Effects of Six-Food Elimination Diet on Esophageal Symptoms and Histopathology in Adult Patients with Eosinophilic Esophagitis

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ABSTRACT

Background and aim: Patients with eosinophilic esophagitis (EoE) usually present with dysphagia and food impaction events. A subgroup of EoE patients do not experience symptomatic improvement despite the use of corticosteroid therapy. The effectiveness of an empiric six-food elimination diet (SFED) has been demonstrated in children and adults suffering from EoE, but this diet has not yet been tested in a Norwegian cohort. We aimed to assess the effects of the SFED on esophageal symptoms and histopathology in Norwegian adult patients with EoE. Subsequently, systematic reintroduction of the eliminated foods was carried out to identify potential dietary triggers of EoE.

Methods: A total of 10 adults with EoE underwent upper endoscopies with esophageal biopsies, blood tests, skin-prick tests for dietary allergens and aeroallergens, impedance manometry and ambulatory pH-monitoring. After following the SFED for a minimum of six weeks, the following procedures were repeated on each patient: endoscopy with biopsies, blood test, and impedance manometry. Symptomatic responders, defined by decreased frequency of dysphagia episodes from baseline to post-SFED, underwent sequential reintroduction of each eliminated food at 14-day intervals. Symptom scores and health-related quality of life (HRQOL) before and after the SFED were assessed by the Eosinophilic Esophagitis Activity Index (EEsAI) and 36-Item Short Form Survey (SF-36), respectively.

Results: The median peak eosinophil count in esophageal biopsies decreased from 80 eos/HPF before to 10.5 eos/HPF after the SFED ($p=0.0078$). Overall symptom score measured by the EEsAI did not change significantly from baseline (mean 44.9) to after the SFED (mean 30.7). When assessed through patient consultations and change in dysphagia frequency from baseline to after the SFED, seven patients reported improvement in esophageal symptoms. The most common trigger food identified during reintroduction was wheat, and SPT did not effectively predict trigger foods. Notable changes in esophageal peristalsis were not evident, as assessed by impedance manometry. There was no significant change in HRQOL before and after the SFED, as measured by the SF-36.

Conclusion: The SFED effectively reduced histopathological signs and improved esophageal symptoms of EoE in adult patients. Sequential reintroduction identified trigger foods, corroborating the role of dietary allergens in EoE pathogenesis. The empiric SFED represents an important alternative treatment modality to corticosteroids in adults, although further research is warranted on its long-term effects on EoE disease activity.

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LIST OF ABBREVIATIONS

AMS - Food Avoidance, food Modification and Slow eating

APC - Antigen-presenting cell

APT - Atopy patch testing

BP - Bodily Pain

CC - The Chicago classification

CDP - Contractile deceleration point

CTD - Connective tissue disorders

DCI - Distal contractile integral

DL - Distal Latency

DSG1 - Desmoglein 1

DSQ - Dysphagia symptom questionnaire

EC - Eosinophilic colitis

EE - Esophageal eosinophilia

EEsAI - Eosinophilic esophagitis activity index

EGD - Esophago-gastro-duodenoscopy

EGE - Eosinophilic gastroenteritis

EGID - Eosinophilic gastrointestinal disorder

EGJ - Esophagogastric junction

EoE - Eosinophilic esophagitis

Eos/HPF – Eosinophils per high-power field

EPT - Esophageal pressure topography

EWB - Emotional Well-Being

FDA - Food and Drug Administration

GERD - Gastroesophageal reflux disease

GH - General Health (GH)

GWAS - Genome-wide association studies

HPF - High-power field

HRM - High-resolution manometry

HUS - Haukeland University Hospital

IgE - Immunoglobin E

IL - Interleukin

IRP - Integrated relaxation pressure

LDS - Loeys-Dietz syndrome

LES – Lower esophageal sphincter

MCS - Mental Component Summary

PCS - Physical Component Summary

PF - Physical Functioning

PPI - Proton-pump inhibitor

PRO - Patient reported outcome

RE - Role limitations due to Emotional functioning

REK - Regional Committees for Medical and Health Research Ethics

RP - Role limitations due to Physical health

RRR - Recurrence risk ratios

SAM - Severe dermatitis, multiple allergies and metabolic wasting

SF - Social Functioning

SF36 - 36-Item Short Form Survey

SFED - Six-food elimination diet

SNP - single-nucleotide polymorphism

SPT - Skin prick testing

TSLP - Thymic stromal lymphopoietin

TTS - Through-the-scope

UES - Upper esophageal sphincter

UiB - University of Bergen

VAS – Visual analogue scale

VDQ - Visual Dysphagia Question

VT - Energy/vitality

INTRODUCTION

The term ‘esophageal disease’ encompasses a wide range of conditions affecting the anatomy, physiology and motility of the esophagus (1). Among the most prevalent esophageal diseases are gastroesophageal reflux disease (GERD), Barrett’s esophagus, esophageal adenocarcinoma, as well as eosinophilic esophagitis (EoE) (1).

EoE has been classified as an eosinophilic gastrointestinal disorder (EGID), a term collectively referring to EoE, eosinophilic gastroenteritis (EGE) and eosinophilic colitis (EC). In EoE, eosinophilic inflammation is limited to the esophagus, whereas the entire gastrointestinal tract may be affected in EGE or EC (2). EoE is a relatively recently identified chronic immune-mediated disease of the esophagus (3). Histologically, EoE is characterized by eosinophilic influx into the esophageal epithelium, and clinically by symptoms related to esophageal dysfunction (4).

1.1 Disease definition

EoE was initially recognized as a distinct clinical entity in the early 1990s (5). The first consensus recommendations for the diagnosis and management of EoE were written in 2007, whereas a revised version was published in 2011, presenting the first formal definition of the disease (6). At present, EoE is defined as a clinicopathological disorder that meets the following requirements (7):

(1) Presence of symptoms related to esophageal dysfunction, e.g. dysphagia, food impaction, chest pain or heartburn
(2) With certain exceptions, esophageal biopsy must demonstrate 15 or more eosinophils per high-power field (eos/HPF)
(3) Unresponsiveness to acid suppression therapy using proton-pump inhibitor (PPI)
(4) Mucosal eosinophilia should be isolated to the esophagus, and secondary causes of esophageal eosinophilia (EE) should be excluded, e.g. EGE, infection, drug hypersensitivity, Crohn’s disease, or hypereosinophilic syndrome.

1.2 History of eosinophilic esophagitis

1.2.1 Eosinophilia linked to GERD

Eosinophils are present in most parts of the gastrointestinal mucosa, though they do not inhabit the normal esophageal epithelium (8). There are reports from the 1960s and 1970s that describe cases that could have potentially been identified as EoE today (9). Esophageal biopsies from these patients showed basal zone hyperplasia, papillary lengthening and intraepithelial eosinophilia. Despite being uncommon in GERD, these histological findings were interpreted as GERD-associated complications (9). However, it remained unclear why acid reflux only altered the esophageal epithelium in certain patients. Regardless of the inconsistencies, the association of GERD with esophageal eosinophilia persisted for several years (8).

1.2.2 Eosinophilia linked to EGE

While GERD-related eosinophilia was considered the main cause of esophagitis for years, multiple case series started to report clinical characteristics that differed from the typical clinical features associated with GERD (8). In 1978 Landres et al. described a case of vigorous achalasia in a subject with marked smooth muscle hypertrophy and esophageal eosinophilia (10). It was suggested that this subject represented a subtype of EGE that could potentially predispose to esophageal achalasia. However, eosinophilic infiltration was known to be unusual in tissues affected by motor disorders such as achalasia, making the proposed theory subject to debate (8).

In 1981, Picus and Frank presented a case of progressive dysphagia in a 16-year-old boy (11). Endoscopy results showed proximal dilation of the esophagus as well as several 1 mm nodular filling defects close to a stricture. Radiological studies revealed narrowing of the lumen, wall rigidity as well as elevated levels of circulating eosinophils. Yet again, these findings were considered to represent a variant of EGE (12). This was followed by new case reports from Munch et al. in 1982 (13), and Matzinger and Daneman in 1983 (14). They described isolated incidents of esophageal eosinophilia accompanied by dysphagia in patients who allegedly suffered from EGE (12). In 1985, Feckzo et al. (15) described three cases of esophageal eosinophilia, out of which two subjects suffered from EGE. Among the three patients, two developed submucosal fibrosis, which eventually led to esophageal stricture (15). However, these reports did not include any etiology, and concluded that reflux was

involved. In retrospect, these were presumably cases of EoE (12). In 1985, Lee published a more extensive report of 11 patients with mucosal esophageal eosinophilia (16). This cohort consisted of patients with an average age of 14.6 years, who experienced reflux symptoms alongside low eosinophil density. In retrospect, these patients likely suffered from GERD (12).

1.2.3 Recognition of EoE

Characterization of EoE as a separate disease entity took place in 1993, when Attwood et al. published a case series of 12 adult patients affected by dysphagia (17). These patients exhibited normal pH monitoring, as well as high eosinophil density in the esophageal mucosa (>20 eos/HPF). Notably, patients diagnosed with GERD had a mean eosinophil density of 3.3 eos/HPF. Within the cohort, seven patients suffered from food hypersensitivity, and all were dependent on advanced intervention such as dilatation and/or steroids in one case (17). Thereafter, Straumann et al. published a case series of 10 patients with acute recurrent dysphagia observed over a four-year span. Endoscopy results revealed distinct changes and elevated concentrations of eosinophils in esophageal epithelia, managed with antihistamines and systemic steroids (18).

The first pediatric work on EoE was published by Kelly et al. in 1995 (19). They described 10 children who had been diagnosed with EoE, based on clinical observations and histological examination. Six of the children had received antireflux treatment without resolution of symptoms, whereas two of the children had been subject to fundoplication. All 10 children responded well to amino acid formulas, indicating an allergic etiology for EoE (19).

Between 1995 and 2005, there was a substantial increase in clinical studies and the recognition of EoE (20). In 2007, consensus guidelines on the diagnosis and management of EoE were formulated by a multidisciplinary group, known as the First International Gastrointestinal Eosinophil Research Symposium Subcommittees (21). This publication further facilitated the identification of EoE and led to increased awareness of the disease (20).

1.3 Epidemiology and risk factors

Cases of EoE have been reported in children and adults from all continents, with the highest burden of disease being recognized in North America, Western Europe and Australia (22).

Several studies have aimed to address epidemiological questions in EoE, including retrospective and prospective case registries, series of endoscopies and biopsies, as well as population-based studies (6). Despite varying methodologies, epidemiological studies from industrialized countries have consistently described an increasing prevalence and incidence of EoE over the past decades (23).

1.3.1 Prevalence of EoE

Prevalence estimates of EoE differ, depending on several factors, including study design, study population, and the case definition being used (22). Most prevalence estimates of EoE have been obtained through single-center studies with defined catchment areas (24-29). However, some studies have used national databases or population-based methods, aiming to generate prevalence estimates applicable to the general population (23, 30-32). Due to the chronic and non-fatal nature of EoE, studies tend to report increasing prevalence rates regardless of geographic location (22). EoE may present throughout the lifespan, from infancy to old age, although most patients present with the disease in third and fourth decades (33).

Generally, studies report prevalence estimates of EoE ranging between 0.5-1 cases per 1000, translating to 50-100 cases per 100 000 persons. In the USA, most prevalence estimates vary between 30-90 cases per 100 000 persons (24, 28, 31, 34-38). The most extensive American epidemiological study was conducted by Dellon et al. in 2014, comprising more than 35 million individuals (31). Health insurance claims were collected from a database representing the commercially insured population of the USA. Using a previously validated disease definition, an overall EoE prevalence of 56.7 per 100 000 persons was estimated (31). Furthermore, in 2016, Mansoor et al. (37) aimed to address the epidemiology of EoE in the US. Using an extensive commercial database of electronic health records, patients diagnosed with EoE and a history of PPI use between 2010 and 2015 were identified. An overall EoE prevalence of 25.9 per 100 000 persons was reported (37).

The prevalence estimates obtained from the mentioned studies are consistent with estimates from other countries e.g. Australia (26), Canada (32), Switzerland (25) and Spain (27). However, some studies have reported prevalences that deviate from the normal range. For instance, a Danish study demonstrated a prevalence rate of 13.8 per 100 000, whereas a study from Northern Sweden estimated a prevalence rate of EoE at 400 per 100 000 (30).

