PATHOPHYSIOLOGICAL AND NUTRITIONAL ASPECTS IN THE ETIOLOGY AND MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE

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Short Title: NUTRITIONAL ASPECTS OF REFLUX

List of abbreviations

AC-III	Carbonic anhydrase-III
BMI	Body mass index
CCK	Cholecystokinin
DASH	Dietary approaches to stop hypertension
GERD	Gastroesophageal reflux disease
GPx	Glutathione peroxidase
GI	Glycemic index
HCl	Hydrochloric acid
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-22	Interleukin-22
IκB	NF-κB inhibitor
IBS	Irritable bowel syndrome
LPR	Laryngopharyngeal reflux
LES	Lower esophageal sphincter
LCFAs	Long-chain fatty acids
MCTs	Medium-chain triglycerides
MASLD	Metabolic dysfunction-associated steatotic liver disease
MS	Metabolic syndrome
NCDs	Non-communicable chronic diseases
NF-κB	Nuclear factor kappa-B
PPIs	Proton pump inhibitors
SOD	Superoxide dismutase
RAP-2	Protease-2 receptor
TNF-α	Tumor necrosis factor-α
T2DM	Type 2 diabetes mellitus
VEGF	Vascular endothelial growth factor

ABSTRACT:

Gastroesophageal reflux disease (GERD) is a prevalent condition observed across various medical specialties, including gastroenterology, otorhinolaryngology, surgery, and primary care. Despite the routine prescription of proton pump inhibitors (PPIs), some patients fail to experience adequate symptom relief. This review delves into the multifactorial mechanisms of reflux, which extend beyond hydrochloric acid to include pepsin, bile acids and trypsin. These factors significantly contribute to mucosal injury in GERD and are influenced by dietary composition. Moreover, dietary patterns with anti-inflammatory properties, such as the Mediterranean and DASH (dietary approaches to stop hypertension) diets, have shown potential in GERD managing, particularly in the context of obesity–an important risk factor.

Keywords: gastroesophageal reflux; obesity; dietary patterns; esophagitis.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is frequently encountered by gastroenterologists, otorhinolaryngologists, surgeons and primary health care physicians(1). While GERD is primarily associated with lower esophageal sphincter (LES) dysfunction, several other factors also contribute to its development(2). The prevalence of GERD is significantly higher among individuals aged 50 years and older, smokers, chronic users of non-steroidal anti-inflammatory drugs (NSAIDs), those with obesity(3), and individuals with lower education and income levels(4).

When gastric contents ascend into regions above the esophagus, laryngopharyngeal reflux (LPR) may occur(5), potentially affecting the larynx, pharynx, paranasal sinuses, and middle ear(6). Recent evidence even links this condition to eye diseases(7). Left untreated, GERD can lead to complications ranging from erosive esophagitis, bleeding and peptic strictures to pre-malignant and malignant lesions such as Barrett's esophagus and esophageal adenocarcinoma(8).

Although proton pump inhibitors (PPIs) alleviate symptoms in more than 70% of GERD cases, a subset of patients do not achieve adequate relief(9). This suggests that components beyond hydrochloric acid (HCl), such as pepsin, bile acids and trypsin, alongside, may play significant roles in GERD pathophysiology(10), in addition to factors such as low adherence to treatment and the presence of functional heartburn(11). Concerns regarding the long-term use of PPIs, particularly their effects on the absorption and homeostasis of key micronutrients (e.g., vitamin B12, calcium, iron and magnesium), have further complicated GERD management(12).

Given these complexities, non-pharmacological approaches, particularly dietary and nutritional interventions, have gained increasing attention in GERD management. This is partly driven by the observation that mucosal irritants in gastroduodenal contents are secreted in response to food intake and can be modulated by altering the diet’s nutritional composition(13). Additionally, the strong association between obesity and GERD has further emphasized the role of dietary interventions, as addressing obesity through healthy dietary patterns not only aids in weight management but also directly contributes to GERD symptom control(4,14)

PATHOPHYSIOLOGY OF GERD AND ESOPHAGEAL MUCOSAL INJURY

At the esophagus-stomach junction lies the circular smooth muscle structure called the LES(15). During swallowing, mechanoreceptors in the pharynx stimulate the LES to relax, allowing the food bolus to enter the stomach. Subsequently, the LES contracts to prevent retrograde flow of stomach contents into the esophagus and underlying regions(16,17). This complex regulatory process is mediated by the vagus nerve(18) and also responds to the hormonal action of gastrin and cholecystokinin (CCK). Gastrin increases LES tone(19,20), while CCK promotes its relaxation(21).

Under normal conditions, LES's tonic pressure surpasses that of the stomach, effectively preventing the reflux of gastric contents(22). However, dysfunction in this protective mechanism allows the retrograde flow of gastric or gastroduodenal contents into the distal portions of the esophagus and, in cases of LPR, into the laryngopharynx, oropharynx or even the nasopharynx, triggering the characteristic symptoms of this condition. This is because these regions lack the protective mechanisms of the stomach, making them vulnerable to mucosal injury from gastric juice, digestive enzymes, and other irritants(23–25).

Reflux is classified based on pH(26)pH falls below 4, characterized by a predominance of HCl. Reflux with a pH between 4 and 7, containing mixed contents, is classified as lightly acidic reflux. Lastly, slightly alkaline reflux is defined by a pH above 7, where the gastroduodenal content is primarily composed of pepsin and bile acids(27,28).

The esophageal mucosa responds to acid injury by increasing bicarbonate secretion via carbonic anhydrase-III (AC-III) activity, in an attempt to neutralize the acid(29). However, HCl downregulates the expression of E-cadherin, a transmembrane glycoprotein essential for cellular junction integrity, resulting in increased intercellular permeability and, thus, damage to the esophageal mucosa(30). Increased proton pump expression in esophageal tissue may also contribute to local acid secretion, causing inflammation, mitochondrial damage and, ultimately, carcinogenesis(31).

