

Differential Diagnoses of Food-Related Gastrointestinal Symptoms in Patients with Anorexia Nervosa and Bulimia Nervosa: A Review of Literature¹

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Zusammenfassung

Differentialdiagnosen nahrungsassoziiertes gastrointestinaler Symptome bei Patienten mit Anorexia nervosa und Bulimia nervosa: Eine Literaturübersicht⁴

Fragestellung: Diese Übersichtsarbeit untersucht die Prävalenz und Pathogenese nahrungsassoziiertes gastrointestinaler Beschwerden bei Essstörungspatientinnen und -patienten und liefert Empfehlungen hinsichtlich deren differentialdiagnostischer Abklärung.

Methode: Es wurde eine Literaturrecherche, in die Publikationen von Januar 2000 bis Januar 2017 eingeschlossen wurden, durchgeführt.

Ergebnisse: Über 90% der Essstörungspatienten leiden an nahrungsassoziierten Beschwerden. Es gibt keine Hinweise auf eine erhöhte Prävalenz struktureller oder immunologischer gastrointestinaler Erkrankungen im Vergleich zur Allgemeinbevölkerung. Der überwiegende Teil nahrungsassoziiertes Beschwerden bei Essstörungspatienten scheint funktioneller Natur zu sein.

Diskussion: Die differentialdiagnostische Abklärung sollte Anamnese basiert erfolgen; nur wenn der zeitliche Verlauf oder die Art der Symptome Hinweise auf eine zusätzliche gastrointestinale Erkrankung gibt, sollte eine umfassende Abklärung erfolgen.

Z Psychosom Med Psychother 64/2018, 4–15

Keywords

Eating Disorder – Anorexia Nervosa – Bulimia Nervosa – Gastrointestinal Disorder – Food Allergy – Food Intolerance

Summary

Objectives: The present review investigates the prevalence and medical causes of food-related gastrointestinal symptoms in eating disorder (ED) patients and recommends a diagnostic algorithm based on the current literature.

Methods: A literature search was conducted, which included publications from January 2000 until January 2017.

¹ The present work was performed in fulfillment of the requirements for obtaining the degree Dr. med. (MD).

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⁴ Die Vorliegende Arbeit wurde zur Erlangung des Doktorgrades (Dr. med.) an der Friedrich-Alexander-Universität Erlangen-Nürnberg verfasst.

Results: Over 90% of ED patients suffer from food-related symptoms. There is no evidence for a higher prevalence of immunological or structural gastrointestinal disorders in ED patients compared to the healthy population. Most food-related symptoms in ED patients are likely to be functional.

Conclusion: Diagnostic work-up of food-related symptoms in ED patients needs to be based on clinical history. Only if timing and quality of symptoms point towards a disorder independent from the ED is a comprehensive diagnostic work-up necessary.

1. Introduction

Food-related gastrointestinal (GI) symptoms in patients with eating disorders (EDs) might complicate therapy. However, the origin of GI symptoms in ED patients is not yet fully understood. It is assumed that GI symptoms are the consequence of an unbalanced diet, purging habits, starvation, and underweight. Lee et al. (2001) showed that with longer duration of anorexia nervosa, abdominal pain and stomach bloating are increasingly reported as reasons for restricted eating. Patients affected by unspecific gastrointestinal complaints often see specific foods or food components as the cause. Thus, the diagnostic process constitutes a major challenge: unspecific conditions like selective eating, tiredness, elevated transaminases, and anemia as well as gastrointestinal symptoms like nausea/vomiting, abdominal pain, bloating, and stool irregularities may occur within the context of restricted eating and purging habits in EDs on the one hand, or be the signs of GI conditions like celiac disease, food intolerance or food allergies on the other (Zopf 2009 et al.).