Among the most recent epidemiological evidence on EoE is a systematic review by Arias et al. (39). This review summarizes a selection of population-based studies investigating the epidemiology of EoE in North America, Europe and Australia. Based on the included population-studies, the pooled EoE prevalence rate was calculated to be 22.7 per 100 000 persons per year, adjusted to 28.1 when considering studies with a lower risk of bias (39). See Appendix 1 for an overview of prevalence estimates from population-based studies.

1.3.2 Incidence of EoE

Incidence rates of EoE vary widely, ranging from 2.07 in the Netherlands to 12.8 in Ohio, USA (4, 40). A recent meta-analysis estimated a pooled EoE incidence rate of 3.7 per 100 000 persons per year in children and adults (39). See Appendix 2 for an overview of incidence estimates from population-based studies.

When interpreting incidence data, it is essential to consider variations in study methodology and geographic location. Regardless of methodological differences, studies unanimously report increasing trends in EoE incidence (41). This rapid surge is likely related to the growing recognition of EoE and increasing use of endoscopy in clinical practice (2). However, studies have shown that the increase in EoE incidence outpaces the increase in rates of endoscopy with biopsy, indicating a true increase in EoE incidence (2).

1.3.3 EoE risk factors

Presently, the most well defined risk factors for EoE include sex, ethnicity as well as atopic disorders including asthma, rhinitis and atopic dermatitis (42). Additionally, IgE-mediated food allergies have been linked to EoE development (6).

Studies have consistently reported a male predominance in EoE, with an estimated male-to-female risk ratio of 3:1 (43). Male predominance is reported in epidemiologic studies from Europe, Canada, the US, and in some Asian EoE cohorts (6). One suggested mechanism for the gender discrepancy is male inheritance of a risk related single-nucleotide polymorphism (SNP) in the gene for thymic stromal lymphopoietin (TSLP) on chromosome regions Xp22.3 and Yr11.3. A similar association has not been found in females (44).

While cohorts of EoE patients have been reported worldwide, studies have reported that Caucasian populations seem to be disproportionally affected by EoE compared to Asian and African-American populations (33). The prevalence of EoE in Caucasians has been found to be three-fold higher compared with other races (45). A recent population-based study among more than 7000 EoE patients in the USA, reported that approximately 90% of the included subjects were Caucasian, while only 5.6% were Asian and 6.1% were African-American (37). Comparison studies have shown that African-American subjects are more likely to present with a normal appearing esophagus at endoscopy than Caucasians. Therefore, the diagnosis of EoE may be missed if biopsies are not obtained. However, studies controlling for referral and population bias have demonstrated that among patients suffering from symptoms of esophageal dysfunction, Caucasians are at higher risk of presenting with EoE (5).

Furthermore, EoE is strongly associated with atopic diseases. Compared to the general population, EoE patients exhibit significantly higher rates of bronchial asthma, atopic dermatitis and allergic rhinitis (46). However, it remains unclear whether atopy predisposes to EoE (6). In 50-60% of cases, a personal history of atopy is documented prior to diagnosis of EoE. A systematic review comprising 21 studies and a total of 53,542 EoE patients and 54,759 controls found that most of the studies did not provide standardized definitions of atopy (46). Regardless of this limitation, overall allergic rhinitis, eczema and bronchial asthma were significantly more common among EoE patients compared to controls (46). It has further been estimated that between 15-43% of EoE patients concomitantly suffer from IgE-mediated food allergies. This indicates that presence of IgE-mediated food allergy may represent a predictive factor in the subsequent development of EoE.

1.4 EoE Pathogenesis

The pathogenesis of EoE is believed to be complex, with disease development being under the influence of genetic, immunological, as well as environmental factors (47). However, EoE pathogenesis remains under investigation, and the precise mechanism of disease is yet to be elucidated (33).

1.4.1 Genetic factors

Studies of family history and twin concordance, genome-wide association studies (GWAS) as well as the consistently reported male predominance, point toward the presence of a genetic component to EoE (48). The genetic predisposition involved in EoE has been explored using

different approaches, such as the association with Mendelian and non-Mendelian diseases, GWAS, and the search for a specific gene (49).

A higher prevalence of EoE has been reported in patients with hypermobile connective tissue disorders (CTDs), such as Loeys-Dietz (LDS), Marfan and Ehler-Danlos syndromes (50). The co-existence of EoE with these diseases is termed EoE-CTD, and it has been estimated that EoE increases the risk for CTD eightfold (51). Notably, the underlying pathologies of both EoE and CTD involve abnormal TGF-ß signaling and excessive production of TGF-ß (51). For instance, LDS results from gain-of-function mutations in the TGF-ß receptors, while Marfan syndrome type II is caused by mutations in connective tissue proteins that bind to TGF- ß, e.g. fibrillin 1 (52).

Moreover, a Mendelian disease that has been reported to frequently co-occur with EoE, is severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome (53). This rare syndrome stems from homozygous mutations in desmoglein 1 (DSG1), a key constituent of desmosomes. Desmosomes are structures that attach the cell surface to the keratin cytoskeleton in order to maintain gastrointestinal barrier function and epidermal integrity. Interestingly, it has been demonstrated that DSG1 is decreased in EoE and is associated with impaired barrier function (54). Current literature also suggests an association between EoE and other atopic Mendelian disorders, including autosomal dominant hyper-IgE syndrome as well as a syndrome involving elevated levels of mast cell tryptase in the blood (54).

GWAS have led to the recognition of various genetic alterations in EoE patients, including the genes encoding TSLP and calpain-14 (49). TSLP, a cytokine produced by epithelial cells, is responsible for initiating a Th2 cell-mediated response in dendritic cells (44). An SNP has also been identified in the TSLP receptor gene, located on the Y-chromosome, and may explain the high prevalence of EoE observed in males (33). Similarly, a genome-wide genetic association of EoE has been described at the CAPN14 gene encoding calpain-14, a member of the calpain large subunit family (55). Calpains are cytosolic cysteine proteases that participate in several biological processes, such as cleavage of pro-interleukin-33 and STAT6 which in turn regulate allergic responses (55). It has been found that the expression of CAPN14 mRNA in esophageal epithelium is increased in active EoE, when compared with inactive EoE and controls. Interleukin-13 gives rise to an epigenetic alteration of the CAPN14 promotor,

thereby upregulating CAPN mRNA in esophageal epithelial cells. However, the precise role of CAPN14 in EoE development requires further investigation (55).

Furthermore, single candidate-gene identification studies have described potential factors associated with EoE (56). For instance, an SNP in the CCL26 gene encoding eotaxin-3 has been related to EoE (56). Eotaxin-3 plays an essential role in the chemotaxis of eosinophils, and it has been demonstrated that its expression is increased in esophageal epithelial cells of EoE patients (57). A SNP has also been identified in the FLG gene encoding filaggrin, a structural membrane protein implicated in epithelial cells-extracellular matrix interaction (51).

In 2014, Alexander et al. (58) investigated the respective roles of genetic heritability and environmental factors in EoE pathogenesis. The overall risk of EoE for first-degree relatives was reported to be 1.8%, whereas the risk for a sex-matched relative was reported to be 2.3%. Higher recurrence risk ratios (RRR) were demonstrated in brothers (64-fold), fathers (43-fold) and men (51-fold) when compared with sisters, mothers and women, respectively (58). In the same study, analysis of the Twins cohort found common family environment to play a greater role (81%) than genetic inheritance (14.5%) in EoE susceptibility (58).

1.4.2 Environmental factors

Due to the increasing prevalence, attention has been drawn to the role of environmental factors in EoE development (48). Factors that have been associated with a higher risk of EoE include premature delivery, birth by cesarean section, early exposure to antibiotics, food allergy, lack of breastfeeding, and residing in an area of lower population density (59). This may indicate that altered immune system stimulation in the early years of life confers a predisposition to EoE (60).

Additionally, it has been suggested that an altered microbiome as well as the absence of microbe exposure at an early age may promote EoE susceptibility, as is the case for other atopic diseases e.g. asthma and atopic dermatitis (61). In 2015, Harris et al. demonstrated that EoE patients seemed to have an increased esophageal bacterial load relative to healthy subjects. In particular, they found Haemophilus to be significantly increased in untreated EoE patients (62). Another study showed a reversed association between Helicobacter pylori and pediatric EoE, suggesting a putative link between EoE and microbiota alterations (63).

1.4.3 Immune system factors

In EoE, the lamina propria and submucosa of the esophagus is characterized by extensive eosinophilic infiltration. Various cytokines are believed to participate in the maturation and migration process of eosinophils, e.g. IL-5, IL-13 and granulocyte-macrophage colony stimulating factor (64). These cytokines are generated by different cell types, including esophageal epithelial cells, in response to stimulation by the antigen-presenting cells (APCs) (65). Interestingly, esophageal biopsies from EoE patients have disclosed a pattern of dilated interepithelial spaces, changed epithelial barrier function and a decrease in adhesion molecules and proteins involved in maintaining epithelial barrier integrity (66, 67).

Pertaining to the evidence that shows a desmoglein-1 dependent altered barrier function in EoE, it has been proposed that increased esophageal permeability may promote the passage of antigens (65). These antigens may then lead to the activation of APCs and natural killer T-cells. If adequately stimulated, these cells can further initiate a Th2 response through the production of IL-4 and IL-13. It remains unclear whether the diminished barrier integrity represents a contributor or a consequence in the context of eosinophilic inflammation (49).

1.4.4 Disease mechanism and tissue remodelling

EoE is presently recognized as an allergy-mediated disorder, triggered by the ingestion of casual food allergens and/or aeroallergens (2). However, it is not a traditional Immunoglobin E (IgE)-mediated reaction, reflected by the lack of resolution in EoE patients receiving anti-IgE therapies (68). Alternatively, the eosinophilic inflammation in EoE is believed to be caused by an enhanced Th2 type immunological reaction driven by TSLP produced by esophageal epithelial cells (69). TSLP is a principal cytokine, involved in the initiation and enhancement of the Th2 type immunological reaction and is largely produced by epithelial cells and basophils (70).

Initially, allergens are ingested and exposed to the esophageal epithelium. This is followed by permeation to the subepithelium, leading to the activation of dendritic cells via TSLP induction (71). Activated dendritic cells strongly promote Th2 cell proliferation, resulting in an increased production of IL-5, IL-3, IL-15 and several other cytokines associated with eosinophilic inflammation (71). IL-5 differentiates and contributes to the recruitment of eosinophils residing in the intramedullary or intravascular space (72). Furthermore, IL-13 and IL-15 trigger epithelial cells to secrete eotaxin-3, a strong chemotactic factor for eosinophils

(56). Additionally, IL-13 decreases the gene expression of epidermal differentiation complex, leading to an impaired barrier function of the epithelium (57). In cooperation with mast cells, locally accumulated and activated eosinophils produce TGF-β1. This, along with the activity of fibroblasts and periostin, generates fibrotic changes in the esophageal wall, giving rise to smooth muscle dysfunction (71).

1.5 Clinical presentation

1.5.1 Symptoms in children and adults

EoE may debut at any age with a varied range of symptoms. However, the clinical presentation considerably differs between pediatric and adult populations (40). Infants and toddlers commonly present with nonspecific features, such as feeding difficulties, vomiting, nausea, heartburn, abdominal pain and failure to thrive (48). Older children typically exhibit symptoms that are more closely related to the esophagus, e.g. heartburn, chest pain and early signs of dysphagia, including slow and picky eating habits (73). In adolescents and adults, symptoms are more specific to esophageal narrowing and mainly include dysphagia and food bolus impaction (48). In a few cases, food bolus impaction can persist to the extent that an endoscopic removal procedure is required. Esophageal perforation has been reported as a possible endoscopy-induced complication, although spontaneous transmural esophageal rupture (Boerhaave's syndrome) may also occur as a primary manifestation of EoE (74).