Pepsins, a group of proteases secreted by gastric chief cells, are released in their inactive precursor form,pepsinogen(32). Under acidic conditions, pepsinogen is converted into its active form through the cleavage of acid-labile bonds, initiating

protein digestion(33). This enzyme, along with other gastric contents, can damage the mucous membranes and epithelial barrier it contacts, digesting intercellular connections(28).

Another mechanism by which pepsin can perpetuate its harmful effects is by reducing AC-III levels, which play a fundamental role in local protection against the deleterious effects of stomach acid content(34). AC-III promotes the secretion of bicarbonate, leading to the alkalinization of the esophageal environment and the consequent deactivation of pepsin activity(35). Thus, decreased levels of AC-III may favor the action of pepsin by maintaining an acidic pH favorable to its action(32). Although pepsin operates optimally at a pH of 2 to 3.2, it remains active at pH levels of 6 to 7.2, values compatible with those of the oral cavity and respiratory tract (whose pH is around 6.4 to 7.2). This means that pepsin can inflict damage even in non-acidic environments(28).

Pepsin can also negatively regulate E-cadherin levels and increase the release of β-catenin into the cytoplasm, thereby increasing the risk of tumor cell infiltration and metastasis(36,37). This occurs because β-catenin accumulated in the cytoplasm can migrate to the nucleus and promote the transcription of various oncogenes associated with carcinogenesis and tumor progression through the Wnt/β-catenin pathway(38,39). Furthermore, pepsin can be reactivated in acidic environments or in cells with low pH. In these circumstances, pepsin is internalized by cells through endocytosis, stored in vesicles, and transported to organelles like the Golgi complex, causing mitochondrial damage and promoting the expression of genes related to carcinogenesis(35). In summary, the harmful effects of pepsin on the esophageal mucosa include increased intercellular permeability, local accumulation of reactive oxygen species, oxidative stress, inflammation, mitochondrial injury, and an increased risk of neoplastic development(28,35,38,39).

Bile acid reflux is another contributor to inflammatory damage of the esophageal mucosa(40). Physiologically, the function of bile acids secreted together with bile is to facilitate the digestion and absorption of fats and fat-soluble nutrients in the small intestine(41). However, when refluxed, bile acids can induce epithelial-to-mesenchymal cell transformation via vascular endothelial growth factor (VEGF) signaling(42) and nuclear factor kappa-B (NF-κB) activation, leading to local inflammation and the abnormal expression of tumor factors(43,44). Additionally,

trypsin activates the protease-2 (RAP-2) receptor, inducing the secretion of interleukin-8 (IL-8), a neutrophil chemotactic factor involved in the inflammatory response (45,46). These mechanisms collectively increase oxidative stress(47) and pro-inflammatory cytokine expression in the esophageal mucosa(46).

Certain factors are known to decrease LES tone or increase intra-abdominal pressure, contributing to acid-gastric reflux. These include alcohol consumption(48) and tobacco use(49), obesity(50), particularly abdominal obesity (51), central nervous system depressants(52), pregnancy(53), hiatal hernia(54), delayed gastric emptying(55), and increased gastric volume(13).

THE IMPACT OF OBESITY

Obesity is an independent risk factor for GERD(4,56) and its associated complications, such as erosive esophagitis and esophageal adenocarcinoma (57). In individuals with GERD, higher body mass index (BMI) correlates with increased frequency and severity of pyrosis, regurgitation and esophagitis(58). In fact, more than a third of patients with overweight report GERD symptoms proportional to their BMI, with improvement in symptoms observed following weight loss. These findings support the role of obesity treatment in managing GERD(59).

A study with 34 participants with overweight and GERD symptoms found a significant association between weight loss and symptom improvement, leading the authors to recommend weight loss as a first-line treatment(60). Another study, involving 10,545 women, detected that even those with a baseline BMI within the normal range had an increased risk of frequent reflux symptoms with a BMI increase of more than 3.5 kg/m^2 (61).

The relationship between abdominal obesity and increased risk of esophagitis was investigated in a meta-analysis of 42 observational studies, which found a significant association between abdominal obesity and esophagitis, especially with waist circumference exceeding 87 cm(51). Even in individuals with a normal BMI, abdominal obesity was associated with a higher risk of esophageal adenocarcinoma (62)These findings highlight the impact of not only excess weight, as assessed through BMI, but also body fat distribution on GERD(59).

Several mechanisms by which obesity contributes to reflux have been proposed, including mechanical and humoral factors as well as gastrointestinal motility disorders (figure 1). Among these mechanisms, increased intra-abdominal pressure combined with LES relaxation and prolonged exposure of the esophageal mucosa to gastric acid content are significant(56).

GERD is often associated with other components of the metabolic syndrome (MS), such as type 2 diabetes mellitus (T2DM)(63) and metabolic dysfunction-associated steatotic liver disease (MASLD)(64). Although the exact causal mechanism remains unclear, insulin resistance, a hallmark of obesity, appears to play an important role in GERD pathophysiology. A positive relationship has been demonstrated between HOMA-IR values, components of MS, and GERD symptoms, with higher insulin resistance correlating with increased severity of GERD symptoms and a higher risk of erosive esophagitis(65,66). Furthermore, gastroparesis, a feature of autonomic neuropathy caused by poorly controlled T2DM(67), can predispose individuals to GERD symptoms (68). Conversely, weight loss not only reduces GERDF symptoms but also improves insulin resistance, with a reduction of at least 5% promoting improvements in hepatic and muscular insulin sensitivity and pancreatic β-cell function. Greater benefits are observed with weight losses above 5%, following a dose-response relationship(69).

THE ROLE OF MACRONUTRIENTS

The appropriate distribution of macronutrients in the diet can play a fundamental role in controlling GERD symptoms. As described earlier, gastroduodenal content contains several mucosal irritants whose secretion depends on food intake and can be altered by changes in the nutritional composition of the diet(13). Table 1 provides a summary of studies that have evaluated the role of dietary components in GERD.

Carbohydrates and fiber:

While the intake of simple sugars and starch can exacerbate reflux symptoms, dietary fiber has shown protective and therapeutic effects. These findings underscore the

importance of carbohydrate quality(13). Wu and colleagues(70) investigated the effect of dietary carbohydrates on GERD. Twelve patients diagnosed with GERD were given 500 mL of a liquid meal with identical protein and fat content but varying carbohydrate levels: one group received 84.8 g of carbohydrates, while the other received 178.8 g. Individuals with higher carbohydrate intake had worse symptom scores, longer total reflux times, and more frequent reflux episodes.