The present review of the literature aimed at investigating the prevalence of food-related diseases in ED patients, providing an overview of differential diagnoses for GI symptoms in ED patients, and exploring, whether food-related diseases themselves pose a higher risk for anorexia nervosa (AN) and bulimia nervosa (BN) (Figure

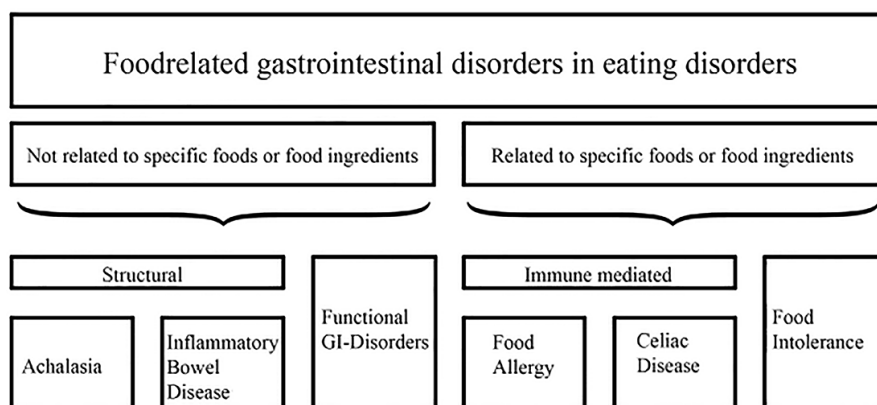


Figure 1: Differential diagnosis of food-related gastrointestinal symptoms in eating disorders (Zopf et al. 2009, modified)

1). Based on these findings, a possible approach for the diagnostic clarification of GI symptoms in ED patients is suggested.

2. Methods

For the purposes mentioned above, a comprehensive literature search was conducted. The search was conducted using the databases PubMed, the Cochrane Library, and ScienceDirect and included empirical studies and case reports in English and German language published from January 2000 until January 2017. The MeSH Browser was used to generate keywords. Keywords were: eating disorder, anorexia nervosa, bulimia nervosa, psychosomatic disorder, somatization, gastrointestinal disorder, food hypersensitivity, food allergy, food intolerance, celiac disease, chronic inflammatory bowel disease, achalasia, functional gastrointestinal disorder, irritable bowel disease, dyspepsia. Search terms were also used truncated and the connective AND was used. In addition, the citation lists of included articles were searched; a total of 801 records were identified and screened for adequacy. A total of 62 full-text articles were then selected. Finally, 28 articles were excluded (reviews or studies not related to the subject). A total of 34 research articles were included in this review (Figure 2). Only studies on AN and BN and not binge eating disorder were considered.

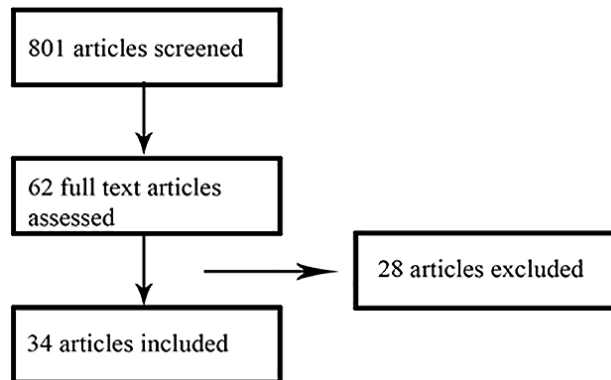


Figure 2: Flow diagram of the literature search

3. Results

Gastroenterological consultations in ED patients

Winstead and Willard (2005) compared 63 ED patients to 47 healthy controls (HCs) with regard to the frequency of gastroenterological consultations and found a significantly higher utilization behavior in patients with BN compared to HC. In a study in 47 ED patients, a total of 40% had a history of gastroenterological consultations

due to GI symptoms (Salvioli et al. 2013). In addition, AN patients consulting a gastroenterologist prior to a psychiatric/psychosomatic specialist, were found to be significantly older and have a longer duration of AN compared to those AN patients who sought help in an eating disorder unit first (Emmanuel 2004 et al.). In a cohort of 135 BN patients, one third of patients had a history of GI complaints reaching back to childhood, although, in all but one patient, symptoms were remitted by the onset of the ED (Gendall et al. 2005).

Symptoms not related to specific foods or food ingredients

Esophageal achalasia

In esophageal achalasia, the smooth muscle fibres of the esophagus and esophageal sphincter are functionally impaired, resulting in dysphagia (O'Neill et al. 2013).