Despite the discrepancy in clinical presentation between children and adults, EoE focused research has recently highlighted that symptoms may overlap across age groups. For instance, data show that some adults also experience chest pain and heartburn as prominent symptoms, possibly indicating an inflammatory component. In the same manner, children can also present with dysphagia (75). Furthermore, a recent study has proposed that gender is a factor in the initial clinical presentation of EoE. (76). The collected data suggest that men suffer from dysphagia and food bolus impaction more frequently than women. Conversely, heartburn and chest pain seem to be more commonly experienced by women (76)

1.5.2 Natural history

EoE is a chronic condition that usually has its onset during childhood, although in some individuals it becomes clinically evident in adulthood when they start to complain of dysphagia (77). Generally, symptoms appear in a hierarchal and pyramidal pattern from

infancy to adulthood, and largely depend on patients' ability to communicate (73). The difference in symptoms between pediatric and adult populations with EoE, seems to be related to the time dependent disease progression. In children, the esophagus is typically characterized by active eosinophilic inflammation, whereas subsequent fibrostenotic changes, stricture formation and motility disorders represent key complications in adult patients (2). Damage of the esophageal muscularis propria is also believed to participate in symptom generation, although subepithelial fibrosis or muscle dysfunction is challenging to detect using conventional endoscopic procedures. This partly explains the inconsistency between the severity of clinical symptoms and the extent of endoscopic abnormalities that are found in EoE (78).

The severity of symptoms varies widely among EoE patients, ranging from no notable symptoms, sporadic dysphagia with certain solid foods, to repeated events of food impaction nearly daily (79). Patients who experience mild and rare swallowing difficulties, may not seek medical care, likely considering the symptoms as part of their normal state. Therefore, it is essential to address that underdiagnosis as well as delayed diagnosis of EoE remains a challenge (79).

Upon inquiring, several patients report that they have developed coping mechanisms to facilitate eating, thus symptoms may be overlooked or underestimated (5). Accommodations that are frequently made by EoE patients include eating slowly, avoiding dry or textured foods, cutting foods into small pieces prior to consumption, lubricating foods with sauces, using liquids to dilute and wash down solid foods, as well as avoiding foods that are likely to trigger dysphagia and impaction events (80).

1.5.3 Symptom scoring

As is the case for several chronic diseases, it is essential to identify the frequency, persistency and intensity of symptoms. Various scoring systems have been developed to provide a comprehensive assessment of EoE symptoms (73). In addition to providing greater precision in evaluating symptoms, scoring systems also function as standardized tools that are useful to monitor EoE over time and evaluate treatment effects in clinical trials (73).

Patient-reported outcome (PRO) instruments have newly been developed and validated for the use in adult patients, such as the Eosinophilic Esophagitis Activity Index (EEsAI) and

Dysphagia Symptom Questionnaire (DSQ) (81). This scoring system aims to assess symptoms, behavioral accommodations, as well as biologic activity of adult patients with EoE over a 7-day recall period. It is extensive, accounting for frequency, severity and duration of dysphagia. Other factors, such as food impaction events, time required to eat a regular meal, frequency of pain while eating, as well as the use of coping mechanisms are also documented by the EEsAI (81). However, a prospective, observational study found that EEsAI score alone cannot predict endoscopic or histologic remission accurately (82).

1.6 Diagnosis and evaluation

1.6.1 Diagnostic criteria

Essentially, the diagnosis of EoE relies on the presence of clinical, endoscopic and histological features, following exclusion of other etiologies (83). Current diagnostic criteria for EoE include presence of symptoms related to esophageal dysfunction, at least one esophageal mucosal biopsy demonstrating ≥ 15 eos/HPF, and persistence of esophageal eosinophilia following a PPI-trial, with exclusion of other causes of eosinophilia (7). Despite being a pathological feature, esophageal eosinophilia may be caused by various conditions including GERD, EGID, Crohn's disease, celiac disease, achalasia, hyper-eosinophilic disorders, drug hypersensitivity and CTDs (84).

1.6.2 Differential diagnosis: GERD

The initial consensus guidelines for the diagnosis of EoE particularly focused on the exclusion of GERD, as evidenced by a normal esophageal pH monitoring or unresponsiveness to high-dose PPI therapy (85). Thus, EoE and GERD were suggested to be mutually exclusive disorders (86). However, the idea of establishing a clear distinction between the two entities was soon challenged, drawing attention to the complex interplay that may exist between EoE and GERD (87). It was proposed that esophageal eosinophilia may appear as a manifestation of GERD, resulting from repeated exposure of the esophageal lining to gastric acid. Furthermore, GERD can predispose to EoE development by increasing esophageal mucosal permeability, thereby facilitating translocation of causal allergens (86). Conversely, EoE may contribute to GERD development via production of substances that trigger reflux and decrease esophageal acid clearance. Lastly, considering the high prevalence of GERD in Western adult populations, it is likely for EoE and GERD to coexist independently (88). Hence, EoE is not excluded by concurrent GERD (87).

1.6.3 Differential diagnosis: PPI-REE

The initial goal of using a PPI trial was to distinguish GERD from EoE. This was based on the assumption that PPIs only exert acid-suppressive and anti-secretory effects, making GERD the only disorder responsive to PPIs (85). However, evidence emerged regarding a new subset of patients who have clinical, endoscopic and histological features compatible with EoE and yet experience clinical and histological remission in response to PPI therapy. These patients were recognized to have PPI-responsive esophageal eosinophilia (PPI-REE) (89).

In 2016, a meta-analysis comprising 33 studies showed that administration of PPIs in patients with an EoE phenotype achieves clinical and histological remission in 61% and 51% of patients, respectively (90). A number of studies have proposed theories regarding the mechanisms of PPI-REE. One theory suggests that PPIs decrease levels of key mediators such as eotaxin-3, IL-4, IL-5 and IL-13. It remains unclear whether PPI-REE represents a subtype of EoE or GERD, although recent data indicate that EoE and PPI-REE share a similar molecular basis. Current diagnostic guidelines recommend EoE unresponsive to PPIs to be discriminated from PPI-REE. Before performing a diagnostic esophago-gastro-duodenoscopy (EGD), patients should be subjected to an 8-12 week PPI trial consisting of 20-40 mg x2 per day of any available PPI (91).

Diagnostic approach and monitoring of EoE depend on repeated EGD, as there are currently no symptom tools, biomarkers, or pathognomonic traits that can replace clinicopathological monitoring (43).

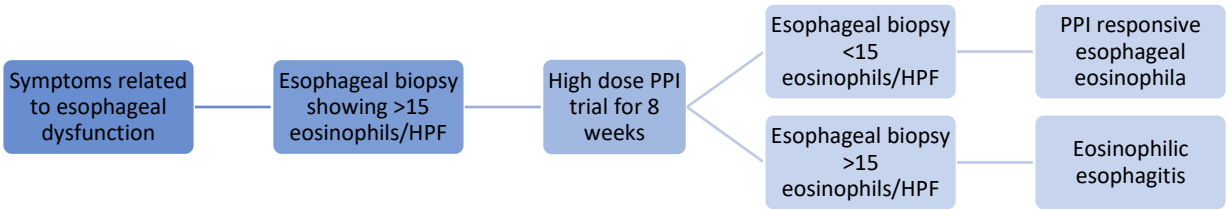

Figure 1: Simplified diagnostic approach of EoE

1.6.4 Endoscopic features

The endoscopic presentation in EoE is often characteristic, although not pathognomonic. Several endoscopic findings have been reported, including linear furrows, concentric rings, white exudates, esophageal strictures and reduced vascularity in the esophageal mucosa (77). Endoscopy and subsequent biopsies remain the most critical diagnostic assessments for EoE, allowing the identification of gross abnormalities as well as esophageal eosinophilia (33).

Linear furrows which appear in a longitudinal manner in the esophagus, are rather frequent and specific compared with other endoscopic features of EoE (92). Concentric rings exist along the horizontal axis of the esophagus, a feature that is termed ‘ringed esophagus’ or ‘trachealization’ in severe cases (93). Concentric rings require careful evaluation as subtle or transient rings may be found in GERD patients as well as in normal subjects exhibiting a potent gag reflex during the endoscopic procedure (93). White exudates histologically identify as microabscesses with the aggregation of a few eosinophils, which considerably resemble esophageal candidiasis (2). Persistence of eosinophilic inflammation may progress to subepithelial fibrosis in the esophageal wall, resulting in a narrow-caliber esophagus or esophageal stricturing. Occasionally, esophageal rupture occurs during the passage of the endoscope, suggesting mucosal fragility. In contrast to GERD, the middle and upper esophagus is also prone to perforation. Extensive inflammation and edema results in decreased vascularity, which manifests as thickening and whitening of the esophageal mucosa, commonly present in GERD patients. In some adolescent and adult patients with EoE, multiple polypoid lesions resembling esophageal papilloma are also observed.

The underlying mechanism of each endoscopic feature remains unclear, although important knowledge has been gained from studies investigating prevalence and age-dependent variations (94). There is a considerable difference between clinical and endoscopic features in children and adults, which may be explained by the inflammatory nature of pediatric EoE versus the progressive fibrosis that develops with increasing age (94). In 2012, Kim et al. performed a meta-analysis that mainly consisted of retrospective studies in adult populations with EoE (95). The following pooled prevalence estimates of endoscopic findings were reported: 48% linear furrows, 44% concentric rings, 27% white exudates, 21% esophageal strictures, 9% narrow-caliber esophagus and 41% reduced vascularity in the esophageal mucosa. At least one endoscopic finding was present in 93% of the subjects (95).

The mentioned meta-analysis also highlighted the differences in endoscopic abnormalities between pediatric and adult populations with EoE. Concentric rings, strictures and furrowing were found to be more common in adults, while children more frequently presented with narrow-caliber esophagus, white exudates and decreased vasculature (95). The effect of age on endoscopic findings is related to the natural course of inflammation and indicates that several phenotypes of EoE exist. Furthermore, it may partly explain the significant differences in symptoms experienced by children and adults (96).

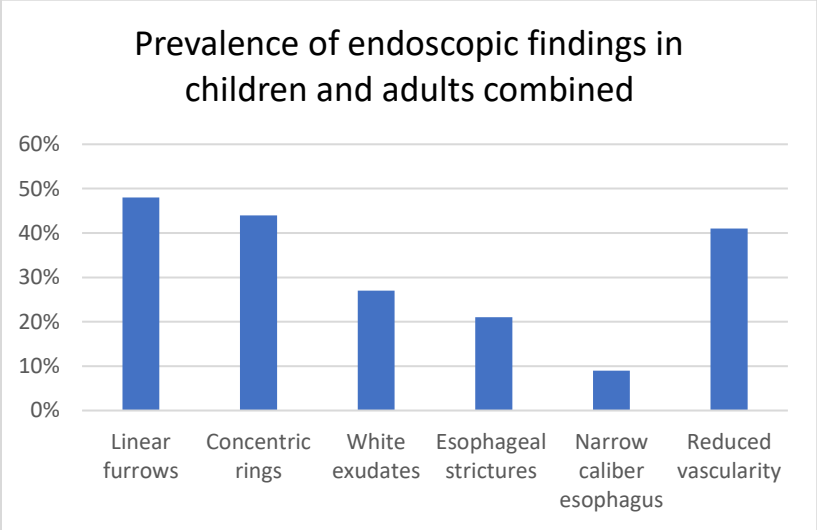

Figure 2: Prevalence estimates of endoscopic findings. Based on data from Kim et al. (2012)

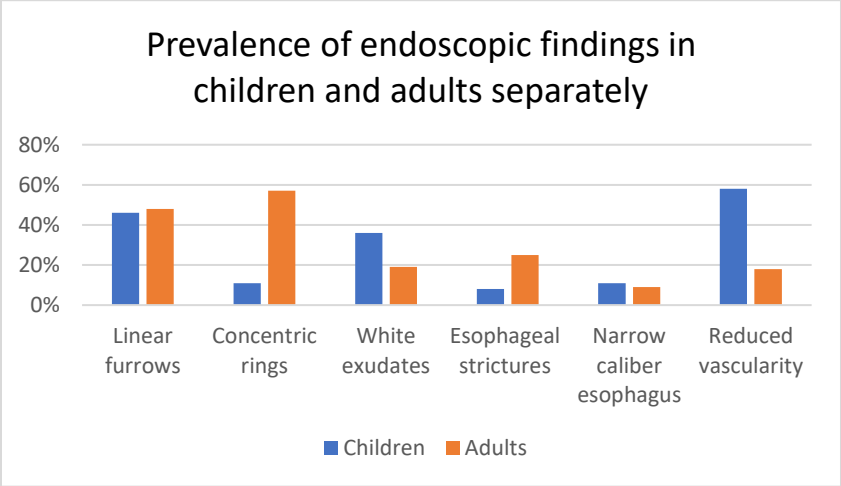

Figure 3: Prevalence estimates of endoscopic findings, by age. Based on data from Kim et al. (2012)

1.6.5 Histological features

A recent meta-analysis demonstrated that the esophageal mucosa may appear normal in 20% and 7% of EoE patients from retrospective and prospective analyses, respectively (95). Prasad et al. reported that the diagnose of EoE was entertained in 10% of all patients with dysphagia and an esophageal mucosa that appeared normal at endoscopy (97). Therefore, a macroscopically normal esophagus does not exclude EoE as a potential diagnosis, making it necessary to obtain esophageal biopsies. This is particularly important in patients with unexplained dysphagia or food impaction (2).