A study involving participants with obesity and GERD found that a very low-carbohydrate diet, starting with less than 20 g/day, decreased esophageal exposure to gastric acid and reduced symptoms(71). The effects of a low-carbohydrate diet were also evaluated in a pilot study with 42 women with obesity, showing reduced GERD symptoms and medication use(72). In a prospective, randomized, single-blind, controlled dietary intervention study involving 98 individuals, reducing carbohydrate intake–particularly simple sugars–improved pH monitoring results and GERD symptoms(73).

A recent meta-analysis assessing the effectiveness of dietary interventions in GERD showed that low-carbohydrate diets significantly reduced esophageal acid exposure time(74). Additionally, a higher glycemic index (GI) was associated with an increased risk of esophageal adenocarcinoma, with each 10-unit increase in GI amplifying the risk (75). The effect of carbohydrates on GERD symptoms is primarily attributed to their ability to reduce LES tone(13).

Regarding dietary fiber, El-Serag and colleagues(76) demonstrated an inverse association between higher fiber intake and GERD symptoms. Similarly, Mulholland and colleagues(75) found that increased fiber intake was associated with a decreased risk of Barrett's esophagus and esophageal adenocarcinoma. Importantly, fiber source appears to play an important role, with fiber from fruits and vegetables being associated with a lower risk of Barrett's esophagus, whereas no significant association was observed for fiber from other sources(77). A cohort study from the Nurses' Health Study II reinforced these findings, showing that higher total fiber intake was associated with a decreased incidence of GERD symptoms, with the strongest associations observed for fiber from fruits and vegetables, but not from cereals(78).

Supplementation with 15 g/day of psyllium significantly improved reflux symptoms by increasing LES resting pressure and decreasing both the number of GER episodes and the frequency of pyrosis. Participants in this study had an average baseline

fiber intake of 6 g/day, and the supplementation brought their intake closer to dietary reference values. This highlights the importance of adjusting fiber consumption in individuals whose intake falls below recommended guidelines(79).

Protein:

The role of dietary protein in GERD is not well described in the scientific literature, with studies yielding heterogeneous results(80). While the exact relationship between protein intake and GERD symptoms is uncertain(13), some evidence suggests that high-protein diets may reduce reflux symptoms(59). The presence of oligopeptides from protein digestion in the stomach stimulates gastrin release, which enhances LES constriction(81–83). Of note, plant-based proteins are associated with fewer reflux episodes, particularly acid reflux, and a reduced number of symptoms in the first postprandial hour(84).

Lipids:

In addition to being calorie-dense, dietary fats require the secretion of mucosal irritants, such as bile salts and hormonal mediators like CCK, for digestion and absorption(13). CCK plays a multifaceted role in GERD pathophysiology: it inhibits gastric emptying, promotes gallbladder contraction, and relaxes the LES, thereby contributing to reflux symptoms(13,85).

Comparing individuals with and without GERD symptoms, those with reflux had higher daily intakes of total fat, saturated fat, and cholesterol. A dose-response correlation was observed between fat and cholesterol intake and GERD risk. However, after adjusting for BMI, the impact of dietary fat on GERD became statistically nonsignificant(76).

A systematic review by Zhang et al.(80) assessed the influence of dietary and lifestyle factors on GERD and found a significant correlation between high-fat diets and reflux. Nevertheless, a literature review by Heidarzadeh-Esfahani et al.(86) revealed highly variable outcomes among studies investigating the effect of dietary fat on GERD.

Pehl et al.(87) examined the effects of an isocaloric liquid-solid meal with low (10%) or high fat content (50%) on LES motility and GER in healthy individuals. The study found no discernible differences across the analyzed parameters, including LES pressure, frequency of transient LES relaxation, reflux episodes, percentage of transient relaxation with GER, and fraction of time at pH < 4. In contrast, a study by Sun et al.(88) assessed the impact of two test meals (standard vs. high-fat) in individuals with GERD. They found a notable increase in transient LES relaxation frequency following both meals, with no substantial differences observed within the initial hour. However, two hours after consuming the high-fat meal, they observed a significant increase in transient LES relaxations, acid reflux episodes and prolonged periods of pH < 4, alongside a reduction in LES pressure.

It is important to highlight that the impact of different types and sources of fats on GERD symptoms can vary. For example, polyunsaturated fats (PUFAs), particularly omega-3 fatty acids, are associated with a lower risk of Barrett's esophagus, while increased consumption of trans fats has been linked to an elevated risk(77). Additionally, PUFAs may exhibit a protective effect against adenocarcinoma, especially in individuals with normal BMI(89). On the other hand, medium-chain triglycerides (MCTs), unlike long-chain fatty acids (LCFAs), do not require bile acids for digestion and absorption and do not stimulate CCK secretion(90–92), which can be advantageous for managing GERD. Furthermore, MCT intake, even in the presence of LCFAs, inhibits CCK secretion and gallbladder contraction, potentially reducing reflux symptoms(93). However, these benefits require further confirmation(94).

MICRONUTRIENTS AND BIOACTIVE COMPOUNDS IN MODULATING THE ANTIOXIDANT AND INFLAMMATORY RESPONSE

Dietary micronutrients and bioactive compounds are important modulators of antioxidant(95) and anti-inflammatory(96) responses. As previously described, oxidative stress and inflammation play critical roles in GERD(47). Individuals with GERD have significantly lower levels of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase, underscoring the importance of reducing oxidative stress in managing this condition(97). Nutrients

capable of modulating antioxidant and anti-inflammatory pathways are therefore important(98).

Retinoids and carotenoids:

Retinoic acid, an active metabolite of vitamin A, promotes homeostasis and mitigates inflammatory responses in mucous membranes and tissues by. increasing the expression of IL-10 and IL-22(99), two key anti-inflammatory cytokine(100,101). Carotenoids, some of which are vitamin A precursors, exhibit significant anti-inflammatory and antioxidant effects. These pigments become more bioavailable when consumed with lipids and when plant cell walls are broken down during preparation, such as through heating(102,103).