Since the year 2000, there have been published 16 case studies describing patients with achalasia, initially diagnosed with an ED. Symptoms were: spontaneous vomiting in 9 patients, self-induced vomiting to relieve symptoms in two patients, weight loss in 13 patients, retrosternal pain in 4 patients, dysphagia in 6 patients, abdominal pain in one patient. In none of these cases a combined diagnosis of achalasia and ED was finally established, although in four patients the desire to lose weight as well as weight and shape concerns were reported. One patient showed misuse of laxatives and excessive exercise, another had a history of compulsive eating, obesity, and a pronounced preoccupation with food (Reas et al. 2014).

Inflammatory bowel disease

The term inflammatory bowel disease (IBD) includes several autoimmune disorders affecting parts of the digestive system. The two main types of IBD are Crohn's disease and ulcerative colitis (Molodecky et al. 2012).

Raeuori et al. (2014) conducted a retrospective analysis of the clinical data of 2342 patients with EDs and compared it with data from 9333 healthy controls (HCs). The authors found a significantly higher prevalence of Crohn's disease in ED patients (1.1%) compared to HCs (0.4%). The prevalence of ulcerative colitis was higher in ED patients (1%) as well. Two case studies report a co-morbidity of AN and Crohn's disease. The first of these studies reports restricted eating and shape concerns following weight gain due to corticosteroid therapy; the diagnosis of AN, however, was delayed (Baylé & Bouvard 2003). The other case study describes an improvement of preexisting AN symptoms following treatment for IBD (Solmi et al. 2013).

Functional gastrointestinal disorder

The term functional gastrointestinal disorder (FGID) describes idiopathic esophageal, gastric, and bowel disorders with disturbed gastric motility and visceral sensation. About one fourth of the population is affected by functional dyspepsia and irritable bowel syndrome, the two most common FGIDs. The most widely used classification for FGIDs are the criteria developed in the ROME process (Wouters 2015).

Studies in 1003 ED patients altogether show a high prevalence of FGIDs. At least one functional GI complaint was found in 79.4–98% of ED patients (Abraham & Kellow 2011, 2013; Boyd et al. 2005; Boyd et al. 2010; Lee et al. 2012; Salvioli et al. 2013; Santonicola et al. 2012; Wang et al. 2014). It may be assumed, that FGID symptoms in ED patients do not differ from those in non-ED patients (Abraham & Kellow 2013). In the majority of ED patients (77%), FGIDs persist even after weight rehabilitation (Boyd et al. 2010). Boyd et al. (2005) found a significant correlation of GI symptoms with neuroticism, somatization, as well as state and trait anxiety. In another study, persistent GI symptoms following weight rehabilitation correlated with higher values on hysteria and hypochondria scales (Salvioli et al. 2013). Lee et al. (2013) examined the reasons for food restriction in fat phobic and non-fat phobic AN patients and found that fat phobic patients reported significantly more GI complaints than non-fat phobic patients. Moreover, ED patients with GI symptoms had higher depression scores.

Functional esophageal disorder

Functional esophageal disorders (FED) include functional heartburn, dysphagia, and retrosternal pain (Boyd et al. 2005).

Studies in ED patients found a prevalence of 23–51% for FED (Abraham & Kellow 2011, 2013; Boyd et al. 2005; Wang et al. 2014). Abraham and Kellow (2011) found an association between FEDs and excessive exercising. Wang et al. (2014) reported high somatization scores as predictor for functional heartburn. No correlation was found between FEDs and underweight, vomiting, or binge eating (Abraham & Kellow 2011, 2013; Boyd et al. 2010; Wang et al. 2014). Salvioli et al. (2016) assessed esophageal symptoms and psychological traits in 48 ED patients before and after weight gain and found that esophageal symptoms improved in patients who had normal hypochondriasis and hysteria scores. Boyd et al. (2010) studied 73 ED patients and found a significant decrease in dysphagia and heartburn, but not in other forms of FEDs following weight rehabilitation; there was also no correlation between FED symptoms and psychological traits such as anxiety, depression, and somatization.

Functional dyspepsia

According to the ROME criteria, functional dyspepsia (FD) (also termed non-ulcerative dyspepsia) comprises symptoms like early satiety, abdominal fullness, abdominal pain, belching, and nausea without obvious organic cause after evaluation (Santonicola et al. 2012).