The histological demonstration of eosinophilic infiltration remains crucial for the diagnosis of EoE. Being the only gastrointestinal organ devoid of eosinophils, an esophagus with even a few infiltrating eosinophils is considered to be pathogenic (2). The density of mucosal eosinophils increases gradually from stomach to cecum. However, eosinophilic infiltration of the esophagus is not specific for EoE (2). Other clinical entities that may cause esophageal eosinophilia include, but are not limited to, GERD, celiac disease, Crohn's disease, drug hypersensitivity, scleroderma, EGE and vasculitis. In clinical practice, GERD is known as the most common etiology behind secondary esophageal eosinophilia (98). Previously conducted studies suggest that GERD can cause <10 eosinophils to emerge in the esophageal mucosa. In contrast, a cut-off value of >15 eos/HPF has been proposed as the histological definition of EoE (7).

Histological traits that are relatively pathognomonic of EoE include superficial distribution of eosinophils in the esophageal epithelium, degranulation of eosinophils, lamina propria fibrosis, and eosinophilic microabscesses (99). On the other hand, basal cell hyperplasia, papilla elongation and dilated intercellular space are abnormalities commonly found in EoE as well as GERD (99).

In EoE, eosinophils have been observed to distribute in a heterogenous manner. Previous studies have reported diagnostic sensitivity to increase from 40-50% when obtaining a single biopsy to almost 100% with five or more biopsies (100). Consensus guidelines recommend two to four mucosal biopsy specimens to be obtained from the proximal and distal esophagus (7). Since some EoE patients present with a normal appearing mucosa at endoscopy, the importance of random biopsies has been emphasized in consensus recommendations. However, in patients with endoscopic abnormalities, white exudates and linear furrows

represent areas of more intense eosinophilia (2). This indicates that the histological site as well as the number of biopsies taken influences the histological detection of EoE.

1.7 Management of EoE

The current therapeutic approach of EoE includes pharmacological, dietary and endoscopic therapy (101). Treatment largely depends on the severity of symptoms or endoscopic findings e.g. esophageal narrowing and stricturing. Due to difficulties in evaluating symptoms objectively and systematically, histological improvement is generally used as the primary outcome parameter in clinical trials (81).

1.7.1 Corticosteroid therapy

When PPI therapy is unable to induce symptomatic and histological remission, topical glucocorticoids represent first line therapy for EoE (2). Glucocorticoids exert their effects by targeting key mechanisms involved in EoE: they inhibit proinflammatory cytokines in the esophageal mucosa, thus reducing mucosal migration of eosinophils (48).

In 1998, systemic corticosteroids were demonstrated to be effective therapy for active EoE in a pediatric population (102). Ten years later, a prospective, controlled trial reported oral systemic prednisolone and swallowed topical fluticasone to be equally effective in terms of achieving histologic and symptomatic remission (103). However, systemic reactions, e.g. hyperphagia, weight gain and/or cushingoid characteristics were demonstrated in 40% of patients receiving oral prednisolone. In contrast, esophageal candidiasis was the only noted side effect of topical fluticasone, affecting 15% of patients (103).

Various randomized trials in children and adults support the efficacy of topical corticosteroids for histologic remission in EoE patients (104, 105). In 2016, Murali et al. conducted a systematic review and meta-analysis of 5 randomized, placebo-controlled trials investigating the efficacy of topical corticosteroids (104). In total, 89 children and 85 adults were included. Patients receiving topical corticosteroids showed significantly higher complete histologic remission than the placebo group (odds ratio 20.81 and 95% CI 7.03-61.63). However, topical corticosteroid therapy did not show a statistically significant effect on symptom improvement in EoE (104).

In contrast to histologic remission, data on symptomatic resolution are uncertain. A range of

clinical trials have not been able to show a statistically significant benefit of topical corticosteroids compared to placebo. A recent meta-analysis by Chuang et al. was not able to describe a clear effect of topical corticosteroids on symptomatic resolution, when compared with placebo (106). The discrepancy between histologic and clinical outcomes may be explained by variability regarding inclusion criteria, definition of symptomatic response, administered agents, dosing regimens, and treatment duration (6).
Although consensus guidelines recommend topical corticosteroids as first-line medical treatment for EoE, no formulations are currently approved by the Food and Drug Administration (FDA) (5). The most frequently used topical corticosteroids include nebulized fluticasone and oral viscous budesonide. Recommended dosage of fluticasone is 440 mcg twice daily and 880 mcg twice daily in children and adults, respectively. Alternatively, budesonide 2 mg twice daily in adults and 1 mg twice daily in children can be administered (98). One study found that oral viscous budesonide, when compared with nebulized fluticasone, covers a greater length of the esophagus, has significantly longer contact time with the esophageal mucosa and attains significantly higher histologic remission (64% vs. 27%) (107). Hence, histologic remission seems to be directly associated with higher mucosal contact time and the importance of appropriate administration methods in EoE treatment was emphasized (107).

Current evidence does not indicate that an 8 to 12-week course of topical corticosteroids is associated with adrenal axis suppression (84). Other known side-effects of corticosteroids e.g. local candidiasis, bone demineralization and growth retardation in children, appear to be uncommon since swallowed topical corticosteroids undergo first-pass metabolism (48). Being a chronic disease, symptoms and eosinophilic inflammation commonly relapse within few weeks after discontinuation of topical corticosteroids, making several patients dependent on long-term therapy (73). At present, only 1 long-term, placebo-controlled trial has investigated the effect of low-dose swallowed budesonide 0.25 mg x2 daily. Low-dose budesonide maintained histologic and clinical remission more effectively than placebo, although complete histologic remission was only maintained in 35.7% of EoE patients over a 1-year period (108). Long term use of topical corticosteroids in EoE management is a subject of growing interest (84).

1.7.2 Dilation

Esophageal dilation is a treatment modality reserved for patients who present with esophageal strictures or narrowing, the most severe complication associated with EoE (2). Most patients undergoing dilation are adults, as esophageal remodeling is a result of progressive and chronic eosinophilic inflammation (79).

Three main types of dilation procedures have been described, and include the simple bougie, the wire-guided bougie and through-the-scope (TTS) balloon dilation (109). In a retrospective study, Runge et al. reported that during a 12-year period, 164 of 509 EoE patients underwent dilation 486 times in total at their hospital. The bougie procedure was performed in approximately 20% of the cases, while TTS dilation was used in 80% of the cases. The TTS procedure was able to extend the esophageal lumen further than the bougie method, with no significant increase in complications (109).

The dilation must be carried out gently to avoid chest pain and esophageal tears secondary to mucosal fragility. The most critical complication associated with dilation is esophageal perforation (2). Previously it was suggested that dilation-related complications occur frequently, whereas recent systematic reviews report perforation rates of less than 1%, deeming dilation a safe procedure with the ability to induce short-term alleviation of symptoms in many patients (110, 111). Predictors for dilation-related complications include young age, upper esophageal stricturing, repeated dilations, and unsuccessful passage of the endoscope through strictures (112). Most patients experience symptomatic relief after dilation, although its durability seems to be insufficient. An extensive cohort study reported that more than 50% of EoE patients with dilation, required repeated procedures, particularly during the first year (113).

1.7.3 Dietary therapy

Initially, dietary therapy was observed to be an effective treatment option in children, emphasizing the role of food-allergen sensitization in EoE pathogenesis. Present literature describes three main types of dietary-restriction therapies in children and adults with EoE: the elemental diet, the allergy testing-directed elimination diet and the empiric elimination diet.

The elemental diet

The elemental diet is based on exclusive feeding with a hypo-allergenic formula. As food allergies are commonly a reaction to ingested protein, the elemental diet aims to substitute whole protein with amino acids (84).

In 1995, Kelly et al. described the beneficial effects of an exclusive amino acid-based diet in pediatric EoE management. The study found that a 6-week trial of elemental formula significantly reduced esophageal eosinophilia and clinical symptoms, with 8 out of the 10 included children exhibiting complete remission (19). Peterson et al. confirmed the efficacy of the elemental diet in an prospective trial in adults, producing histologic response in 72% of subjects (114). More recently, a study in 17 adults showed significant reduction in eosinophilic inflammation and clinical symptoms following 4 weeks of elemental diet therapy (115). In 2014, a meta-analysis reported the elemental diet to have a histologic remission rate of >90% in children and adults, combined (114).

The elemental diet is particularly beneficial in children who present with various IgE-mediated food allergies and feeding difficulties, as it ensures complete nutrition while symptoms are treated concurrently (116). Retrospective cohort studies and a meta-analysis have confirmed superiority of the elemental diet, when compared with empiric and allergy-testing directed diets (114). However, the acceptance of the elemental diet remains low among adults due to the high cost, unpalatability, the potential need for a gastric feeding tube, and the social isolation that may be experienced (43).

Allergy-testing directed elimination diet

Given the challenges and lack of patient adherence associated with the elemental diet, other dietary approaches have been developed and tested (101). The allergy-testing directed elimination diet is based on removal of foods to which the patient is sensitized (33). However, current evidence suggests that skin prick testing (SPT), atopy patch testing (APT) and serum food antigen-specific IgE-testing are not reliable methods for identifying causal food triggers (2). The etiology is not fully clarified, but likely supports the involvement of a delayed type, non-IgE-mediated mechanism underlying EoE pathogenesis (117).

In 2002, Spergel et al. used a combination of SPT and APT to identify specific food triggers in a series of EoE children from Philadelphia (118). The results obtained from the SPT and

APT were used to tailor an allergy testing directed elimination diet for each child. Histological and clinical remission was achieved in 49% of the treated patients. Later, the research group revised the results, and reported an overall efficacy of 53% (119). However, allergy skin testing exhibited varying sensitivities and specificities, with less than 10% accordance between positive results in SPTs and APTs (119). Furthermore, a retrospective study among 22 adult EoE patients subjected to allergy testing directed elimination diet, clinical improvement was seen in 68% of the patients, while endoscopic improvement with significant reduction in esophageal eosinophilia was seen in 53% of the patients (120).

Although some studies have proposed that allergy testing is useful in tailoring diets devoid of specific food triggers, similar results have not been reproduced by controlled studies (114). In a prospective study among EoE patients, SPT was able to identify food triggers correctly in only one of 20 patients (121). Furthermore, a study by Gonsalves et al. described poor performance of the SPT, revealing a positive predictive value of 13% for the identification of food triggers implied in EoE (122). A recent meta-analysis reported an overall remission rate of 45.5% with wide heterogeneity (95% CI 35.4%-55.7%) for the allergy testing directed elimination diet (114).

Empiric elimination diet

Due to the many challenges related to the elemental diet and the variable efficacy of skin allergy testing to identify specific food triggers in EoE, the six-food elimination diet (SFED) was developed (84). The SFED is based on empiric elimination of the six most common food groups associated with food allergy: wheat, cow's milk, egg, soy, peanuts/tree nuts, and fish/shellfish (101). The SFED approach consists of a six-week diet period, followed by esophageal biopsies and clinical monitoring as each food group is reintroduced sequentially to allow identification of trigger foods (101).

