

Can We Use Diet to Effectively Treat Esophageal Disease? A Review of the Current Literature

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Abstract

Purpose of Review Esophageal diseases represent a wide variety of conditions affecting esophageal anatomy, physiology, and motility. Therapy focuses on pharmacotherapy and endoscopic or surgical management. Dietary therapy can be considered in management algorithms for specific esophageal diseases. This review focuses on outlining the literature related to dietary therapy in gastroesophageal reflux disease, eosinophilic esophagitis, Barrett's esophagus, and esophageal adenocarcinoma.

Recent Findings Currently, data are strongest for dietary manipulation in eosinophilic esophagitis, specifically the six-food elimination diet. Dietary effects on gastroesophageal reflux disease are less clear, though newer research indicates that increased fiber with reduction in simple sugar intake may improve symptoms. In terms of Barrett's esophagus and esophageal adenocarcinoma, antioxidant intake may affect carcinogenesis, though to an unknown degree.

Summary Outcomes data regarding dietary manipulation for the management of esophageal diseases is heterogeneous. Given the rising interest in non-pharmacological treatment options for these patients, continued research is warranted.

Keywords Esophageal diseases · GERD · Eosinophilic esophagitis · Barrett's esophagus · Esophageal adenocarcinoma · Dietary therapy

Introduction

Esophageal diseases represent a wide variety of conditions affecting esophageal anatomy, physiology, and motility. Therapy generally focuses on pharmacotherapy and endoscopic or surgical management. However, diet may affect and even treat underlying pathophysiology. As a relatively low-risk treatment option, patients often ask for dietary therapy counseling. This article will provide a comprehensive review of the current data for the dietary management of some of the most common esophageal diseases including gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), esophageal adenocarcinoma (EAC), and eosinophilic esophagitis (EoE).

Gastroesophageal Reflux Disease

GERD is a common esophageal disease affecting up to 28% of the American population [1]. It is defined as the reflux of stomach contents resulting in troublesome gastrointestinal symptoms [2]. Mechanistically, the disease is associated with defects in both esophageal anatomy and function of the lower esophageal sphincter (LES) [3]. Complications of GERD include erosive esophagitis, peptic strictures, and Barrett's esophagus [4], which lead to significant patient morbidity and cost to the health care system [5]. Cornerstones of therapy rely on lifestyle modifications including elimination of modifiable risk factors as well as initiation of acid-suppressing medications [6] with surgical management offered in cases

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of severe refractory disease [7]. Modifiable risk factors include cessation of tobacco smoking, weight reduction, and head-of-bed elevation while recumbent [8•]. Additionally, dietary modifications such as avoidance of specific types of foods, reduction in food quantity per meal, and avoiding meal intake within 3–4 h of sleep have been implicated in GERD pathophysiology (Table 1). We will further discuss the data for dietary therapy in GERD.

Elimination Diets

Several beverages and foods have been implicated in exacerbation of GERD symptoms including coffee, carbonated beverages, alcohol, chocolate, citrus fruits, tomato-based products, and any foods that are spicy, acidic, or fried [6]. Data supporting such dietary avoidance remain sparse with conflicting results. For instance, coffee consumption has been implicated in developing reflux symptoms and is routinely recommended to be avoided in patients with GERD [9]. However, a recent meta-analysis examining coffee's effect on both incidence of heartburn episodes as well as presence of acid-mediated mucosal disease found no correlation between coffee intake and disease activity. This lack of statistical significance remained during subgroup analysis of low-intake (<4 cups/day) versus high-intake (>5 cups/day) users [10]. Carbonated beverages have also been implicated in development of GERD secondary to inherent effervescence, high levels of acidity, added sugars and artificial sweeteners, and presence of caffeine, which are thought to alter LES pressures and intraesophageal pH [11]. For example, a small study in healthy volunteers noted a 20–50% reduction in LES pressures associated with carbonated beverages versus tap water [12]. This has not, however, correlated with alterations in clinical GERD symptoms as evidenced by a systematic review of 17 studies [13].

