the treatment of hemorrhagic peptic ulcer [39]. He presented two case histories: the first, a 62-year-old man who presented with "typical scurvy of his leg, with punctate hemorrhages about the hair follicle." He was given large doses of vitamin C and told to take citrus juice twice daily. The patient returned 5 years later with similar symptoms and a history of multiple hospitalizations for bleeding from his stomach. He had stopped taking vitamin C and citrus juice; therapy with citrus juice was restarted. At the time of publication, the patient had been adherent to

the dietary therapy and had remained symptom-free for 3 years. The second case was a 45-year-old man with a 5-year history of gastric ulcer and two hospitalizations for gastric bleeding. He was started on the same regimen as the first patient and with strict adherence remained symptom-free for 5 years (the time of publication).

In 1955, Weiss et al. [40] evaluated the use of vitamin C in treating bleeding ulcers. The author graded the response of patients to vitamin C, based on recurrence of symptoms and scheduled guaiac tests, as "good" in 12 of 14 subjects with duodenal ulcers and two patients with gastric ulcer. More recently, McAlindon et al. [41] evaluated vitamin C for the prevention of aspirin-induced gastroduodenal injury and noted a statistically significant reduction in duodenal injury and bleeding in the vitamin C group as assessed by the Lanza score ($p < 0.05$).

H. pylori and Vitamin C Levels

In the pre-*H. pylori* era, investigators clearly showed that vitamin C deficiency was common in gastritis and peptic ulcer disease and they advocated a diet with fresh fruits and vegetables as a part of the treatment regimen. We now know that *H. pylori* infection underlies both gastritis and gastritis-associated peptic ulcers. Predictably, based on the prior work with gastritis and peptic ulcers, vitamin C levels have consistently been confirmed to be low in patients with *H. pylori* infections. For example, in 1995, Rokkas et al. [42] from Greece reported that gastric juice vitamin C levels were significantly lower in 58 *H. pylori*-positive patients than 30 *H. pylori*-negative subjects (12.4 vs. 29.8 mg/dl, $p < 0.001$). In 2001, Woodwall et al. [43] determined *H. pylori* status and plasma vitamin C levels of 1,106 UK subjects; 716 *H. pylori*-positive subjects had vitamin C levels of 64.5 % of that of *H. pylori*-negative subjects ($p < 0.0001$). Capurso et al. [44] reported similar findings using gastric juice vitamin C levels in 32 *H. pylori*-positive patients and 12 healthy controls (0.55 vs. 1.49 mg/dl, respectively; $p < 0.036$). Finally, Simon et al. [45] using the third National Health and Nutrition Examination Survey in the United States reported the serum ascorbic acid levels of 2,189 subjects with *H. pylori* and 4,557 controls to be 0.71 and 0.75 mg/dl, respectively ($p < 0.05$). In subgroup analysis among whites, age-adjusted and multivariate models revealed an inverse association between serum ascorbic acid level and *H. pylori* seropositivity. Each 0.50 mg/dl increase in serum levels was independently associated with a decrease in seropositivity (OR = 0.89, $p < 0.01$). The presence of CagA-antibody was associated with an even stronger inverse relation in whites (OR = 0.31; $p < 0.05$) [45].

Helicobacter pylori eradication was also shown to improve vitamin C levels. For example, Rokkas et al. [42] treated 58 patients with *H. pylori* infection and a mean pre-treatment gastric juice ascorbic acid level of 12.4 mg/dl. Treatment was successful in 45 subjects and the post treatment mean vitamin C level increased to 31.6 mg/dl ($p < 0.001$). There was no significant increase when treatment failed (14.2 mg/dl; p = N.S.). Banerjee et al. [46] studied gastric tissue ascorbic acid levels among 19 *H. pylori*-positive subjects and ten controls; tissue levels were 2.8 versus 17.8 μg/ml for *H. pylori*-positive and -negative, respectively ($p < 0.0005$). Following *H. pylori*-eradication treatment, 11 of 19 subjects became *H. pylori*-negative and their gastric vitamin C level rose from 2.4 to 11.2 μg/ml ($p = 0.01$) with no significant change in the eight subjects who failed eradication therapy (3.6–4.3 μg/ml; p = NS) [46].