A study evaluating the consumption and serum levels of antioxidant vitamins, including vitamin A, found a relationship between serum vitamin levels and the severity of reflux disease ((104). Nam and colleagues (105) reported that a high intake of vitamin A and retinol was associated with a 22% and 27% reduction in the risk of non-erosive reflux disease, respectively, although no association was observed with erosive esophagitis (105). Beta-carotene intake has also been inversely associated with Barrett's esophagus (106,107)

Vitamin D:

Vitamin D is crucial for immune regulation and proper mucosal function(108). Its active metabolite, 1α,25-dihydroxy-vitamin D, modulates the inflammatory response by suppressing pro-inflammatory cytokines(109) and upregulating anti-inflammatory ones(110). It inhibits NF-κB activity and increases the expression of NF-κB inhibitor (IκB), resulting in reduced expression of pro-inflammatory genes responsible for IL-6, IL-8, tumor necrosis factor-α (TNF-α), and COX-2, thereby reducing prostaglandin levels(111–113). Additionally, Vitamin D acts as an antagonist in the Wnt/β-catenin pathway(114), interfering with the expression of genes linked to carcinogenesis(115). It has also been shown to enhance the expression of the transmembrane glycoprotein E-cadherin(116).

Despite these promising mechanisms, no consistent association was found between vitamin D levels and the presence of Barrett's esophagus, erosive esophagitis, or GERD symptoms (117). A Mendelian randomization study also found no link

between vitamin D status and the risk of Barrett's esophagus or esophageal adenocarcinoma ((118)). However, the vitamin D receptor (VDR) may be overexpressed in precancerous lesions, especially in males (119). Individuals with polymorphisms in the VDR gene associated with reduced receptor expression in esophageal tissue have been found to have lower incidences of reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma(120). Further studies are needed to elucidate the role of vitamin D in GERD.

Vitamin E:

Vitamin E, a lipid-soluble vitamin, functions as a primary antioxidant in cellular membranes, scavenging free radicals and preventing lipid peroxidation(121). It also exhibits significant anti-inflammatory effects (122), including the modulation of eicosanoids and the suppression of NF-κB, IL-6, and IL-8(123). Its major dietary sources include vegetable oils, nuts, and certain cereals(124).

Although studies in experimental models have shown vitamin E's beneficial effects(125,126), its role in preventing GERD-related complications in humans remains inconclusive. For instance, Kubo et al.(106) found that individuals in the highest quartile of vitamin E intake had a lower risk of Barrett's esophagus. However, Murphy et al.(127) reported no association between vitamin E intake and reflux esophagitis, Barrett's esophagus, or esophageal adenocarcinoma.

Vitamin C:

Vitamin C is a potent antioxidant due to its high electron-donating capacity(128). It regenerates vitamin E from the tocoferoxyl radical formed by α-tocopherol interaction with lipid peroxides in membranes(129). Furthermore, as a cofactor, vitamin C maintains proper epithelial barrier function(130).

Nam et al.(127) reported that individuals in the highest quartile of vitamin C had a 22% lower risk of erosive esophagitis. Similar findings were described by Wu et al.(131). Furthermore, Murphy et al(105) demonstrated that a higher dietary intake of vitamin C was associated with a reduced risk of esophageal adenocarcinoma.

Zinc:

Zinc regulates the antioxidant response through multiple mechanisms. Low zinc levels correlate with increased cellular oxidants, disruptions in antioxidant defense, and elevated markers of tissue oxidative stress(132). Additionally, zinc modulates the activity of glutathione, the most important low molecular weight antioxidant in cells(133,134), and serves as a cofactor for numerous enzymes involved in cellular repair(135). Zinc deficiency has been associated with increased expression of inflammatory factors in the pathogenesis of esophageal cancer(136), a process that can be reversed with supplementation(137). In individuals with GERD, low zinc levels may pose an additional risk factor for esophageal cancer(138). However, zinc supplementation in patients with GERD did not affect the severity of symptoms ((139)).

Selenium:

Selenium's primarily functions are antioxidant(140), involving enzymes that maintain redox homeostasis, a process influenced by its organic status(141). Additionally, selenium's exhibits chemopreventive properties(142). In line with this, Cai et al.(143), in their meta-analysis investigating the relationship between selenium exposure and the risk of various types of cancers, demonstrated an association between this micronutrient and a reduced risk of esophageal cancer. However, studies specifically evaluating selenium intake or supplementation in patients with GERD are limited.

Magnesium:

Magnesium is the fourth most abundant mineral in the body, influencing directly and indirectly approximately 800 metabolic reactions(144,145). Magnesium deficiency is associated with increased inflammation and oxidative stress(146). Due to its involvement in DNA and RNA synthesis, as well as mitochondrial membrane stabilization, magnesium may play a crucial role in cellular repair processes and the resolution of inflammation in GER(147). Individuals with the highest dietary magnesium intake had significantly reduced odds of reflux esophagitis and Barrett's esophagus compared to those with the lowest intake. However, no significant association was observed between magnesium intake and the risk of esophageal adenocarcinoma ((148)).

Bioactive compounds:

Dietary bioactive compounds or phytochemicals are substances produced by the secondary metabolism of plants in response to environmental stressors(149). Within the human body, these compounds can modulate various metabolic pathways, acting as direct antioxidants(150) and influencing the expression or activity of antioxidant enzymes(151). They also play a beneficial role in regulating inflammatory pathways(152).

The cytoprotective effects of dietary bioactive compounds are partly mediated through the activation of the transcription factor NRF2(153). When activated, NRF2 induces the expression of key antioxidant enzymes, including SOD, GPx, and peroxiredoxin while simultaneously downregulating NF-κB-mediated expression of pro-inflammatory cytokines (154). This dual action reduces oxidative stress and inflammation, protecting the gastrointestinal mucosa from damage. Indeed, several phytochemicals have been shown to upregulate the expression of antioxidant enzymes, providing protection against oxidative damage to the gastrointestinal mucosa(155). A prominent example is curcumin, which inhibits the NF-κB signaling pathway activated by bile acids and genes associated with carcinogenesis in human hypopharyngeal cells(156). However, it is important to note that curcumin exhibits a potent cholecystokinetic effect, with a 40 mg dose causing up to a 50% contraction of the gallbladder (157). This highlights the need for consideration of individual tolerance and clinical context when recommending curcumin supplementation.