Four studies in 529 ED patients reported a prevalence of FD in ED patients ranging from 45% to 97% (Boyd et al. 2010; Salvioli et al. 2016; Santonicola et al. 2012; Wang et al. 2014). Early satiety was more frequent in AN, while epigastric pressure and nausea were increased in BN (Santonicola et al. 2012). Perez et al. (2013) measured post-meal antral diameter and gastric residual volume in 16 AN patients and 22 HCs via sonography and recorded GI symptoms, somatization, and anxiety scores. The authors found impaired gastric accommodation in AN patients compared to HCs; this finding improved after weight gain. There was no difference of gastric

residual volume between AN patients and HCs. Somatization scores and GI symptoms in AN patients improved after refeeding, while anxiety scores remained higher than in HCs even then.

In an MRI assessment of gastric half emptying time (T50) in 24 AN patients and 20 HCs, Bluemel et al. (2017) found the T50 in AN patients to be slower than in the control group. Antral contractions did not differ between groups. Patients' self-report of postprandial gastric fullness and T50 improved after refeeding. Similarly, Benini et al. (2004) explored gastric emptying in 23 AN patients before and after weight rehabilitation and found a significantly delayed gastric emptying in AN patients accompanied by with higher gastric symptom scores compared to healthy controls. While in the restrictive AN subtype gastric emptying improved after refeeding, it remained unchanged in AN of the purging subtype (Benini et al. 2004). Finally, Kuyumcu et al. (2013) assessed gastric contractions and gastric emptying time in 11 AN patients and 20 HCs via MRI. In contrast to the findings of Benini et al. (2004) and Bluemel et al. (2017) mentioned above, gastric emptying did not differ in the two groups, while gastric contraction frequency was found to be lower in AN patients compared to HCs. Gastric contraction frequency and postprandial fullness improved with refeeding, while other dyspeptic symptoms did not.

Functional bowel disorder

The functional bowel disorder or irritable bowel syndrome (IBS) describes patterns of symptoms such as abdominal pain and altered bowel motility without a clear underlying pathology to be found (Abraham & Kellow 2013).

The reported prevalence of IBS in ED patients ranges from 32–64.4% (Abraham & Kellow 2013; Boyd et al. 2005; Perkins et al. 2005; Wang et al. 2014). The use of laxatives was significantly associated with an IBS in four studies and 839 ED patients (Abraham & Kellow 2011, 2013; Perkins et al. 2005; Wang et al. 2014). Underweight was significantly associated with IBS in ED patients in the study by Abraham and Kellow (2013) in 160 patients, but not in the studies conducted by Perkins et al. (2005) and Wang et al. (2014) with a total of 494 patients. Perkins et al. (2005) examined the onset of IBS symptoms in 225 ED patients; the onset of the ED prior to the IBS was reported by 87% of patients, while the onset of both conditions coincided and the IBS symptoms preceded the onset of the ED in 5.6% and 6.7% of patients, respectively (Perkins et al. 2005). In another study out of 46 ED patients, 17% sought medical treatment due to IBS (Salvioli et al. 2013). The study conducted by Reed-Knight et al. (2016) addressed the question, whether adolescent patients with an IBS have a higher prevalence of disordered eating. IBS patients reported more disordered eating and a lower calorie intake than HCs. The BMI, however, was not lower in the IBS group and there was no higher prevalence of a manifest ED.

Functional constipation

Constipation as a symptom of a FGID is reported by 24–86% of ED patients (Abraham & Kellow 2013; Boyd et al. 2005; Perkins et al. 2005). A study of colonic function in 12 AN patients showed slowed colonic transit time in 66.7% of AN patients com-

pared to HCs. In 41.7% of patients, pelvic floor dysfunction was present and persisted after refeeding (Chiarioni et al. 2000). On the other hand, comparing oro-cecal transit time in 24 AN patients and 20 HCs, no differences were found (Bluemel et al. 2017). Two further studies in a total of 208 patients found no association between constipation and underweight (Abraham & Kellow 2011; Salvioli et al. 2013).

Symptoms related to specific foods or food ingredients

Food allergy

The term food allergy refers to an acute or late phase immune response to food (Zopf et al. 2009).