Effect of an Acute *H. pylori* Infection

Sobala et al. [47] studied the changes in gastric ascorbic acid during an acute *H. pylori* infection in an endoscopist previously known to be *H. pylori*-negative. The endoscopist had an gastric ascorbic acid level of 37 μmol/l and a brisk increase in gastric ascorbic acid content (1,862 μg in gastric juice recovered over 45 min of nasogastric suction) following a 500 mg intravenous ascorbic acid load 170 days prior to *H. pylori* infection [47]. On day 37 after infection, gastric pH rose to 7.5 and the gastric ascorbic acid level was 2 μmol/l with a minimal response in gastric ascorbic acid content (9 μg) to a 500 mg intravenous load. On day 161, the gastric pH normalized to 2.0 but the gastric ascorbic acid concentration was only 8 μmol/l with a slightly improved response (292 μg) to a 500 mg intravenous load [47].

H. pylori Gastritis and Vitamin C

Helicobacter pylori-induced gastritis inhibits active intragastric secretion of ascorbic acid in the stomach and reduces the total vitamin C concentration in the gastric mucosa by converting the majority of the vitamin to dehydroascorbic acid, which is further oxidized to irreversible metabolites such as 2,3-diketo-L-gulonic acid [8, 47–49]. Rood et al. [50] studied 145 *H. pylori*-infected patients and found elevated gastric pH and damage to the gastric epithelium secondary to *H. pylori* infection to be directly related to decreased gastric ascorbic acid concentration. They showed a direct relationship between increased pH in *H. pylori*-associated gastritis and oxidization of ascorbic acid to the reversible product dehydroascorbic acid and the irreversible product diketogulonic acid. At gastric pH < 2, the average ascorbic

acid was found to be 0.29 mg/ml and the average dehydroascorbic acid was 0.32 mg/ml. The average ascorbic acid value dropped to 0.08 mg/ml at pH 2–4 and to zero at pHs > 6, while the average dehydroascorbic acid value increased to 0.40 mg/ml at pH 2–4 and fell to 0.23 mg/ml at pHs > 6. Dehydroascorbic acid is unstable at higher pH values; consistent with impaired bioavailability of vitamin C being more marked in hypochlorhydric subjects than in normochlorhydric ones. There was also an inverse correlation between damage to the gastric epithelium and ascorbic acid levels. With only superficial damage, the mean gastric ascorbic acid level was 0.48 mg/ml, falling to 0.12 mg/ml with moderate damage and 0 mg/ml with severe damage. Rokkas et al. [51] confirmed the significant inverse correlation between the gastritis activity score and gastric juice vitamin C levels. They studied 30 *H. pylori*-positive subjects and compared their gastric ascorbic acid levels to ten controls. They divided the *H. pylori*-positive subjects into CagA-positive and CagA-negative groups. The gastric ascorbic acid for the *H. pylori*-infected group was 16.3 mg/l compared to 35.5 mg/l for the control group ($p < 0.001$) and 13.8 mg/l for the CagA-positive group compared to 24.8 mg/l for the CagA-negative group ($p < 0.01$) [51]. They noted no significant difference in gastric pH between the groups to account for the changes in gastric ascorbic acid levels. Since gastric ascorbic acid levels are considerably higher then plasma levels, the authors suggested that impaired active secretion of ascorbic acid plays a role in *H. pylori*-induced gastritis [51].

Several groups have also shown that potent acid suppression with PPI therapy is associated with conversion of ascorbic acid to the irreversible product 2,3-diketo-L-gulonic acid leading to a reduction of serum and gastric ascorbic acid levels [29, 35, 38]. The changes in intragastric concentration of ascorbic acid are most marked in *H. pylori*-positive subjects likely related to the more potent acid suppression and the extension of gastritis into corpus mucosa associated with PPI therapy in *H. pylori* infection [52–55].