The data linking alcohol to GERD also reveals mixed results. Mechanistically, alcohol consumption has been correlated with increased acid secretion, impairment of gastric emptying and esophageal motility, and induction of spontaneous LES relaxation leading to increased reflux episodes [14]. For instance, a prospective cohort study of 25 subjects, 15 of whom were diagnosed with non-erosive reflux disease, found a statistically significant increase in acidic reflux episodes by pH monitoring with ingestion of wine or beer compared to tap water [15]. Whether this increase in episodes is associated with increase in GERD symptoms is less clear, with several larger cross-sectional analyses showing no correlation between alcohol and presence of reflux-like dyspepsia or its complications [16, 17]. In fact, some studies have even shown a reduction in patient-reported reflux symptoms in those who consume alcohol [18].

In terms of culprit foods, there are only weak associations between consumption patterns and GERD prevalence. For example, chocolate is commonly cited as a GERD trigger; however, a recent population cohort study of 500 patients in Italy showed no association between chocolate ingestion and GERD symptoms [19]. Citrus fruits and tomato-based products are also implicated in heartburn symptoms secondary to high acidity and alteration of LES tone [20]. While avoidance of these acidic foods is often recommended, studies linking them to incidence of heartburn are scant and unconvincing [6]. For instance, a survey of 394 patients with classic GERD noted that only a third of patients felt symptom exacerbation with highly acidic beverages (mean pH 3.4), with no correlation between the pH itself and heartburn induction [21]. The avoidance of spicy and fried foods also lacks convincing evidence in the context of GERD management [20]. Given these findings, avoidance of specific food and beverage triggers should not necessarily be routinely recommended in GERD patients, though those patients that derive symptomatic benefit can be encouraged to continue such restriction.

Table 1 Proposed mechanisms of common dietary triggers implicated in GERD

Dietary trigger	Reduction in LES pressure	Increased gastric acid production	Decreased gastric motility	Decreased intraesophageal pH	Increased abdominothoracic pressure gradient
Coffee	X	X			
Carbonated beverages				X	X
Alcohol	X	X	X		
Acidic foods and beverages				X	
Chocolate	X				
Spicy food		X			
Dietary fat			X		
Dietary carbohydrate		X			
High-volume meal		X	X		X
Late onset meal	X	X			

Low-Fat and Low-Carbohydrate Diets

The caloric density and delivery of meals has also been studied to determine the effect of macronutrient manipulation on GERD symptoms. Two primary dietary approaches have emerged as a part of this research. These include avoidance of dietary fat as well as the reduction of carbohydrate intake with substitution of dietary fiber for simple sugars [17, 21]. In terms of dietary fat, data are mixed. For example, a small study examining the effect of fat intake on 12 healthy volunteers who were fed an isocaloric meal with fat content of either 10% or 50% found no difference in LES pressures, frequency of transient LES relaxations, or reflux episodes between the groups [22]. These negative findings were replicated in an additional, larger study [23]. These studies contrast, however, with a number of positive studies showing significant correlation between dietary fat intake and reflux symptoms [24, 25]. Therefore, the recommendation to avoid dietary fat remains controversial.

Low-carbohydrate diets have also been investigated. For instance, a small prospective cohort study of eight obese patients with GERD placed on a very low carbohydrate diet (20 g/day) showed statistically significant reduction in esophageal acid exposure and symptom severity [26]. A follow-up study was later performed targeting obese women with heartburn and noted a positive correlation between simple sugar intake (monosaccharides or disaccharides) and reflux induction [27••]. These findings, in addition to multiple studies reporting symptom improvement with high dietary fiber intake [9, 22, 28], indicate that carbohydrate type may also play an important role in symptom modulation. Additional studies are warranted to confirm these promising preliminary results.