THE ROLE OF DIETARY PATTERNS IN GERD

Dietary patterns play a crucial role in the risk and management of non-communicable chronic diseases (NCDs), as evidenced by multiple observational and intervention studies(158,159). Given that obesity is closely linked to GERD, dietary pattern-focused interventions have gained increasing importance in addressing this condition(14).

A Western dietary pattern, characterized by a high intake of saturated fats, refined grains, sugar, salt, alcohol, and other harmful components, along with reduced consumption of fruits and vegetable (160), has been linked to reflux(161). In contrast,

dietary patterns such as the Mediterranean diet, rich in fruits, vegetables, whole grains, and unsaturated fats(162), may offer potential benefits for GERD(163).

Adherence to anti-inflammatory diets, like the Mediterranean diet, has been shown to reduce the risk of NCDs(164), while pro-inflammatory dietary patterns increase these risks(165). In the context of GERD, adherence to a pro-inflammatory diet has been correlated with increased risks of reflux esophagitis, Barrett's esophagus(166), and esophageal adenocarcinoma(167). This is likely mediated by the upregulation of the inflammation-metaplasia-adenocarcinoma pathway in esophageal carcinogenesis(166).

Similarly, the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes high intake of fruits and vegetables, low-fat dairy, reduced saturated and total fat, and low cholesterol, along with moderate consumption of whole grains, nuts, poultry, and fish, has proven effective in managing NCDs(168) Evidence suggests that it may also benefit GERD patients. For instance, a cross-sectional study involving 5,141 adolescents aged 13 to 14 years found that those with higher adherence to the DASH diet were less likely to develop GERD(169).

In addition, various studies have explored the impact of specific food groups on GERD prevalence. A cross-sectional study of 1,146 participants compared adherence to an omnivorous diet versus a vegan diet and found a twofold higher prevalence of GERD among those following an omnivorous diet, suggesting that a diet high in animal-derived foods may increase GERD risk(170). Supporting this notion, a case-control study conducted among Irish adults examined the associations between fat and meat consumption and the risks of reflux esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. The study revealed that participants in the highest quartile of fresh red meat consumption faced a significantly greater risk of esophageal adenocarcinoma, whereas those in the highest quartile of processed meat consumption had a higher risk of reflux esophagitis(171). In contrast, with respect to dairy, no significant differences in common GERD symptoms such as heartburn and acid regurgitation were observed between individuals consuming higher amounts of full- or low-fat dairy (3 servings/day) and those following a diet with limited dairy intake (172).

The efficacy of dietary interventions like the low-FODMAP diet has also been explored. Rivière et al.(173) found no significant advantage of this diet compared to standard dietary counseling in GERD treatment. However, in individuals with irritable bowel syndrome (IBS) overlapping with GERD, high-FODMAP meals were associated

with a higher frequency of symptoms compared to low-FODMAP meals(174). Similarly, Patcharatrakul et al.(175) demonstrated that postprandial reflux symptoms were more pronounced after consuming wheat noodles (high in FODMAPs) compared to rice noodles (low in FODMAPs). These results support the utility of low-FODMAP diets for individuals with overlapping IBS and GERD, emphasizing the need for personalized nutritional interventions based on individual food sensitivities and intolerances.

Additionally, histamine-free diets have shown promise in managing LPR symptoms. A case study reported substantial improvements in symptoms, such as persistent cough and throat clearing, in a patient who underwent Nissen fundoplication and followed a histamine-free diet. This suggests a potential link between LPR and food sensitivities, particularly in patients unresponsive to standard treatment(176).

THE ROLE OF ESOPHAGEAL MUCOSAL IRRITANTS

Several lifestyle and dietary risk factors have been implicated in GERD symptoms, with alcohol emerging as a significant contributor(177). Alcohol exhibits a dose-response relationship with GERD risk, serving as a predisposing factor for symptom exacerbation(178). Consequently, individuals experiencing reflux symptoms after alcohol consumption are advised to limit their intake(179). The direct contact of alcoholwith the mucosal lining of the upper GI tract induces numerous metabolic and functional alterations, which may lead to a broad spectrum of acute and chronic ailments. Additionally, alcohol influences esophageal motility by reducing LES tone, further predisposing individuals to reflux symptoms(180).

Similarly, coffee consumption has been extensively studied for its gastrointestinal effects(181). While coffee stimulates gastrin release–primarily through its caffeine content–thereby increasing gastric acid secretion, its components also reduce LES tone, potentially contributing to reflux(182). However, a meta-analysis investigating the association between coffee consumption and GERD risk yielded inconclusive results(183).

The role of carbonated beverages in GERD remains controversial(86). Cuomo et al.(184) found that carbonated and sweetened beverages did not significantly alter

upper digestive tract physiology in healthy individuals. Johnson et al.(185) further argued that these beverages neither directly cause esophageal damage nor are consistently associated with GERD.

Citrus fruit consumption between meals has been linked to increased GERD(186). Some studies indicate that citrus increases the risk of GERD recurrence in individuals undergoing PPI treatment(187). These findings were validated by a systematic review assessing the relationship between dietary habits and GERD risk(86). Although these effects are believed to be partially due to the reduction in esophageal pH caused by citrus fruit consumption, a dietary strategy involving acidic pH foods has been associated with symptom reduction and even resolution(188).

Chocolate has also been investigated for its impact on GERD. While most studies systematically reviewed by Heidarzadeh-Esfahani et al.(86) found no direct association between chocolate consumption and GERD risk, chocolate was shown to significantly lower LES mean basal pressure(20). Moreover, in individuals with reflux esophagitis, chocolate consumption significantly increased acid exposure during the first postprandial hour(189). This effect is primarily attributed to methylxanthines, such as theobromine, which induces LES relaxation through a mechanism similar to caffeine(190).