Intragastric ascorbic acid destruction by bacteria was suggested by Kendall and Chinn in 1938 when they isolated bacteria from gastric aspirates of patients with achlorhydria and showed that they rapidly degraded ascorbic acid [33]. In 1995, Odum and Andersen demonstrated *H. pylori* could itself oxidize and inactivate gastric ascorbic acid. They isolated two factors, one intracellular and one membrane bound, that oxidized ascorbic acid to inactive forms [56].

Vitamin C and Acquisition of *H. pylori*

Low ascorbic acid levels itself may also be a risk factor for *H. pylori* acquisition [57]. Goodman et al. surveyed 684 Colombian households with regards to exposures related to infectious disease transmission and dietary intake and determined the *H. pylori* status of children in the household using the ^{13}C-urea breath test. After accounting for confounding factors such as socioeconomic variables and transmission related exposures using maximum likelihood logistic regression they noted that daily vitamin C intake of less than 40 mg/day of vitamin C resulted in 12.5 (CI = 2.5–62.1) times higher odds of acquiring *H. pylori* compared to those ingesting greater than 120 mg/day. It remains unclear whether vitamin C intake is actually a surrogate for other factors that may correlate with vitamin C intake and also affect transmission such as the level of household hygiene.

Ascorbic Acid and Gastritis

As noted previously, ascorbic acid deficiency has been associated with all forms of gastritis, whether the etiology was autoimmune (pernicious anemia), chemical (in animals), and bacterial (*H. pylori*) [32, 34, 42–45]. *Helicobacter pylori* infection is the most common cause of gastritis in humans; the organisms attach to the mucosal surface and chronically stimulate production of inflammatory cytokines that results in an influx of polymorphonuclear and mononuclear cells characterized as "acute on chronic" inflammation. Since *H. pylori*-induced gastric inflammation is life-long, it can decimate total body ascorbic acid stores by continually quenching high levels of ascorbic acid at inflammatory sites and destroying it in a hypochlorhydric environment.

Effect of Ascorbic Acid on Gastric Inflammation

The clinical outcome of *H. pylori* infections (duodenal ulcer, gastric ulcer, gastric cancer) varies in different regions. This is best illustrated by the marked differences in the geographic distribution of gastric cancer and with the fact that in many areas the incidence of gastric cancer has decreased rapidly over time [58]. The outcome of an individual *H. pylori* infection can best be correlated with the pattern and severity of gastritis; duodenal ulcer is associated with corpus sparing or antral predominant gastritis and gastric ulcer and gastric cancer with atrophic pangastritis [59]. The pattern of gastritis is determined by an interplay between host factors, bacterial virulence factors, and environmental factors. The fact that in the West, the predominant pattern has changed rapidly from one of atrophic pangastritis with a high prevalence of gastric cancer to one where atrophy is no longer common points to the predominance of environmental factors as the

determinant of outcome within a population [59]. The environmental factors that correlate best with the presence of gastric cancer and the change in incidence are diet and the methods of food preservation. Seasonal diets and the use of salt as a primary method of food preservation are associated with atrophic pangastritis and gastric cancer, where as the year around availability of fresh fruits and vegetables protect against it [60]. The increase in the consumption of fresh fruits and vegetables and the use of refrigeration for food preservation have been associated with the significant decrease in gastric cancer incidence in the Western world and with the ongoing decrease in Asia. This has been termed the banana hypothesis [60] and is supported by a large number of published studies and observations [58, 61, 62].

Since at least 1950, it has been recognized that the precursor lesion or soil within which gastric cancer develops is atrophic gastritis/gastric atrophy [59, 63], and, as noted above, fresh fruits and vegetables (i.e., phytonutrients) appear to play a protective role in its pathogenesis. Prior to endoscopy at a dyspepsia clinic, Sobala et al. [64] studied 77 patients who completed a food-frequency questionnaire, with a sensitivity of 73 % and specificity of 81 % at identifying vitamin C intake less then the recommended daily allowance. The data revealed a significant positive correlation between lower vitamin C intake and severity of gastritis (CC = 0.41; $p = 0.0046$). Similarly, Fontham et al. [65] found dietary vitamin C consumption to significantly reduce the risk of gastric cancer precursor lesions while studying 93 subjects with advanced chronic atrophic gastritis and hospital controls (OR = 0.40; $p < 0.01$).