In cross-sectional telephone interviews which included 5165 adolescents aged 10–16 years, 2.9% of the subjects reported food allergies within the past 12 months. In the food allergy group, an association with AN was found; this association remained stable after controlling for other psychological variables. In follow-up interviews in the same cohort, food allergies were not found to be a predictor for EDs (Shanahan et al. 2014).

Food intolerance

The term food intolerance summarizes adverse reactions to food which result from a deficiency to digest or absorb nutrients and natural or synthetic chemicals due to the malfunction or absence of specific enzymes (Zopf 2009).

Considering the fact that ED patients frequently consume diet products which usually contain high amounts of fructose and sorbitol, Friesen et al. (2009) investigated whether the occurrence of GI symptoms in ED patients is associated with the intake of fructose and sorbitol. For this purpose, 26 ED patients and 20 HCs took part in a fructose/sorbitol provocation test followed by an H₂-breath test. The ingestion of fructose and sorbitol provoked symptoms in 15 ED patients (58%) and one HC (5%). The H₂-breath test was positive in 13 (50%) ED patients and 14 (70%) HCs. Symptom provocation due to fructose/sorbitol ingestion was not associated with a positive H₂-breath test result. However, an association was found between symptoms provoked by fructose/sorbitol intake and underweight (BMI < 17,5 kg/m²).

There is one case report describing a patient with histamine intolerance suffering from severe underweight, GI symptoms, and selective eating, firstly diagnosed as AN and later as a case of histamine intolerance. Complete weight rehabilitation and remission of GI symptoms after treatment of the histamine intolerance were reported (Stolze et al. 2010).

Celiac disease

Celiac disease (CD) is a gluten-triggered autoimmune inflammatory reaction of the small bowel. Typical age at onset is six months to two years with symptoms of diarrhea, malabsorption, malnutrition, and failure to grow, although CD may develop at any age with less marked symptoms (Zopf et al. 2009).

Three studies investigated the prevalence of EDs and subclinical disturbed eating in patients with CD. In a sample of 177 adult CD patients, clinically relevant scores in the Eating Disorder Examination-Questionnaire (EDE-Q) were found in 22% of patients (Arigo et al. 2012; Fairburn & Beglin 1994). In another study in 100 CD patients, 11% showed clinically relevant scores in the Eating Disorder Inventory-2 (EDI-2) and 16% in the Eating Attitude Test-26 (EAT-26) (Garner 1991; Garner et al. 1982; Passananti et al. 2013). A cross-sectional survey among 283 adolescents with CD found a clinically relevant ED in 2.4% of the female subjects (Karwautz et al. 2008). Investigating the associations between ED scores and gastrointestinal symptoms, Arigo et al. (2012) found the scores in the EDE-Q subscales “eating-related concerns,” “weight-related concerns,” and “shape-related concerns” significantly associated with the severity of GI symptoms. Passananti et al. (2013), however, found no associations between ED scores and GI symptoms. While Arigo et al. (2012) reported high EDE-Q scores (indicating a more severe psychopathology) associated with high depression scores and increased perceived stress, Passananti et al. (2013) did not find associations between ED and psychological parameters.

Some studies investigated the inverse relation: the prevalence of CD in ED patients. In three studies with a total sample of 725 ED patients, screening for the presence of CD was carried out. If the screening test was positive, the diagnosis was confirmed by biopsy. The authors reported a prevalence of 0% (n = 154), 0.8% (n = 494), and 0.6% (n = 177), respectively (Kaltsa et al. 2015; Saldanha et al. 2016; Basso et al. 2013).

Raevuori et al. (2014) performed data analyses of the medical files of 2326 ED patients. The authors compared the data with that of 9324 non-ED patients and found the prevalence of CD to be 0.7% in ED patients compared to 0.5% in the control group (Raevuori et al. 2014). Two cases reported by Ricca et al. (2000) were patients with a combined diagnosis of ED and CD, with a diagnosis of ED both, before and after diagnosis of CD. A gluten-free diet had positive effects on the GI symptoms, but not on weight or eating disorder symptoms (Ricca et al. 2000). Two additional studies presented clinical cases in which weight loss due to CD was misdiagnosed as an ED and rapidly improved after gluten-free diet (Leffler et al. 2007; Yucel et al. 2006).