In general, several foods have been reported to precipitate GERD symptoms(191), and the elimination of entire categories of foods or beverages is a common practice in primary care and gastroenterology clinics(13). However, studies have shown conflicting associations for most foods(86). Therefore, it is more prudent to recommend that dietary adjustments be made on a personalized basis, taking into account each patient's individual response.

BEHAVIORAL MEASURES ASSOCIATED WITH DIET

Behavioral measures, in addition to dietary factors, play a significant role in GERD. A case-control study involving 47 GERD patients and 294 age- and sex-matched controls found that a shorter interval between dinner and bedtime (< 3 hours) significantly increased GERD risk compared to longer intervals (≥ 4 hours), even after adjusting for smoking, alcohol consumption, and BMI(192). Similar findings were confirmed in subsequent studies, which also associated behaviors such as skipping

breakfast, midnight snacking, rapid eating, and consuming very hot foods with higher GERD prevalence(80).

CONCLUSION

Numerous studies have examined the impact of diet and specific nutritional components on GERD, but findings often remain inconclusive. Among macronutrients, carbohydrates–particularly refined sources–have been consistently linked to GERD. Conversely, dietary fiber from fruits and vegetables appears protective and even therapeutic. Overall, encouraging weight loss in individuals with overweight and obese, along with promoting adherence to healthy dietary patterns emphasizing minimally processed plant-based foods, , while reducing ultra-processed foods, refined carbohydrates, and unhealthy fats, should be prioritized in GERD management.

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P. C. B. supervised the project. D. F. S. and P. M. L. drafted the original manuscript, while R. L. V. L., D. R. M., and P. C. B. contributed to the review and critical editing of the manuscript. All authors have reviewed and approved the final manuscript and take full responsibility for its content.

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Table 1. Summary of Studies Evaluating the Impact of Macronutrients, Micronutrients, and Bioactive Compounds on Gastroesophageal Reflux Disease (GERD) and Related Conditions

STUDY CHARACTERISTICS	MAIN FINDINGS
Authors: Austin et al., 2006 **Country:** USA **Study Type:** Single-arm intervention study **Sample Size:** 8 **Population:** GERD patients with obesity **Nutrients investigate:** Dietary carbohydrates	Starting a very low-carb diet significantly decreased Johnson-DeMeester scores (34.7 ± 10.1 vs. 14.0 ± 3.7, p= 0.023) and GSAS (1.28 ± 0.15 vs. 0.72 ± 0.12, p= 0.0004), and acid exposure time in the distal esophagus (5.1 ± 1.3% vs. 2.5 ± 0.6%, p= 0.022).
Authors: Pointer et al., 2016 **Country:** USA **Study Type:** Prospective cohort study **Sample Size:** 42 **Population:** Women with GERD **Nutrients investigate:** Dietary carbohydrates	Baseline intake of total carbohydrates (r=0.34, P<0.001), sugars (r= 0.30, p= 0.005), and glycemic load (r= 0.34, p= 0.001) were associated with GERD only in European American women. After intervention with a low-carb/high-fat diet, reflux symptoms resolved, and medication discontinuation occurred in all women.
Authors: Wu et al. 2018 **Country:** Taiwan **Study Type:** Non-randomized crossover clinical trial **Sample Size:** 12 **Population:** GERD patients **Nutrients investigate:** Dietary carbohydrates	The group that received the high-carbohydrate meal compared to the low-carbohydrate meal had had significantly higher Johnson-DeMeester scores (39.7 ± 11.0 vs. 14.3 ± 5.3, p= 0.019), longer reflux time (21.8 ± 5.7% vs. 8.8 ± 3.8%, p= 0.028), a greater number of reflux periods (12.7 ± 2.1 vs. 7.1 ± 2.3, p= 0.026), more reflux periods lasting greater than 5 minutes (1.3 ± 0.5 vs. 0.3 ± 0.3, p= 0.02) and longer mean reflux duration (5.8 ± 1.5 min vs. 2.8 ± 0.9 min, p= 0.015).
Authors: Gu et al., 2022 **Country:** USA **Study Type:** Randomized clinical trial **Sample Size:** 98 **Population:** GERD patients with overweight or obesity **Nutrients investigate:** Dietary carbohydrates	Significant reduction in GERDQ scores with the following diets: HTLS (-3.1 ± 3.6, p< 0.01) LTHS (-3.7 ± 3.4, p< 0.001) and LTLS (-3.5 ± 3.9, p< 0.001). Median improvement in esophageal acid exposure was observed in the HTLS (-3.0%) and LTHS (-2.7%) groups, alongside a reduction in the number of reflux episodes lasting longer than 5 minutes in the HTLS (-2.1) and LTHS (-1.6) groups.
Authors: El-serag et al., 2005 **Country:** USA **Study Type:** Cross-sectional study	Total fiber intake (g/day) was inversely associated with the risk of GERD symptoms (OR: 0.72, 95% CI: 0.53-0.99, p= 0.04).