Vitamin C is an important phytonutrient and evidence suggests that ascorbic acid may play a protective role against *H. pylori* gastritis and gastric cancer in part by significantly reducing inflammation-associated oxidative damage to the gastric mucosa [66, 67].

Correa et al. [68] studied the effect of ascorbic acid and *H. pylori* eradication on the progression of pre-cancerous lesion in Colombian towns with high incidence of gastric cancer. A study of 852 patients with a gastric cancer precursor lesion (non-metaplastic atrophy and intestinal metaplasia) at baseline endoscopy, randomized to treatment groups consisting of placebo, anti-*H. pylori* therapy (amoxicillin 500 mg *tid*, metronidazole 375 mg *tid* and bismuth subsalicylate 262 mg *tid* for 14 days), ascorbic acid supplementation (1 g b.i.d. until follow-up), and anti-*H. pylori* therapy with ascorbic acid supplementation. Follow-up endoscopy at 72 months revealed a significantly higher relative risk of histologic regression in the anti-*H. pylori* therapy, the ascorbic acid group and the anti-*H. pylori* therapy plus ascorbic acid group in relation to placebo. In the metaplastic atrophy group the relative risk of regression in comparison to placebo was 4.8 (95 % CI: 1.6–14.2) for anti-*H. pylori* group, 5.0 (95 % CI: 1.7–14.4) for ascorbic acid group and 6.3 (95 % CI: 1.6–24.3) for anti-*H. pylori* plus ascorbic acid group. In the intestinal metaplasia group the relative risk of regression compared to placebo was 3.1 (95 % CI: 1–9.3) for anti-*H. pylori* group, 3.3 (95 % CI: 1.1–9.5) for ascorbic acid group and 4.1 (95 % CI: 1.1–15.9) for anti-*H. pylori* plus ascorbic acid group [68].

Intragastric formation of carcinogenic *N*-nitroso compounds (NOC) has been proposed to be possibly involved in gastric carcinogenesis [54]. NOCs are generated in a nitrosation reaction between gastric nitrite and gastric nitrogenous organic compounds derived from diet [69, 70]. NOC generation is inhibited by ascorbic acid, which scavenges nitrites in gastric juice by converting it to nitric oxide [70, 71]. The ability of ascorbic acid to scavenge nitrite is dependent on the ratio of vitamin C to nitrite and gastric pH. Increased NOC generation occurs with a decreased ratio of vitamin C to nitrite and pH $>$ 2–4 and [72] elevated gastric pH results in conversion of active ascorbic acid to inactive dehydroascorbic acid as well as higher levels of nitrite generation [52]. Several recent studies have linked the use of PPI to decreased vitamin C to nitrite ratio, an effect especially marked in *H. pylori*-infected patients [35]. For example, Mowat et al. [35] demonstrated statistically significant elevation in pH, an increase in fasting and post nitrate bolus nitrite levels, and a decrease in active and total vitamin C in individuals receiving 40 mg of omeprazole daily. The changes in pH, nitrite levels, and vitamin C levels were significantly higher in *H. pylori*-positive subjects compared to uninfected individuals [29, 73]. These studies suggest that PPI therapy in *H. pylori*-infected individuals results in not only a more marked rise in intragastric pH and gastric inflammation but also higher nitrite and lower ascorbic acid levels [53, 74].