Meal Timing and Volume

Patients with GERD are often instructed not to eat large meals, especially later in the evening, in order to avoid symptom exacerbation. This is based on small studies correlating sustained increases in nocturnal gastric pH with subsequent reduction of GERD symptoms with earlier meal time [29, 30]. Other studies, however, have reported no difference in overall reflux events or degree of gastric acidity with changes in eating patterns [31]. Meal volume has also been hypothesized to be associated with GERD symptoms, though this hypothesis is based on limited data linking esophageal acid exposure time with increased meal size [23] without any studies investigating correlation with symptom activity. Therefore, it also remains largely unclear if altering meal size or timing affects overall reflux episodes.

Barrett's Esophagus and Esophageal Adenocarcinoma

One of the complications of uncontrolled GERD is development of Barrett's esophagus, which is a premalignant condition characterized by metaplastic changes in the distal esophagus largely in response to gastric acid exposure [32]. Approximately 5–15% of patients with GERD will be diagnosed with BE on subsequent endoscopic evaluation with increased rates noted in higher-risk populations including obese white men >50 years old with a smoking history and long-standing disease [33]. Progression to EAC depends on extent of dysplasia and is estimated at 0.33–7% annually [34]. Therapy of BE is dependent on acid suppression and endoscopic or surgical procedures, with radiation and chemotherapy reserved for disease that progresses to EAC [32]. Besides ethnicity, age, and BMI, lifestyle has more recently been investigated with variations in dietary intake linked to increased risk of developing BE and subsequent progression to EAC (Table 2). The following is a review of these factors and their supporting literature.

Fruits and Vegetables

Fruits and vegetables are known to contain high levels of antioxidants including vitamins A, C, E, and selenium, which have been shown to reduce reactive oxygen species and subsequent DNA damage implicated in the progression of BE to EAC [35]. The most protective effects are hypothesized to be from those fruits and vegetables with the highest levels of antioxidants [36] including carrots, tomatoes, spinach, berries, and citrus fruits [37]. However, data on this topic are mixed and often derived from case-control studies which may be significantly biased [38]. For example, a case controlled study of 433 matched patients diagnosed with BE and EAC noted reduction in rates

Table 2 Dietary components associated with carcinogenesis in the esophagus

	Food type or component	Proposed mechanism
Pro-carcinogenic	Red meat, saturated fats	Induces production of advanced glycation end-products (AGEs), which are carcinogenic
Anticarcinogenic	Brightly colored fruits and vegetables (carrots, tomatoes, spinach, berries), green leafy vegetables, soluble and insoluble dietary fiber	Contain high levels of antioxidants and phytic acid which reduce inflammation and enhance cell apoptosis, enhance gastric and esophageal motility reducing exposure to carcinogens

of both diseases with high fruit and vegetable intake [39]. This same study, however, did not control for the presence of obesity, which they also reported to be strongly associated with disease and which may be correlated with specific dietary choices. Additionally, not all case-controlled studies have shown similar findings. A recent investigation of 577 Australian patients found antioxidant intake to be associated with reduction in EAC but not BE [40]. Specific types of fruit and vegetable intake have also been investigated, with a veterans' study that noted an inverse relationship between BE and green, leafy vegetables only [41]. This was also reported in a study of 433 patients with BE and EAC who additionally noted benefit with raw vegetables versus cooked vegetables [42]. Larger prospective studies including the NIH-AARP Diet and Health Study and the European Prospective Study of Cancer and Nutrition (EPIC) demonstrated similar findings [43•, 44]. One explanation for this amplified protective effect may be the variability in dietary fiber, folate, and selenium content in certain vegetable types and preparations [45]. Additional prospective investigations are warranted to flush out these details.

Fiber

The exact role of fiber consumption in BE and EAC prevention is controversial. For example, the consumption of leafy green and raw vegetables has shown a weak but consistent inverse relationship with development of BE and EAC, which may be partially attributable to fiber intake [42–44]. A recent case controlled study of 296 patients diagnosed with incident BE, however, reported that fiber derived from grain or wheat products did not show the same protective effect, raising questions about the true importance of fiber content in disease pathogenesis and the difference in outcomes attributable to soluble versus insoluble fiber subtypes [46]. To add to this ambiguity, a large study of patients with a number of upper gastrointestinal malignancies found significant positive correlation between fiber intake of any type and reduction in EAC incidence. The authors noted that this relationship was significantly stronger with fruit and vegetable fiber sources but also reported an association with grains [47]. Proposed mechanisms of protection against carcinogenesis include high levels of phytic acid in high-fiber foods, which promote apoptosis, reduced levels of the inflammatory mediator interleukin 6, and enhanced esophageal and gastric motility through glycemic stabilization [48]. It is clear, however, that more robust studies need to be performed to evaluate confounding factors and relevant fiber subtypes.