Sample Size: 371 **Population:** Adults with and without GERD symptoms **Nutrients investigate:** Dietary fiber	
Authors: Mulholland et al., 2009 **Country:** Irelend **Study Type:** Case-control study **Sample Size:** 919 **Population:** Adults with EAC (n = 224), BE (n = 220), RE (n = 219) or controls (n = 256) **Nutrients investigate:** Dietary fiber	The risk of BE was significantly reduced among individuals in the highest tertile of fiber intake compared to the lowest tertile (OR: 0.44, 95% CI: 0.25-0.80). Fiber intake was also associated with a reduced risk of EAC.
Authors: Kubo et al., 2009 **Country:** USA **Study Type:** Case-control study **Sample Size:** 913 **Population:** Adults with BE (n= 296), GERD (n= 308) or controls (n= 309) **Nutrients investigate:** Dietary fiber and dietary fat	Higher intakes of omega-3 fatty acids (OR: 0.46, 95% CI: 0.22–0.97), total PUFA (OR: 0.97, 95% CI: 0.94–0.99), total fiber (OR: 0.34, 95% CI 0.15–0.76), and fiber from fruits and vegetables (OR: 0.47, 95% CI 0.25–0.88) were associated with a lower risk of BE. Higher intake of trans fat was associated with an increased risk (OR: 1.11; 95% CI: 1.03–1.21).
Authors: Morozov et al., 2018 **Country:** Russia **Study Type:** Open clinical trial **Sample Size:** 30 **Population:** Non-erosive GERD **Nutrients investigate:** Dietary fiber	After supplementation with 5 g of psyllium taken three times daily, 18 out of 30 participants (60%) reported an absence of heartburn for seven consecutive days (60%) (p= 0.0004). A decrease in the GERDQ score from 10.9 ± 1.7 at baseline to 6.0 ± 2.3 at the end of the treatment period (p< 0.001) was also observed. The number of reflux episodes (excluding non-acid reflux) decreased, with a significant reduction in maximum reflux time from 10.6 ± 12.0 to 5.3 ± 3.7 minutes by the end of the treatment period (p= 0.017).
Authors: Samuthpongtorn et al., 2023 **Country:** USA **Study Type:** Cohort study **Sample Size:** 48.868 **Population**Adult women **Nutrients investigate:** Dietary fiber	Total fiber intake was associated with a decreased incidence of GERD symptoms (P < 0.0001). Comparing the highest with the lowest quintile, the multivariate relative risk was 0.75 (95% CI: 0.70–0.80). The inverse association was particularly strong for fruit fiber (P < 0.0001) and vegetable fiber (P < 0.0001), whereas no significant association was observed for cereal fiber (P = 0.20).
Authors: Martinucci et al., 2018 **Country:** Italy	Participants followed a Mediterranean diet divided into two 847 kcal meals: one predominantly composed of animal proteins and the other of vegetable proteins.

Study Type: Open clinical trial **Sample Size:** 165 **Population:** Patients with heartburn with or without other GERD symptoms **Nutrients investigate:** Dietary Protein	The total number of reflux events was significantly higher after the consumption of animal proteins compared to vegetable proteins (12.4 ± 9.9 versus 6.3 ± 3.9; p< 0.0001). Acid reflux events were more frequent following the animal protein meal (7.5 ± 4.2 versus 3.3 ± 2.8; p< 0.0001). Heartburn recorded during the 1-hour postprandial analysis occurred twice as often after the animal protein meal compared to the vegetable protein meal (3.1 ± 1.2 versus 1.4 ± 0.8; p< 0.0001).
Authors: Sutphen e Dillar, 1992 **Country:** USA **Study Type:** Crossover clinical trial **Sample Size:** 28 **Population:** Children **Nutrients investigate:** Dietary Fat	Infants received two distinct meals, one enriched with MCT and the other with LCT, 4 hours apart. No significant differences were observed in the occurrence of postprandial reflux at 1 and 2 hours after the meals.
Authors: Pehl et al., 1999 **Country:** Germany **Study Type:** Double-blind randomized clinical trial **Sample Size:** 12 **Population:** Healthy volunteers **Nutrients investigate:** Dietary Fat	Volunteers were allocated to receive an isocaloric meal (842 kcal) with either low fat content (10% fat, 14% protein, 76% carbohydrate) or high fat content (50% fat, 18% protein, 32% carbohydrate). No significant differences were observed between the groups in terms of LES pressure, frequency of transient LES relaxation, reflux episodes, percentage of transient relaxation associated with GER, or the fraction of time with pH < 4.
Authors: Sun et al., 2004 **Country:** China **Study Type:** Non-randomized crossover clinical trial **Sample Size:** 8 **Population:** GERD patients **Nutrients investigate:** Dietary Fat	Subjects were given two test meals on separate days: a standard meal (SM) and a high-fat meal (HFM). No significant differences were observed in the frequency or duration of transient lower esophageal sphincter relaxations (TRLES) between the SM and HFM groups during the first hour after the meal (p > 0.05). However, two hours post-meal, the frequency of TRLES was significantly higher in the HFM group compared to the SM group and the fasting state (p < 0.05). LES pressure decreased significantly in the HFM group compared to the SM group (p < 0.05). Additionally, the number of acid reflux episodes and the duration of time with pH < 4 were significantly greater following the HFM compared to the SM (p < 0.05).
Authors: O'Doherty et al., 2011 **Country:** Ireland **Study Type:** Case control study	Patients in the highest quartile of total fat intake had a higher risk of RE (OR: 3.54; 95% CI: 1.32-9.46) and EAC (OR: 5.44; 95% CI: 2.08-14.27). Increased risks of RE and EAC were observed in patients with the highest quartile of SFA

Sample Size: 919 **Population:** RE (N= 219), BE (N= 220), EAC (N= 224), and controls (N= 256) **Nutrients investigate:** Dietary Fat	intake (OR: 2.79; 95% CI: 1.11-7.04; OR: 2.41; 95% CI: 1.14-5.08, respectively) and MUFA intake (OR: 2.63; 95% CI: 1.01-6.86; OR: 5.35; 95% CI: 2.14-13.34, respectively).
Authors: O'Doherty et al., 2012 **Country:** USA **Study Type:** Cohort Study **Sample Size:** 494,978 **Population:** Older adults **Nutrients investigate:** Dietary Fat	An inverse association between PUFA intake and the risk of EAC was observed in individuals with a normal BMI range (18.5-<25 kg/m^2 [HR (95% CI) 0.76 (0.63-0.92)]. However, no significant associations were found between overall dietary fat intake and the risk of esophageal or gastric cancer.
Authors: Kubo et al., 2008 **Country:** USA **Study Type:** Case-control study **Sample Size:** 913 **Population:** BE (N= 296), GERD (N= 308), and controls (N= 309). **Nutrients investigate:** Antioxidant nutrients	Inverse association between BE and dietary intake of vitamin C (OR: 0.48; 95% CI: 0.26-0.90), beta-carotene (OR: 0.56; 95% CI: 0.32-0.99) and vitamin E (OR: 0.25; 95% CI: 0.11-0.59).
Authors: Murphy et al., 2010 **Country:** Ireland **Study Type:** Case-control study **Sample Size:** 919 **Population:** RE (N= 219), BE (N= 220), EAC (N= 224), and controls (N= 256) **Nutrients investigate:** Antioxidant nutrients	GAI was associated with a reduced risk of EAC (OR: 0.57; 95% CI: 0.33–0.98), but not with BE (OR: 0.95; 95% CI: 0.53–1.71) or RE (OR: 1.60; 95% CI: 0.86–2.98). Individuals in the highest category of vitamin C intake had a lower risk of EAC (OR: 0.37; 95% CI: 0.21–0.66; p=0.001) and RE (OR: 0.46; 95% CI: 0.24–0.90; p=0.03) compared with those in the lowest category.
Authors: Lukić et al., 2012 **Country:** Croatia **Study Type:** Case-control study **Sample Size:** 180 **Population:** GERD (N= 70), BE (N=20), EAC (N=20), and healthy controls (N= 70) **Nutrients investigate:** Antioxidant nutrients	Healthy controls consumed higher amounts of vitamins A (p= 0.009), C (p< 0.001) and E (p < 0.001), from both natural sources (fruits and vegetables) and supplements (industrial vitamin additives) compared to patients with GERD, BE and EAC. And higher serum levels of vitamins A, C and E were observed in the control group.
Authors: Ibiebele et al., 2013	Beta-carotene intake was significantly lower in the dysplastic BE group (p=