4. Discussion

The purpose of this review was to investigate the prevalence and differential diagnoses for GI symptoms in ED patients, to explore potential reciprocal interferences, and to provide evidence regarding a reasonable diagnostic approach for GI symptoms in ED patients. As a main result, all publications included in this review reported a high prevalence of food-associated symptoms in ED patients (79–89%) compared to the average adult (15–20%) or adolescent (10–20%) population (Zopf et al. 2009; Gendall et al. 2005). Based on the available current literature, it may be assumed, that most GI complaints in ED patients meet the criteria for FGIDs, while the prevalence of structural and immunological disorders or food intolerance in ED patients is similar to the general

population (CD 0.5–1% (Basso et al. 2013), food allergy in adults 1–3% and in children 4–7% (Turnbull 2015), food intolerance: fructose 15–25%, sorbitol 8–12%, lactose 7–20% (Raithel 2013), IBD 0.5% in Europe, 0.3% in North America (Molodecky et al. 2012), Achalasia 0.002% (O’Neill et al. 2013)). However, there are no studies specifically evaluating the prevalence of food allergies and food intolerance in ED patients, with the exception of CD in ED, which showed a prevalence comparable to the general population (0–0.8% in ED (Kaltsa et al. 2015; Raevuori et al. 2014; Saldanha et al. 2016)). A limitation, however, is that other food associated diseases were not finally excluded by diagnostic testing in all studies on FGIDs presented here. Hence the functional nature of the gastrointestinal symptoms in the ED patients included in the studies cannot be assumed unequivocally.

Although questions about prevalence and possible pathophysiological links between food-related GI disorders and EDs are not fully answered, the following clinical recommendations for a differential diagnostic work-up are given:

A general screening of ED patients with GI symptoms cannot be recommended for CD, IBD, food allergies, or food intolerance.

Like in non-ED patients with food-related symptoms, the specific diagnostic approach is guided by clinical history (Turnbull et al. 2016; Zopf et al. 2009). In ED patients, however, the key is to obtain information about the onset of GI symptoms and the type of purging behavior, restricted eating, and the kind of foods chosen in the diet, together with detailed information about the quality of symptoms (Figure 3).

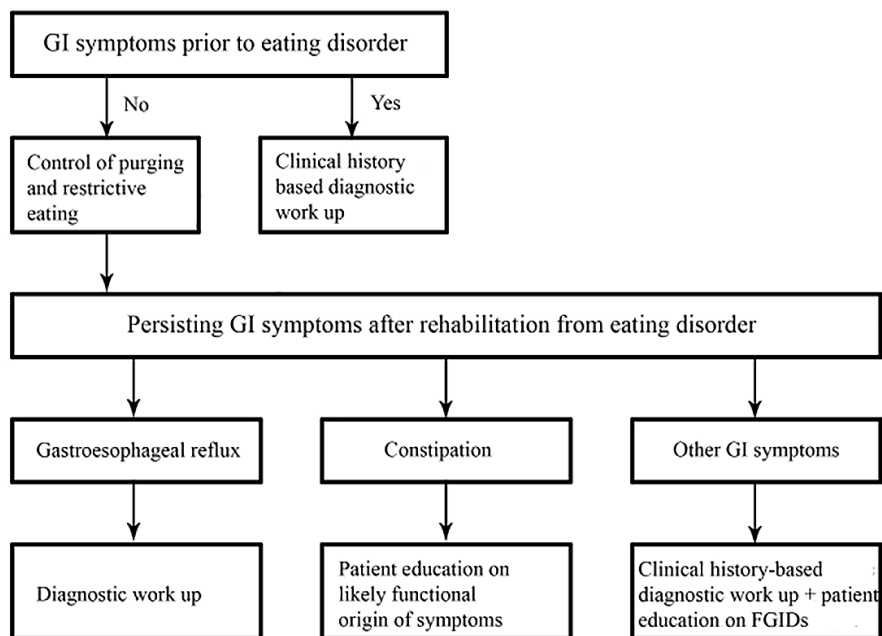


Figure 3: Recommendations for diagnostic work up

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