Meat Products and Saturated Fats

Meat and fat intake have also been examined as a risk factor for development of BE and EAC, though studies show

variable results and are often case-controlled by design, limiting generalizability [38]. For example, a meta-analysis of three cohort and seven case-controlled studies examining the relationship between red and processed meat consumption and development of EAC noted a modest increase in relative risk with meat products in case-controlled trials only [49]. Additionally, although all studies were adjusted for age and sex, only six studies considered BMI, which may further alter results. Prospective trials, including the EPIC study, also showed inconsistent results, noting that only processed meats increased EAC incidence while total meat consumption was not significantly correlated [44]. Variability in results is likely secondary to meat type, preparation technique, and overall nutrient content including fat, protein, and iron levels as these have also been shown to be associated with carcinogenesis to varying degrees [45]. Meat intake and the relationship with BE is even more controversial with one study linking increased overall meat consumption to a lower risk of long-segment BE [46] while another reported increased risk with meat intake of any type [50].

In terms of fat ingestion, a recent observational study examined the correlation between intake of saturated fat derived from meat products and BE, noting a significant increase in the odds ratio of developing disease with increased consumption. They additionally analyzed the presence of advanced glycation end-products (AGEs) and carboxymethyl lysine (CML) in the diet, noting higher intake of these carcinogenic agents in meat and saturated fat eaters. These levels were additionally noted to be inversely correlated to the consumption of dark green leafy vegetables, though it is unclear if this is due to altered dietary patterns or increased antioxidant consumption [61]. Prospective studies, meanwhile, have not replicated these results, with the NIH-AARP study reporting no association between EAC and dietary fat intake when adjusting for confounding factors [55]. Additional larger prospective studies are warranted to further define these associations.

Eosinophilic Esophagitis

Eosinophilic esophagitis is a rare but clinically significant allergic disease that is defined by eosinophilic esophageal infiltration [50]. Estimated to affect 0.4% of the western population, EoE is now thought to represent the most common cause of swallowing dysfunction in children and food impaction in adults. The pathogenesis is a complex combination of environmental factors including exposure to antibiotics, microbes, and food allergens as well as genetic predisposition, with the condition most commonly diagnosed in young males with history of atopic diseases [51]. Therapy includes medications such as swallowed glucocorticoids, endoscopic esophageal dilation, and dietary manipulation including elemental diet

(ELED), six-food elimination diet (SFED), and allergen-directed diet [52–54]. The following is a brief review of dietary treatment options for patients with EoE, which are summarized in Table 3.

Elemental Diet

Originally reported by Kelly et al. in their landmark trial of 10 children diagnosed with EoE exclusively fed an elemental enteral formula for at least 6 weeks [55], the elemental diet has been shown to be highly efficacious in the control of symptoms and esophageal inflammation in patients with EoE [56••]. Based on the principle of exposure to specific proteins leading to eosinophilic predominant esophageal inflammation, the formulas used in elemental diets are comprised of proteins broken down into single amino acids which have limited antigenic capacity due to their small size [57]. After this initial publication, a number of additional studies have been performed confirming positive results with a recent meta-analysis of 13 trials citing a 90.8% histological remission rate with this type of dietary restriction [56••]. Notably, only one of these studies was conducted in an adult population evaluating 18 patients with EoE completing at least a 2-week trial of an elemental diet. This study showed a 72% complete or near-complete mucosal remission rate, with only one patient showing lack of any response [57]. Although highly effective, limitations of this type of diet include poor palatability, high costs, and the social isolation and psychological stress associated with avoidance of all table foods [58]. In fact, 38% of patients in the previously mentioned adult study dropped out during the 4-week trial period due to non-compliance [58]. In clinical practice, the diet therefore is impractical in an adult population and used in limited circumstances, often with reintroduction of food allergens in a step-wise process to identify triggers [59].