The SFED was initially studied in 2006 by Kagalwalla et al. in children with EoE (123). Following a 6-week period, clinical and histologic remission (<10 eos/HPF) was reported in 74% of children who underwent the SFED (123). Subsequently, a retrospective study in EoE children extended the SFED to include foods that exhibited positive results upon allergy testing, leading to histologic remission in 81% of the study population (124). Gonsalves et al. prospectively studied 50 adult EoE patients subjected to an SFED extended to comprise foods showing positive allergy test results (122). Complete histologic remission was achieved in

70% of the study subjects. Furthermore, Lucendo et al. investigated the efficacy of the SFED approach in Spanish EoE patients, reporting a histologic remission rate of 73% whereas significant symptom improvement was achieved in all responder patients (125). Notably, this study extended the SFED to include legumes, corn and rice, as these foods are commonly associated with food allergies in the study population (125).

Recently, a meta-analysis summarized seven observational studies and reported that the SFED was able to induce histologic remission in EoE with an overall efficacy of 72%. Notably, a heterogeneity value of 0% was calculated, indicating high concordance of the remission rate (95% CI 66%-78%). Due to the homogeneity and greater adherence rates, consensus guidelines recommend empiric elimination diets for the initial dietary management of EoE (114).

2 OBJECTIVES

Not all EoE patients experience disease improvement with the use of corticosteroid therapy, and some experience symptom relapse upon completion of the corticosteroid course. Current evidence supports the use of the SFED as a treatment option for children and adults with EoE. However, the SFED has not been tested on the Norwegian population and their dietary habits. The goal of this project is to assess the effect of the SFED on esophageal histopathology and symptoms in adult patients with an established EoE diagnosis. This thesis aims to present the existing results of our study, with emphasis on the histopathological and symptomatic features of EoE.

3 SUBJECTS AND METHODS

3.1 Study population

This prospective intervention study was planned during the spring of 2016 and is currently being conducted at Haukeland University Hospital (HUS) in Bergen, Norway in collaboration with the University of Bergen (UiB). Adult patients (18-60 years of age) with an established diagnosis of EoE, attending the Gastroenterology Outpatient Clinic at HUS were consecutively invited to participate in this study. Diagnostic criteria of EoE are consistent with current guidelines and primarily include i) symptoms of esophageal dysfunction ii) esophageal eosinophilia ≥15 eos/HPF iii) unresponsiveness to PPI-therapy iv) exclusion of other causes of esophageal eosinophilia.

Included patients could or could not have been treated with corticosteroids previously, but experiencing symptom relapse was necessary for inclusion in the study. In case of negative biopsy results or absence of clinical symptoms, patients were excluded from the study. The presence of clinical symptoms was essential, as the second phase of the study was exclusively symptom-based. Patients with reflux esophagitis, as indicated by histologic response to PPI-therapy or a highly abnormal pH-monitoring were also excluded from the study. Patients undergoing medical treatment for their EoE did not meet eligibility criteria and were therefore not informed about the study.

EoE patients below the age of 18 were not included, as this study aims to assess the effect of an empiric SFED in the adult population. The rationale for not including patients above the age of 60 years was to ensure diet compliance to the best possible extent. Subjects below the age of 60 were considered more suited to follow the SFED, as it requires time, motivation as well as comprehensive understanding of the diet.

Table 1: Eligibility criteria for participation in the study

Inclusion criteria	Exclusion criteria
Subjects between 18-60 years of age	Subjects responsive to PPI-therapy
Confirmed EoE diagnosis	Clinical remission
Presence of clinical symptoms	Histologic remission
No concurrent treatment	Highly abnormal pH-monitoring

3.2 Recruitment process

All patients who met inclusion criteria and were interested in participating in the study, were contacted via telephone by one of the two gastroenterologists responsible for the study. During this phone call, the patient received information about the study protocol and was invited to give written consent (Appendix 3). This is an ongoing intervention study with continuous recruitment of patients meeting eligibility criteria. By April 2018, 15 patients had been included, out of which 11 had completed the SFED.

3.3 Study design

This intervention study aims to assess the efficacy of the SFED in the Norwegian population. The dietary treatment consists of two phases and includes elimination and reintroduction of the eliminated food groups.

Baseline assessment

In order to assess the effect of the SFED, a range of measurements and questionnaires were administered before and after the SFED. Corticosteroid formulations (systemic, swallowed, intranasal) were withdrawn at least six weeks prior to baseline procedures, and were prohibited throughout the course of the study. A six-week termination period was considered adequate for the corticosteroids not to interfere with any of the performed baseline measurements. Following this, all patients underwent PPI-therapy for two weeks as a means of excluding acid reflux as the cause of dysphagia. No restrictions were made on concurrent treatment with PPIs and antihistaminic drugs.

At baseline, physical examinations, upper endoscopy with esophageal biopsies, blood tests, SPT, impedance manometry and ambulatory pH-monitoring were performed on each included patient. Additionally, esophageal symptoms were assessed structurally by the EEsAI (Appendix 4), whereas the 36-Item Short Form Survey (SF-36) (Appendix 5) was used for evaluation of functional health and well-being of patients. A questionnaire assessing each patient's dietary habits over the past year was also completed (Appendix 6).

Prior to starting dietary treatment, a master's student in clinical nutrition provided each patient with a thorough introduction to the SFED. Height and weight measurements were also performed. Dietary consultation was tailored according to each patient's lifestyle and consisted of a PowerPoint presentation of the SFED with several illustrations of diet-friendly foods. Along with the presentation, a comprehensive list of foods to eliminate along with substitute products, and a 2-week menu suggestion with recipes were handed out (Appendices 7 and 8).

Phase 1: Elimination

After completion of baseline procedures, all patients were required to follow the SFED for a 6-week period, avoiding consumption of wheat, milk, eggs, fish/shellfish, nuts/treenuts and soy. During the SFED-period, patients were offered reimbursable prescription for two

nutritional supplements: Fresenius Kabi ProvideXtra drink and Nutricia Elemental 028 Extra. Follow-up procedures were performed at the end of the SFED-period and included a new upper endoscopy with esophageal biopsies, blood tests and impedance manometry. A new assessment of esophageal symptoms (EEsAI) and well-being of patients (SF-36) was carried out. A new weight was also recorded for each patient.

Phase 2: Reintroduction

Evaluation of symptomatic response was carried out both through conversation with each patient and qualitative comparison of the EEsAI answered before and after dietary treatment. Symptomatic improvement was considered to be present if the response to the following validated question "In the past 7 days, how often have you had trouble swallowing?" had improved from baseline to the end of the SFED. In cases of symptomatic improvement, patients were subjected to sequential reintroduction of each food group eliminated in the SFED. Patients were requested to consume each reintroduced food daily for a 2-week period. If symptoms did not recur during a single-food challenge, the given food was considered to be well-tolerated. In case of symptomatic relapse, the given food was removed from the diet and a wash-out period was initiated before reintroduction of the next food group. The duration of the wash-out period varied from one patient to another.

3.4 Study timeline

Visit 1: During the first meeting, patients received thorough information about the study, and were requested to document their voluntary participation with a written consent form. Baseline endoscopy with esophageal biopsies, blood tests and SPT were performed, given that the patient had not undergone these tests rather recently. The obtained biopsies as well as blood samples were stored in a biobank at HUS.

Visit 2: During the second meeting, an esophageal manometry and a 24-hour ambulatory pH monitoring was performed. The patient received the following written questionnaires: EEsAI x2, SF36 x2, and diet compliance questionnaires (Appendices 9 and 10), to be filled out during the course of the study.

Visit 3: The third meeting consisted of a thorough consultation with a master's student in clinical nutrition prior to starting the SFED. The patient received detailed information about

the foods to be eliminated and food products that could be used as substitutions. Written and oral information about the SFED was supplemented with a 2-week menu suggestion and a recipe booklet to facilitate the 6-week diet period. During this meeting, the patient was also asked to hand in the following completed questionnaires: EEsAI x1 and SF36 x1.

SFED period: The next six weeks consisted of strictly following the SFED. After three weeks of following the SFED, the patient was asked to complete and hand in a 3-week diet compliance questionnaire. Questions and problems concerning the diet could be directed to the responsible physicians or master's student in clinical nutrition via e-email or telephone.

Visit 4: This meeting took place after the completion of the SFED, with the aim to evaluate the effect of the diet. Follow-up endoscopy with biopsies and blood tests were performed. The patient was requested to hand in the following completed questionnaires: EEsAI x1, SF36 x1 and 6-week diet compliance questionnaire.

Visit 5: A new manometry was performed during this meeting. If clinical remission had been achieved, the patient could enter the reintroduction phase of the study. Systematic reintroduction of food groups was not necessary if the patient did not experience clinical and/or histologic remission, as evidenced by post-SFED biopsy results.

Reintroduction phase: Patients experiencing symptomatic and/or histologic improvement were referred to a new consultation with a master's student in clinical nutrition prior to the reintroduction phase. Each eliminated food group was reintroduced separately at 14-day intervals. Following reintroduction of each food group, the patient was contacted via telephone and inquired about symptomatic relapse.

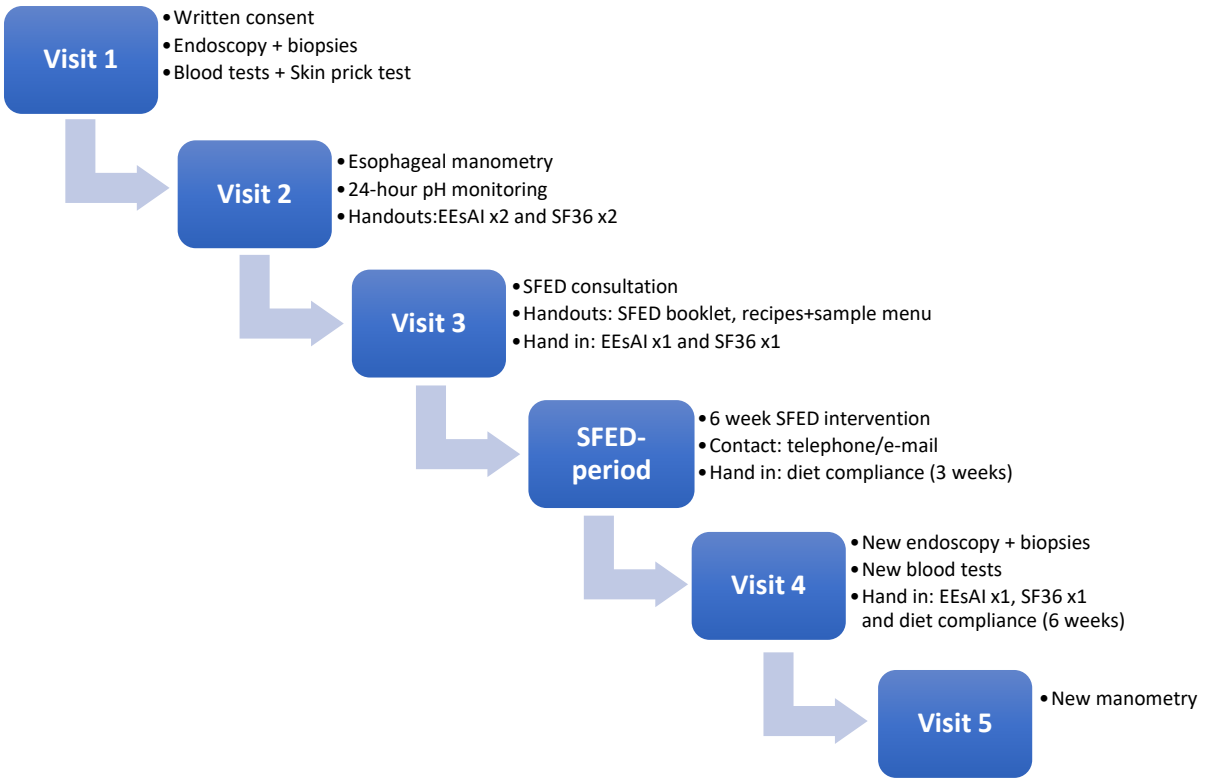

Figure 4: Process chart illustrating phase 1 of the study

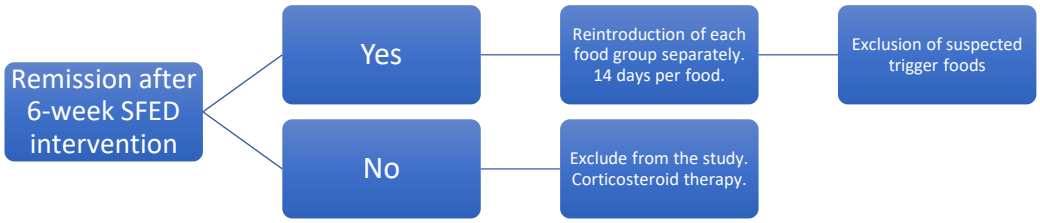

Figure 5: Hierarchy chart illustrating phase 2 of the study

3.5 Design of the SFED

As European Commission legislation concerning labelling of foodstuffs requires producers to label their products as gluten-containing rather than wheat-containing, we implemented a gluten-free diet rather than a wheat-free diet as a practical matter. While following the SFED, foods containing wheat starch and soy lecithin were considered safe to eat, as was the case for foods labelled with "traces of" allergens that cause slow reactions. The rationale for allowing foods containing traces of allergens was that the likelihood of an allergic reaction is minimal, as the amounts are generally very small. Recommended supplements during the elimination phase included calcium, vitamin D and omega-3 fatty acids in addition to a multivitamin/mineral supplement. If patients were unable to eat adequate amounts of food while following the SFED, they were encouraged to consume ProvideXtra drink or Elemental 028 Extra.