Ascorbic Acid and Oxidative Damage to the Gastric Mucosa

Ascorbic acid is thought to decrease oxidative damage to the gastric mucosa by scavenging free radicals and NOCs and attenuating the *H. pylori*-induced inflammatory cascade. In vitro studies using activated polymorphonuclear leukocytes have shown that oxidation of extracellular ascorbate by activated PMNs is stoichiometric with oxygen consumption [75]. The stoichiometric consumption of extracellular ascorbate with respect to oxygen is consistent with the notion that NADPH oxidase production of superoxide on the outside of the cell membrane can be scavenged by ascorbic acid. Electron paramagnetic resonance spectroscopy has also demonstrated that ascorbyl

radicals produced by scavenging of oxygen radicals by ascorbic acid in the gastric mucosa is twofold greater in *H. pylori*-infected gastric mucosa compared to controls [76]. Finally, the concentration of the ascorbyl radical also correlates with markers of radical generation and tissue damage [76]. Of interest, genetic polymorphism in SVCT2 has been shown to be associated with protection against gastric cancer [77]. However, it remains to be shown whether the protective polymorphism is associated with a consistent change in gastric mucosal ascorbic acid levels.

Ascorbic acid supplementation has also been shown to attenuate the *H. pylori*-induced inflammatory response. In one study, 30 *H. pylori*-infected patients with reflux esophagitis were randomized into a groups that received 20 mg of omeprazole with or without 1,200 mg of ascorbic acid daily for 2 weeks and those receiving ascorbic acid had significantly lower levels of gastric corpus mucosal IL-8 and neutrophilic infiltration compared to those who did not ($p < 0.05$) [78].

Ascorbic Acid and Effectiveness of *H. pylori*-Eradication Therapy

In vitro studies show that ascorbic acid produced up to 90 % inhibition of multiple *H. pylori* strains with the highest inhibition occurring at low pH, possibly due to increased stability of vitamin C at low pH [79]. In vivo studies involving 7 days of vitamin C therapy (10 mg/day) given to *H. pylori*-infected gerbils also resulted in a decrease from 10^5 colony-forming units in control to 10^3 in the treatment group [79]. Jarosz et al. [80] randomized patients with *H. pylori* infection and dyspepsia into control ($n = 24$) and treatment ($n = 27$) groups. The treatment group received 5 g of vitamin C daily for 4 weeks, and eight patients achieved *H. pylori* eradication, measured by urease test of gastric biopsy, in the treatment group compared to no patients in the control group ($p = 0.006$) (Table 4). Zojaji et al. [81] randomized 312 patients to two groups; one group received amoxicillin, metronidazole, bismuth, and omeprazole for 2 weeks and the other the same regimen plus 500 mg of ascorbic acid daily. The addition of ascorbic acid resulted in an increase in eradication from 48.8 to 78 % at 4 weeks ($p < 0.0001$) (Table 4). Sezikli et al. [82] randomized 160 patients to receive either lansoprazole, amoxicillin, clarithromycin, and bismuth subcitrate or this regimen plus 500 mg ascorbic acid b.i.d. and vitamin E (200 IU, b.i.d.) for 2 weeks. *H. pylori* eradication increased from 60 to 93.5 % with the addition of the vitamins ($p < 0.005$) (Table 4). Chuang et al. [83] randomized 171 patients into three therapies for 1 week. Group 1 received 20 mg omeprazole daily, 1 g amoxicillin daily and 250 mg of clarithromycin twice daily, group 2 received the same regimen as group 1 plus 500 mg of vitamin C twice daily and group 3 received omeprazole, amoxicillin and 500 mg of clarithromycin twice daily without vitamin C supplementation. The eradication rate increased from 68 % in group 1 to 85 % with the addition of ascorbic acid in group 2 ($p = 0.03$). The difference in eradication rate was not significant between group 2 and group 3 suggesting that vitamin C supplementation might allow a reduction in the dose of clarithromycin required to eradicate *H. pylori* (Table 4). Kaboli et al. [84] found similar results in 214 patients randomized to 250 mg clarithromycin plus ascorbic acid twice daily versus 500 mg clarithromycin twice daily (86.8 vs. 89 %, respectively; $p = 0.623$) (Table 4). Kamiji and Oliveira [85] from Portugal studied 38 *H. pylori*-infected patients without previous antibiotic therapy and eight patients with two previous treatment failures. The 38 patients without previous therapy were divided into a control group ($n = 17$) and a group receiving 5 g of vitamin C daily for 28 days. No patients in the treatment or control group achieved eradication. The eight patients with previous antibiotic treatment failure also failed high dose vitamin C therapy for 28 days (Table 4). Chuang et al. [86] studied 104 *H. pylori*-infected patients randomized to receive either 30 mg lansoprazole, 1 g amoxicillin, and 500 mg metronidazole twice daily for 1 week or lansoprazole, amoxicillin, metronidazole plus 250 mg vitamin C and 200 mg vitamin E twice daily for 1 week, followed by 250 mg vitamin C and 200 mg vitamin E once daily for 6 consecutive weeks. In the patients infected with metronidazole susceptible isolates, the triple therapy only group had a higher eradication rate then triple therapy plus vitamin group (80 vs. 53.1 %; $p = 0.02$), with the authors suggesting a difference in patient compliance and bacterial density as the cause for the result. No statistical difference in eradication was noted in the metronidazole resistant group (26.3 vs. 21.7 %; $p =$ NS) [86].