Table 3 Common diets employed in management of eosinophilic esophagitis

Diet	Description
Elemental diet	Enteral nutrition formulas comprised of carbohydrates, fats, and proteins that are broken down into their most basic derivatives, limiting antigenic potential
Six-food elimination diet	Elimination of the six most common food allergens from the diet (soy, wheat, egg, dairy, peanuts and tree nuts, seafood and shellfish)
Allergen-directed diet	Elimination of food allergens based on comprehensive serum, skin prick, and allergy patch testing

Six-Food Elimination Diet

The most widely employed diet in the management of EoE patients is the SFED, which eliminates the six most common food groups associated with allergic responses (cow's milk, wheat, peanuts and tree nuts, eggs, soy, and fish and shellfish) [60]. Kagalwalla et al. first reported the efficacy of this diet in a landmark trial of 60 children treated with either SFED or ELED for 6 weeks, showing similar histological remission between the two groups [61]. Subsequent trials in both children and adults have shown a consistent response to this diet, with the most recent meta-analysis of 197 patients across 7 studies yielding a 72.1% efficacy rate [56••]. This diet, however, remains challenging to follow due to its inherently restrictive nature and complicated treatment algorithm that reintroduces food categories over specified periods of time [60]. Despite these limitations, the SFED tends to be more palatable than ELED in an adult population and may allow for the identification of specific food triggers. For instance, in a study of 67 EoE patients, 36% were able to identify a single food trigger for their disease, and an additional 31% noted only two offending food groups [62]. Among those patients identifying only one or two inciting agents, cow's milk and wheat have been shown to be the most common allergens, with egg and soy closely following [60]. This finding has led to the investigation of an empiric four-food elimination diet (FFED) focusing on these food categories. A recent prospective trial of 52 adults with EoE noted a 54% histological remission rate with FFED. About one third of FFED non-responders noted later remission with SFED initiation [63]. While it is clear that in the adult population, SFED is better tolerated than ELED for dietary EoE management, SFED remains a challenging dietary model that may not be realistic for long-term disease management [64].

Allergen-Directed Diet

Elimination of foods based on allergy testing is a strategy of continued interest in EoE management, but studies have demonstrated variable results [60]. For instance, a trial of 132 children treated with dietary restriction based on skin prick testing (SPT) and allergy patch testing (APT) noted a 57% histological remission rate, which was maintained at 9 months with continued avoidance of the selected food triggers [65]. An even higher efficacy rate of 77% was noted in an investigation of 146 children undergoing SPT and APT, which identified egg, milk, soy, wheat, and corn as the most common allergic triggers [66]. This high degree of clinical effectiveness is not consistent across all pediatric trials, however, as several subsequent studies reported poor performance of the SPT and APT with remission rates as low as 13–37% [67, 68]. Current data are scant and likewise conflicted with regard to this

dietary approach in adult patients. For example, one small trial including 31 EoE patients reported a 54% histological remission rates with directed dietary therapy using SPT and APT [69], while another investigating 22 EoE patients noted a remission rate of only 26% [70]. Further in-depth analyses of this dietary approach are needed to clarify its potential role.

Conclusion

Data regarding dietary manipulation for prevention and management of esophageal diseases are variable. Of the strategies discussed herein, empiric allergen elimination in EoE patients has the strongest evidence basis. High-fiber diets coupled with reductions in simple sugar intake are of ongoing interest in the realm of GERD prevention, as is dietary manipulation to mitigate carcinogenesis, though definitive roles for these approaches are still emerging. Given rising interest in non-invasive and non-pharmacological treatment options for patients diagnosed with these conditions, continued research is warranted to clarify the value of dietary therapy for esophageal disease.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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