3.6 Measurements

3.6.1 Upper endoscopy and esophageal biopsies

Upper endoscopy with biopsy procedures were performed prior to and after six weeks on the SFED. All analyses of biopsy specimens were performed by an experienced board-certified pathologist at the Department of Pathology, Haukeland University Hospital. The effect of the SFED on histopathology was assessed by comparing results from the biopsies obtained before and after the SFED.

Endoscopies were performed during conscious sedation using a flexible 9 mm caliber Olympus gastroscope. Biopsy specimens were obtained from the proximal, middle and distal part of the esophagus by a standard needle biopsy forceps. A total of 6-9 biopsy specimens were obtained from each patient and fixed in 10% formalin before histopathologic analysis was performed according to routine procedures. Sections from the formalin-fixed specimens were placed on microscope slides to be stained with eosin and hematoxylin. A pathologist examined the histologic stains using a light microscopy for the quantification of eosinophils in the most densely inflamed areas. Peak eosinophil count/HPF was determined after evaluation of the eosinophil count in 2 or 3 HPFs.

In our study, histologic response was categorized into three groups; mild, moderate and severe eosinophilia. Mild eosinophilia was defined as a peak eosinophil count of <25 eos/HPF,

moderate eosinophilia was defined as 25-100 eos/HPF, while severe eosinophilia was defined as >100 eos/HPF.

3.6.2 Blood tests

Blood samples were drawn from each patient before starting and after completion of the SFED. These general blood tests included eosinophilic cell count and a celiac disease panel, consisting of various micronutrients indicative of nutritional status. At baseline, blood tests additionally included standard airway and food panels (RAST), total serum-IgE, and serum-IgE against hazelnut and shrimp. The standard airway panel (Phadiatop) comprised dust mites, cat, horse, dog, moulds, birch, timothy grass and mugwort, while the standard food panel consisted of cow's milk, egg white, cod, wheat, soy and peanut. All blood tests and analyses were performed at the Laboratory for Clinical Biochemistry at HUS.

A total serum IgE concentration ≥120 kU/L is considered to be elevated, suggesting the presence of an allergic process. Specific serum-IgE concentrations ≥0.35 kU/L is considered positive and indicates sensitization to a food allergen.

Table 2: Overview of all blood tests taken at baseline and follow-up

General blood tests	Allergy specific blood tests
B-Hemoglobin	S-Immunoglobulin E (IgE)
E-Mean corpuscular volume (MVC)	S-D1 Dermatophagoides pteronyssinus
B-Leukocytes	S-M2 Cladosporium herbarum
B-Thrombocytes	S-G6 Timothy grass
S-Thyroid stimulating hormone (TSH)	S-T3 Birch
S-Cobalamin	S-W6 Mugwort
S-Folate	S-E1 Cat
S-Ferritin	S-E3 Horse
S-C-reactive protein (CRP)	S-E5 Dog
S-Creatinine	S-F1 Egg white
S-Sodium (Na)	S-F2 Cow's milk
S-Potassium (K)	S-F3 Cod
S-Calcium (Ca)	S-F4 Wheat
S-ALAT	S-F13 Peanut
S-ALP	S-F14 Soy
S-Vitamin D	S-F17 Hazelnut
S-Gamma-Glutamyl transferase (GGT)	S-F24 Shrimp
S-Albumin	
S-Parathyroid hormone (PTH)	
S-IgA	
S-IgG	

3.6.3 Skin prick test

The SPT method is based on the principle that allergens that are exposed to the epidermis in sensitized individuals will bind to IgE-antibodies that are attached to receptors on the surface of mast cells (126). The allergen creates cross-links between Ig-E antibodies, leading to activation and subsequent degranulation of mast cells. Upon degranulation, mast cells release several mediators including histamine, cytokines and chemokines, causing an acute local inflammatory reaction (127).

Each patient underwent an SPT before the SFED period, with the purpose to identify IgE-mediated allergies against specific foods. The results obtained from the SPT, combined with the immunological blood tests were used to direct the reintroduction phase and to prevent adverse reactions. Antihistamine medications e.g. Cetirizin, Aerius, Xyzal, Zyrtec and Phenamin were discontinued 72 hours prior to the SPT (126). The procedure was performed by an allergy specialized nurse at the Section for Clinical Allergology, Department of Occupational Medicine, Section of Allergy, HUS. Patients were tested with a standard panel of inhalant allergens and food allergens, in addition to shrimp and hazelnut.

During the SPT, droplets of solution containing test allergens were applied on the inner forearm using a disposable lancet. Each solution droplet was separated from the next by 1-2 cm to avoid false-positive reactions due to cross-contamination of test allergens (126). With the aid of a small plastic probe, the epidermis was gently pricked to allow the solution to enter just below the surface of the skin. Excess allergen solution was removed with a tissue, and during the next 15-20 minutes, the area of skin was observed for characteristic changes. Appearance of a wheal (raised, itchy bump) and flare confirmed that sensitization to a particular allergen was present (128). The size of the wheal was used as an indicator of the degree of sensitivity to the allergen, although medical history and clinical symptoms were taken into account when interpreting the clinical relevance of the SPT. (126). A mean wheal diameter of ≥ 3 mm was used as the cut-off value for positive SPT. A positive histamine control as well as a negative saline control test was also included. The purpose of the histamine control was to ensure that test allergens were applied appropriately and to exclude negative SPT results due to potential drug interactions. The negative control was used to exclude the presence of dermographism, a condition which complicates interpretation of the SPT (126).

3.6.4 High-resolution manometry

HRM has replaced conventional manometry as the primary method for assessment of esophageal motor function (129). Displayed and interpreted by esophageal pressure topography (EPT), this method provides an in-depth evaluation of esophageal motility by allowing calculation of the amplitude of contractile events occurring in the esophagus and its sphincters (129).

Patients underwent HRM at baseline, and a new HRM was also performed following completion of the SFED. The effect of the SFED on esophageal motility was assessed by comparing HRM data obtained before and after the SFED. The procedure was carried out after at least a 6-hour fasting period, using a high-resolution catheter with 36 solid-state circumferential sensors spaced at 1 cm intervals. Initially, the HRM catheter was calibrated by applying external pressure, and a topical anesthetic was applied to the patient's nasal cavity. The catheter was then positioned transnasally, stretching through the hypopharynx to the stomach. Adhesive tape was used to fix the HRM-catheter to the nose. Once the catheter had been inserted and fixed, resting sphincter pressure was assessed over a 20-30 second period of calm breathing without swallows. The patient was then asked to swallow 10 mL of water in 5-10 turns. Data interpretation was performed according to the Chicago classification (CC), which is used to categorize motility disorders in a systematic manner, by applying objective measures of esophageal sphincter and peristalsis (129).

<u>The Chicago classification and EPT metrics</u>

A key characteristic of the CC is the classification of esophageal motor disorders into pathological conditions never present in normal subjects and conditions deviating from the norm yet not necessarily indicative of pathology. The CC mainly divides physiological dysfunction into the following: i) achalasia ii) esophagogastric junction (EGJ) outflow obstruction iii) major disorders of peristalsis iv) minor disorders of peristalsis (130). See Appendix 11 for a complete overview of The Chicago Classification version 3.0.

A range of metrics have been developed for the quantification of esophageal function in EPT: *Integrated relaxation pressure* (IRP) measures the ability of the EGJ to relax upon swallowing. IRP represents a complex metric and is defined as the mean minimum EGJ pressure during four seconds of relaxation within 10 seconds of swallowing starting at upper esophageal sphincter (UES) relaxation (129). Normal IRP is defined by an upper of

15 mmHg, although reference values may vary depending on the manometric apparatus being used. *Distal Latency* (DL) is another EPT metric, defined as the interval between UES relaxation and contractile deceleration point (CDP), a concept describing the physiologic transition from esophageal peristalsis to emptying. On the basis of DL, contractions are defined as being premature or of normal latency (lower limit of normal: median DL 4.5 seconds). *Distal contractile integral* (DCI) is a measure of the vigor of the distal esophageal contraction, taking into account contraction amplitude, duration as well as the length of the distal esophagus (129). The obtained DCI values are used for the classification of contraction vigor in the following groups (131):

1) DCI >450 mmHg·s·cm and <8000 mmHg·s·cm is defined as normal
2) DCI >100 mmHg·s·cm, and <450 mmHg·s·cm is defined as weak peristalsis
3) DCI <100 mmHg·s·cm is defined as failed peristalsis
4) DCI >8000 mmHg·s·cm is defined as hypercontractile
5) Ineffective – failed or weak

3.7 Questionnaires

3.7.1 Symptom scoring - EEsAI

In our study, patients were considered to have symptomatic response to the SFED if the frequency of troubled swallowing decreased from baseline to follow-up, as assessed by the following validated EEsAI item: "*In the past 7 days, how often have you had trouble swallowing?*". Additionally, symptomatic response was evaluated through conversation with each patient after completion of the elimination phase. If symptomatic improvement was present, the patient underwent sequential reintroduction of foods.

All patients completed the EEsAI before the start of the SFED and at the end of the 6-week SFED period, with the aim to evaluate the effect of the SFED on esophageal symptoms. Prior to the development of the EEsAI, no other PRO instrument fulfilled all validation criteria recommended by the FDA (132). The EEsAI is specifically developed for the assessment of dysphagia severity in EoE patients. A total of 11 questions are asked in the EEsAI. Firstly, the EEsAI focuses on dysphagia induced when consuming eight different food consistencies that have been selected based on dietary consumption patterns in USA, Canada and Europe. Further, it inquires into dietary and behavioral adaptations for the same food consistencies, as

well as frequency, pain severity and duration of dysphagia. The obtained score serves as an indicator of dysphagia, while accounting for accommodating symptoms e.g. food avoidance, slow eating and careful chewing. The score is validated in 7-day recall period, selected after statistical evaluation and patient input (73).

The EEsAI is based on information about EoE patients from Switzerland and the US, collected via surveys, focus groups and semi-structured interviews. The construct validation process of the EEsAI was performed using the Patients Global Assessment of Disease activity (81). However, a recent prospective multicenter study has described a modest correlation between distinct EEsAI cut-offs and endoscopic or histologic disease activity. Thus, it is important to assess EoE activity using a multimodal approach consisting of symptom reporting, as well as objective measures including endoscopic and histologic findings (82).

Scoring system of the EEsAI

The EEsAI international study group has developed a scoring system for the EEsAI. Severity of dysphagia (VDQ) as well as behavioral accommodations (AMS) are assessed by the EEsAI. Question number 1, 3 and 4 provide information, although they are not used for score calculation. Question number 2, known as the Visual Dysphagia Question (VDQ), assesses the degree of dysphagia experienced when consuming the following eight food consistencies: solid meats, soft foods, dry/sticky rice, ground meats, fresh white bread (untoasted), porridge, raw fiber-containing foods and French fries. Questions 5-8 evaluate behavioral adaptations for the same eight food consistencies by inquiring about food Avoidance, food Modification and Slow eating (AMS).

Initially, questions 2, 5, 6, 7 and 8 are used to score the VDQ and AMS. A VDQ score of 0 reflects very mild dysphagia, while a score of 10 reflects highly active dysphagia. In the same manner, an AMS score of 0 and 10 indicate mild and serious behavioral adaptation, respectively. Further, a total EEsAI PRO score can be obtained by scoring questions 9, 10 and 11 in addition to the VDQ and AMS questions.