Conclusions

Gastritis, whether associated with autoimmune process, chemical injury, or infection with *H. pylori*, underlies the development of peptic ulcer disease and gastric cancer. Ascorbic acid plays a key role in healing and protection of the gastric mucosa from injurious insults. Vitamin C deficiency has repeatedly been linked with peptic ulcer disease and its complications. Its role in scavenging free radicals and reducing the inflammatory cascade, particularly in *H. pylori*-induced gastritis, plays a major preventive role in reducing the consequences of gastric inflammation including in reducing the deleterious effects of reactive oxygen species and NOC. These effects are reflected in

Table 4 Effect of ascorbic acid supplementation on *H. pylori* eradication

Study	Regimen	AA dose (mg/day)	Duration (weeks)	Sample (*n*)	Eradication (%)	*p* value
Jarosz et al. [80]	Placebo	0	4	24	0	
	Ascorbate	5,000	4	27	29.6	0.006
Zojaji et al. [81]	O,A,M,B	0	2	162	48.8	
	O,A,M,B + ascorbate	500	2	150	78	<0.0001
Sezikli et al. [82]	L,A,C,B	0	2	80	60	
	L,A,C,B + ascorbate	500	2	80	93.5	<0.005
Chuang et al. [83]	O,A,C250	0	1	55	68	
	O,A,C250	500	1	61	85	0.03
	O,A,C500	0	1	55		
Kaboli et al. [84]	O,A,C250	500	2	114	86.8	0.623
	O,A,C500	0	2	100	89	
Kamiji et al. [85] (Protocol I)	Placebo	0	4	17	0	0–15 % (95 % CI)
	Ascorbate	5,000	4	21	0	
(Protocol II) [85]	Ascorbate	5,000	4	8	0	
Chuang et al.—metronidazole résistant [86]	L,A,M	0	1	19	26.3	NS
	L,A,M + vitamin C,E	500	7	23	21.7	
Chuang et al.—metronidazole susceptible [86]	L,A,M	0	1	30	80	0.02
	L,A,M + vitamin C,E	500	7	32	53.1	

O omeprazole, *A* amoxicillin, *C* clarithromycin, *B* bismuth, *L* lansoprazole, *M* metronidazole

population-based epidemiologic studies showing negative correlations between vitamin C intake and gastric cancer and endoscopic studies suggesting regression of precancerous lesion with ascorbic acid supplementation. Ascorbic acid supplementation has been associated with a decreased incidence of bleeding from peptic ulcer disease and with a reduction in NSAID-associated gastric mucosal damage. Pharmacologic doses of ascorbic acid also may improve the effectiveness of *H. pylori*-eradication therapy. Occasionally, looking back can help plot the way forward.

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Conflict of interest Dr. Graham is also a paid consultant for Otsuka Pharmaceuticals regarding diagnostic testing and has received royalties from the Baylor College of Medicine patent covering materials related to the ^{13}C-urea breath test. Dr. Aditi has no conflicts to declare.

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