Country: Australia **Study Type:** Case-control study **Sample Size:** 2,750 **Population:** Dysplastic BE (N= 101), non-dysplastic BE (N= 266), and matched controls (N= 577); EAC (N= 299) and paired controls (1,507) **Nutrients investigate:** Antioxidant nutrients	0.003). Individuals with EAC had lower intakes of vitamin C (p= 0.004), vitamin E (p< 0.0001), and beta-carotene (p= 0.007). An inverse association was observed between total beta-carotene intake in the fourth quartile and the risk of dysplastic BE (OR: 50.45; 95% CI: 0.20–1.00). Higher total vitamin E intake was associated with a reduced risk of EAC (OR: 50.64; 95% CI: 0.43, 0.96; p= 0.04).
Authors: Nam et al., 2019 **Country:** Corea **Study Type:** Cross-sectional study **Sample Size:** 11,690 **Population:** Adults with and without GERD **Nutrients investigate:** Micronutrients	The highest quartile of calcium (p < 0.001), iron (p < 0.001), phosphate (p < 0.001), vitamin A (p = 0.007), vitamin B2 (p < 0.001), vitamin B6 (p = 0.007), and folic acid (p = 0.020) intake was associated with a reduction in non-erosive GERD. Only the highest quartile of vitamin C intake significantly reduced the risk of erosive esophagitis compared to the lowest quartile in the adjusted analysis (OR: 0.78; 95% CI: 0.62–0.98).
Authors: Rubenstein et al., 2019 **Country:** USA **Study Type:** Cross-sectional study **Sample Size:** 605 **Population:** Men with GERD (N=150), RE (N=216), and BE (N=145), and healthy controls (N=174) **Nutrients investigate:** Vitamin D	No association was observed between vitamin D deficiency and the risk of BE (OR: 0.555; 95% CI: 0.269-1.15). No evidence of an association was found between vitamin D and RE (OR: 0.761; 95% CI: 0.422-1.37) or GERD symptoms (OR: 0.858; 95% CI: 0.357-2.06).
Authors: Dong et al., 2019 **Country:** International consortium **Study Type:** Mendelian randomization study **Sample Size:** 27,438 **Population:** BE (N= 6167), EAC (N= 4112), and controls (N= 17159) **Nutrients investigate:** Vitamin D	No evidence supported an association between genetically estimated vitamin D concentrations and the risk of BE (OR: 1.21; 95% CI: 0.77-1.92; p= 0.41) or EAC (OR: 0.68; 95% CI: 0.39-1.19; p= 0.18).
Authors: Shafaghi et al., 2016 **Country:** Iran **Study Type:** Double-blind randomized clinical trial **Sample Size:** 140 **Population:** GERD patients	Subjects were divided into two groups: zinc supplementation (40 mg pantoprazole/day, lifestyle changes, and 220 mg zinc/day) and placebo (40 mg pantoprazole/day, lifestyle changes, and placebo). RDQ scores decreased after the intervention in both the zinc supplementation (p< 0.001) and the placebo group (p< 0.001). However, the difference in RDQ scores between the two

Nutrients investigate: Zinc	groups was not statistically significant (p= 0.086).
Authors: Dai et al., 2016 **Country:** Ireland **Study Type:** Case-control study **Sample Size:** 890 **Population:** EAC (N= 218), BE (N= 212), RE (N= 208), and controls (N= 252) **Nutrients investigate:** Magnesium	Individuals with the highest dietary magnesium intake experienced significant reductions in the odds of RE (OR: 0.31; 95% CI: 0.11–0.87) and BE (OR: 0.29; 95% CI: 0.12–0.71) to those with the lowest intake. No significant association was observed between magnesium intake and the risk of EAC (OR: 0.77; 95% CI: 0.30–1.99).

Note.

GERD = Gastroesophageal reflux disease; GSAS = Gastroesophageal Reflux Disease Symptom Assessment Scale; GERDQ = Gastroesophageal Reflux Disease Questionnaire; HTLS = High-total/low-simple carbohydrates; LTHS = Low-total/high-simple carbohydrates; LTLS = Low-total/low-simple carbohydrates; LES = Lower esophageal sphincter; GER = Gastroesophageal reflux; TRLES = Transient relaxation of the lower esophageal sphincter; SM = Standard meal; HFM = High-fat meal; EAC = Esophageal adenocarcinoma; BE = Barrett's esophagus; RE = Reflux esophagitis; SFA = Saturated fatty acids; PUFA = Polyunsaturated fatty acids; MUFA = Monounsaturated fatty acids; MCT = Medium-chain triglycerides; LCT = Long-chain triglycerides; LCGAI = General antioxidant index; RDQ = Reflux Disease Questionnaire.