VDQ scoring

Each food consistency is given a score based on the degree of difficulty experienced during its consumption. If the patient does not experience any difficulty when eating a given food consistency, a score of 0 is given. Mild difficulty corresponds to a score of 1, while moderate

difficulty corresponds to a score of 2. In cases of severe difficulty, a score of 3 is given. Finally, all food consistency scores are summarized and divided by the number of relevant food consistencies, then multiplied by 10. The VDQ can be calculated by using the following formula:

$$VDQ = \frac{(N1 \times 1) + (N2 \times 2) + (N3 \times 3)}{(D \times 3)} \times 10$$

N1: the number of food consistencies graded with mild difficulties
N2: the number of food consistencies graded with moderate difficulties
N3: the number of food consistencies graded with severe difficulties
D: the number of relevant food consistencies

AMS scoring

For each of the eight food consistencies, four questions related to behavioral adaptation are scored. For a specific food consistency, no behavioral adaptation is scored as 0. Eating a food consistency slower than others corresponds to a score of 1 (N1), while modifying a food consistency corresponds to a score of 2 (N2). The presence of slow eating as well as modification of a food consistency is given a score of 3 (N3), and avoidance of a specific food consistency is given a score of 5 (N4). The AMS can be calculated by using the following formula, where D represents the number of relevant food consistencies. The AMS can be calculated using the following formula

$$AMS = \frac{(N1 \times 1) + (N2 \times 2) + (N3 \times 3) + (N4 \times 5)}{(D \times 5)} \times 10$$

N1: the number of food consistencies with "Yes" to slow eating only
N2: the number of food consistencies with 'Yes' to food modification only
N3: the number of food consistencies with 'Yes' to both slow eating and modification
N4: the number of food consistencies with 'Yes' to avoidance
D: the number of relevant food consistencies

Overall PRO scoring

The calculated VDQ and AMS scores, as well as the answers to the remaining EEsAI questions can be used to obtain an overall PRO score, ranging between 0 and 100. The higher the PRO score, the more pronounced the symptoms are considered to be. This scoring system was provided by the international EEsAI study group in April 2017.

3.7.2 SF-36

In this study, the SF-36 was used to evaluate the effect of the SFED on health-related quality of life (HRQOL). Hence, all patients were requested to fill out the SF-36 before the start of the SFED, as well as at the end of the 6-week SFED period. The SF-36 is a generic questionnaire designed to quantitatively measure health status in the general population and in subjects suffering from medical conditions (133).

The SF-36 is an abbreviated version of 149 validated health-related questions, originally described in a comprehensive medical outcomes study (134). Studies have reported high reliability and reproducibility of the SF-36 among patients presenting with similar health conditions (135). Validity of the SF-36 has also been established across differing health conditions, with consistent differences observed between subjects with medical conditions and the general population (136). Thus, the SF-36 is a valuable tool that can be used to monitor health status in specific and in general populations, to evaluate treatment effects, and to assess relative burden of diseases (137).

The questionnaire consists of 36 items that can be divided into eight subscales for quantification: Physical Functioning (PF), Role limitations due to Physical health (RP), Role limitations due to Emotional functioning (RE), Energy/vitality (VT), Emotional Well-Being (EWB), Social Functioning (SF), Bodily Pain (BP) and General Health (GH). Further, these subscales can be compiled into two main components: a Physical Component Summary (PCS) and a Mental Component Summary (MCS) for a 4-week recall period (134).

Each subscale is scored separately, providing an eight-scale score profile. Given that the patient has completed at least half of the SF-36 items within each subscale, scores are weighted and transformed into a scale from 0 (reflecting severe disability) to 100 (reflecting no disability) (134). The PCS and MCS scores are generated using specific algorithms, with each subscale contributing differently to these measures (138).

SF-36 scoring

In this study, score calculation was done according to the 36-Item Short Form Survey Scoring Instructions provided on https://www.rand.org/health/surveys_tools/mos/36-item-short-form/scoring.html.

• Step 1: Each of the 36 items are recoded on a scale from 0 to 100.

• Step 2: The scored items belonging to a specific subscale are averaged together to provide a separate score for each subscale. The number of items that constitute a subscale varies. PF is made up of ten items, while EWB and GH consist of five items each. RP and VT consist of four items each, RE of three questions and both SF and BP consist of only two items each.

• Step 3: The PCS and MCS scores are calculated by summarizing the four subscales that constitute each of these components, and then dividing this figure by the number of subscales that the PCS and MCS are made up of.

$$PCS = \frac{(scores\ for\ PF + RP + BP + GH)}{4}$$

$$MCS = \frac{(scores\ for\ RE + VT + EWB + SF)}{4}$$

3.7.3 Dietary habits

Before starting the SFED, patients were requested to complete a questionnaire that assesses dietary habits during the previous 12 months. Specifically, this self-administered questionnaire functioned as a checklist of the food groups that were eliminated during the SFED, with frequency response options for patients to report how often each item had been consumed over the past year. For each food group, frequency response options included "daily", "weekly", "monthly" and "never". In cases where patients responded with "never" they were asked a follow-up question about why the given food had not been consumed. This follow-up question could be answered with "allergic", "I dislike the given food" or "other reasons". When responding with "other reasons", patients were asked to elaborate.

3.7.4 Dietary compliance questionnaires

After completing three weeks of the SFED, dietary adherence was assessed in all patients using a compliance form. Patients were requested to fill out the same compliance form at the end of the 6-week SFED period. The dietary compliance form included visual analogue scales (VAS) of general satisfaction with the diet, self-reported compliance and satisfaction with the diet as symptom management. Additionally, the compliance form consisted of questions with multiple answer options. These questions were related to deviations, inquiring how frequently, which foods and for what reason foods that were not included in the SFED had been consumed during the diet period.

3.8 Data analysis

A database was created in Microsoft Excel® based on biopsy results as well as scores obtained from the study questionnaires. GraphPad Prism version 7.04 for Windows, GraphPad Software (La Jolla California USA) was used for graphic representation and statistical analyses. Two or more different normality tests were applied to all values before performing statistical hypothesis testing.

3.9 Ethical considerations

The intervention was conducted in agreement with the ethical principles of the Declaration of Helsinki (DoH) and was approved by the Regional Committees for Medical and Health Research Ethics (REK Vest) in August 2016 (Reference number: 2016/1090). Informed, written consent was collected from all patients prior to the start of the study. Participation was entirely voluntary, and withdrawal from the study was possible at any time without further justification.

All personal information was de-identified and handled in a confidential manner. The obtained blood samples and biopsies are stored in Biobank Haukeland and are reserved for use in this study only. Study patients had the right to both access and rectify their registered data on oral or written request. In case of withdrawal from the study, patients could demand deletion of all test samples and personal information, unless this material had already been used in analyses or scientific publications.

4 RESULTS

Among the recruited subjects, only one dropped out of the study. Additionally, two patients were excluded as esophageal biopsies at baseline showed no eosinophilic cells, while one patient was excluded due to lack of symptoms at baseline. Currently, a total of 11 patients have completed the SFED. Out of the patients who completed the SFED, one was later removed from the dataset, as it was discovered that baseline biopsies did not show eosinophilic infiltration. This patient was therefore removed from the dataset and was not included in data analyses, despite having completed the entire study course.

4.1 Demographics

Baseline demographics for the total study population, showed a male predominance and a mean age of 29 years at inclusion in the study. Further, all included subjects were of Caucasian ethnicity and presented with dysphagia, while food impaction was present in more than half of the study subjects.

Table 3: Demographics and clinical characteristics for the study population at baseline

Characteristic	Patients completing the SFED (n=10)
Mean age (years) ± SD	28.7 ± 5.64
Mean weight (kg) ± SD	84.8 ± 9.40
Mean BMI (kg/m^2) ± SD	26.7 ± 2.97
Sex (n)	
Male	8/10
Female	2/10
Ethnicity (n)	
Caucasian	10/10
Presenting symptom (n)	
Dysphagia	10/10
Food impaction	6/10
Self-reported allergies (n)	
Dietary allergens	7/10
Aeroallergens	6/10

The questionnaire that was used to assess dietary habits during the past 12 months, showed that 9 out of 10 patients had avoided consumption of at least one of the foods that were inquired about. The reasons for avoiding one or more foods varied between patients, although allergy was most commonly reported as the reason for food avoidance.

Table 4: Food avoidance during the past 12 months obtained via questionnaire at baseline

Patient no.	Foods avoided	Reported reason for avoidance
1	Shellfish	Allergy
2	Nuts	Allergy
3	Yoghurt + Peanuts + Soy	Unintentional
	Nuts	Dislike
4	Egg + Shellfish	Dislike
	Peanuts + Nuts	Allergy
5	Nuts	Allergy
6	Shellfish	Allergy
7	Milk + Bread + Wheat + Peanuts	Weight-loss diet
	Shellfish	Dislike
8	Milk + Dairy products + Egg	Allergy
	Fish + Shellfish + Peanuts + Nuts	Allergy
9	Shellfish	Unspecified reaction
	Nuts	Abdominal distress
10	None	None

4.2 Blood test results and SPT results

Allergy blood tests taken at baseline included total s-IgE, as well as specific s-IgE against egg white, cow's milk, cod, wheat, peanut, soy, hazelnut and shrimp. Standard airway panel testing (Phadiatop) was performed on all patients and was found to be positive in 9 out of 10 patients.

• Reference value of total s-IgE for adults: <120 kU/L.
• Reference value of specific s-IgE for adults: <0.35 kU/L.

Elevated levels of total s-IgE were found in 6 out of 10 patients. Values of specific s-IgE ranged from undetectable food allergen-specific IgE in serum to more than 100 kU/L, reflecting very high levels of food allergen-specific IgE

Table 5: Allergy blood test results for each individual patient at baseline

Patient no.	Total IgE (kU/L)	Eggwhite (kU/L)	Cow's milk (kU/L)	Cod (kU/L)	Wheat (kU/L)	Peanut (kU/L)	Soy (kU/L)	Hazelnut (kU/L)	Shrimp (kU/L)
1	137	Neg	Neg	Neg	Neg	Neg	Neg	Neg	4,6
2	39	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
3	411	0.54	Neg	Neg	0.43	Neg	Neg	0.71	Neg
4	377	0.74	Neg	Neg	1.4	4.84	0.75	52.1	Neg
5	257	Neg	Neg	Neg	Neg	Neg	Neg	9.53	0.85
6	94	Neg	Neg	Neg	Neg	Neg	Neg	Neg	6.78
7	155	1.56	Neg	Neg	2.49	0.63	Neg	1.34	Neg
8	2690	5.87	13.1	43.7	5.37	>100	19.2	67.5	8.33
9	24	Neg	0.37	Neg	Neg	Neg	Neg	Neg	Nm*
10	54	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg

For specific s-IgE, negative test values (<0.35 kU/L) are denoted by 'Neg'. Positive test values (≥0.35 kU/L) are specified with measured concentrations of s-IgE. *Nm = not measured.

SPTs were performed on all patients prior to starting the SFED. In cases where patients had undergone an SPT rather recently, existing test results were used as it was deemed unnecessary to perform the procedure again. In patient no. 2 and 6, SPT results could not be interpreted due to the presence of dermographism and absence of reactivity to the positive histamine control, respectively.

- A wheal diameter <3 mm is considered a negative SPT reaction.
- A wheal diameter ≥3 mm is considered a positive SPT reaction

Among the eight dietary allergens employed, peanut was the most common food found to trigger a response by SPT. Cod, wheat and hazelnut triggered a response in two patients each, while egg white, cow's milk and shrimp triggered a response in one patient each. Soy produced negative test results in all patients. Positive SPT reactions showed wheal diameters ranging from 3 mm to 9 mm.

Table 6: SPT results for each individual patient, obtained at baseline

Patient	Eggwhite	Cow's milk	Cod	Wheat	Peanut	Soy	Shrimp	Hazelnut
1	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
2*	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
3	Neg	Neg	Neg	Neg	Neg	Neg	3 mm	3 mm
4	Neg	Neg	Neg	Neg	3.33 mm	Neg	Neg	Neg
5	Neg	Neg	4.5 mm	Neg	4 mm	Neg	Neg	4 mm
6**	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
7	Neg	Neg	Neg	4.5 mm	Neg	Neg	Nm*	Nm
8	4.5 mm	4.5 mm	4.5 mm	4.5 mm	9 mm	Neg	Neg	Neg
9	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
10	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg

Negative SPT results (<3 mm) are denoted by 'Neg'. Positive SPT results (≥3 mm) are specified with measured wheal diameter in mm. * Dermographism. ** Not testable as positive histamine control showed no reactivity. N.A = not available.

4.3 Clinical response: EEsAI

Symptomatic improvement was evaluated via individual dialogue with each patient and comparison of answers before (baseline) and after the SFED (six weeks) to the following validated EEsAI question (Item 9): *"In the past 7 days, how often have you had trouble swallowing?"*. An improvement in response from baseline to six weeks was required for patients to start the reintroduction phase.

In 7 out of 10 patients, symptomatic improvement was evident when assessed through conversation and change from baseline to six weeks. Patients no. 2, 5 and 10 reported to have negligible or no symptomatic improvement, as was reflected by their unchanged responses to EEsAI item 9 from baseline to six weeks.

Table 7: Symptomatic response of the SFED assessed through change in EEsAI item no. 9

Patient no.	Baseline response to item 9	Follow-up (six weeks) response to item 9
1	1-3 times	0 times
2	>3 times	>3 times
3	>3 times	1-3 times
4	1-3 times	0 times
5	Daily	Daily
6	1-3 times	0 times
7	1-3 times	0 times
8	4-6 times	1-3 times
9	Daily	0 times
10	Daily	Daily

Table 8: Scoring for EEsAI Item 9 regarding frequency of dysphagia, adapted from the EEsAI scoring manual

Question	Short name	Options	Score
How often have you had trouble swallowing?	Frequency of TS	Never	0
		1-3 times / week	15
		4-6 times / week	27
		Daily	31

A Wilcoxon matched pairs signed rank test was conducted to compare frequency of troubled swallowing at baseline and six weeks. Before the SFED intervention, our cohort of patients had a median score of 27 (IQR=15), whereas a median score of 7.5 (IQR=24) was found at six weeks. The p-value of 0.0156 shows statistically significant reduction of troubled swallowing.

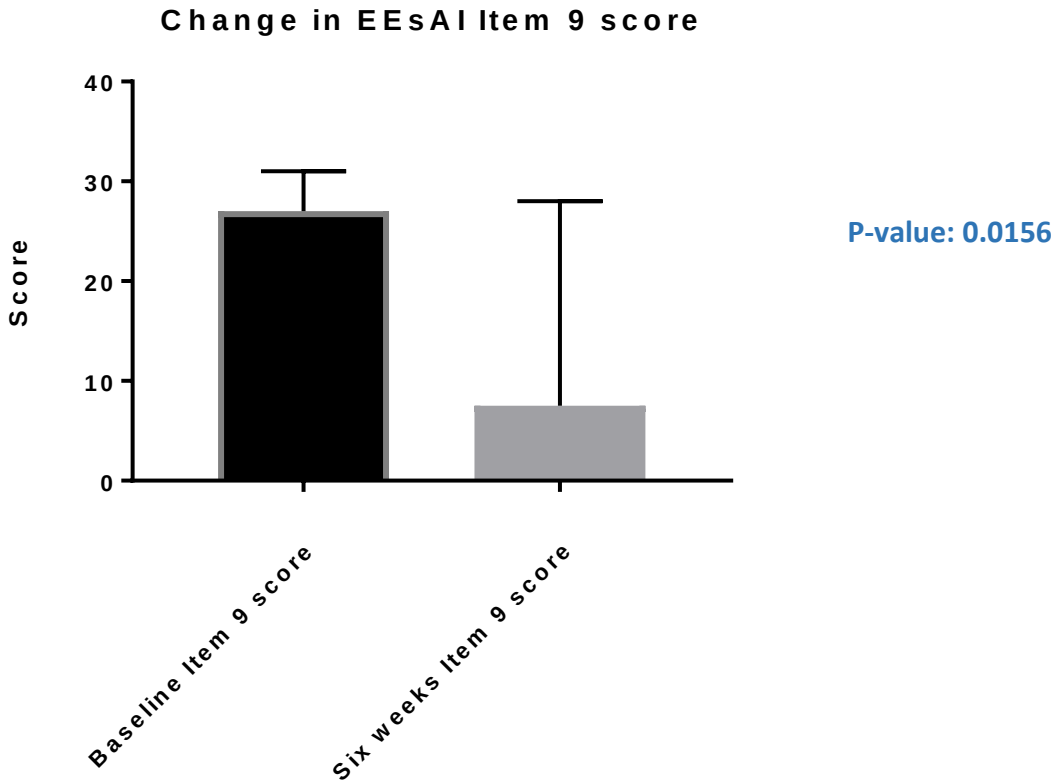

Figure 6: Change in median Item 9 score from baseline to six weeks. Interquartile range is indicated by whiskers.

As stated previously, the effect of the SFED on esophageal symptoms was not exclusively assessed through dialogue and qualitative comparison of troubled swallowing frequency at baseline and six weeks. In addition, the EEsAI was scored to provide additional information about severity of dysphagia and degree of behavioral adaptation in our patients.

VDQ is a measure of dysphagia severity and is scored on a scale from 0 (no symptoms) to 10 (most severe symptoms). A paired-samples t-test was conducted to compare VDQ scores before (baseline) and after the SFED-intervention (six weeks). The obtained p-value demonstrates that there was no statistically significant change in dysphagia severity from baseline (mean=3.63 SD=1.72) to six weeks (mean=2.15 SD=1.79).

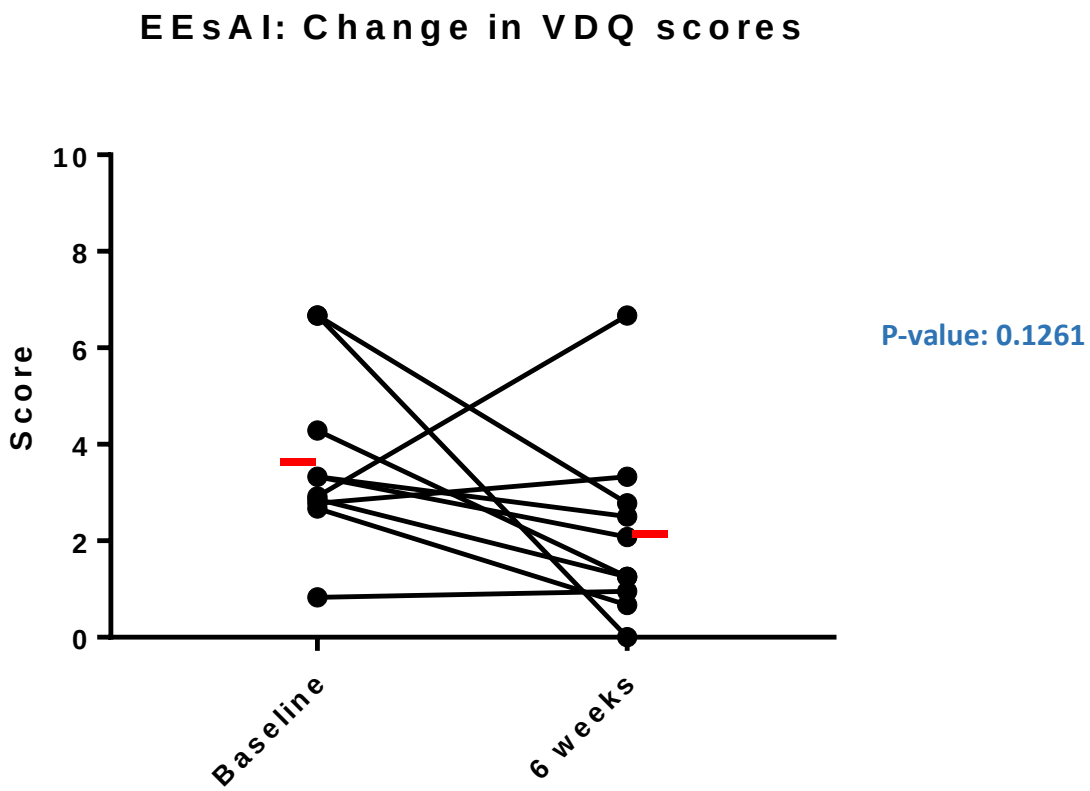

Figure 7: Change in VDQ scores (severity of dysphagia) for each individual from baseline to six weeks. Red line indicates mean.

AMS is a measure of behavioral adaptation by EoE patients and is scored on a scale ranging from 0 (no behavioral adaptation) to 10 (most behavioral adaptation).

A paired-samples t-test was conducted to compare AMS scores before (baseline) and after the SFED-intervention (six weeks). The obtained p-value shows that there was no statistically significant change in behavioral adaptation from baseline (mean=1.71 SD=1.24) to six weeks (mean=2.07 SD=1.69).

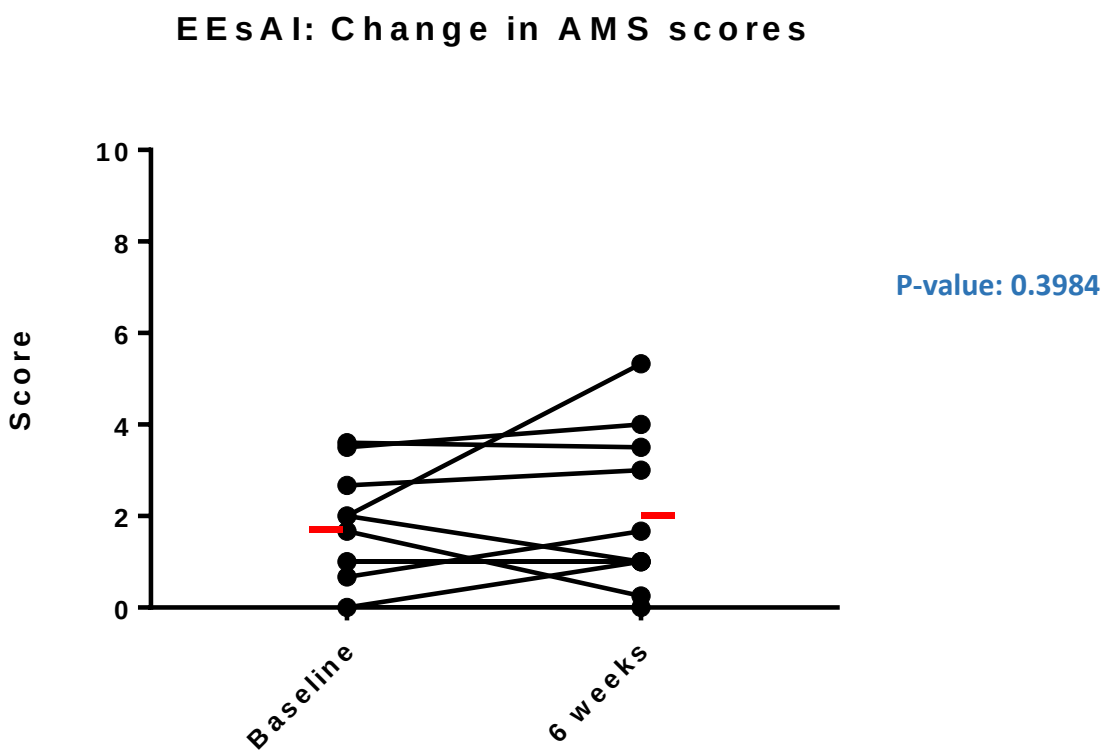

Figure 8: Change in AMS scores (behavioral adaptation) for each individual from baseline to six weeks. Red line indicates mean.

The total PRO score considers both the VDQ score and AMS score, in addition to three EEsAI items related to frequency, duration and pain perception of troubled swallowing. The PRO is scored on a scale from 0 (no symptoms) to 100 (most severe symptoms).

A paired-samples t-test was conducted to compare total PRO scores at baseline and after the SFED-intervention. The obtained p-value shows that there was no statistically significant change in total PRO score from baseline (mean=44.90 SD=16.15) to six weeks (mean=30.7 SD=18.93).

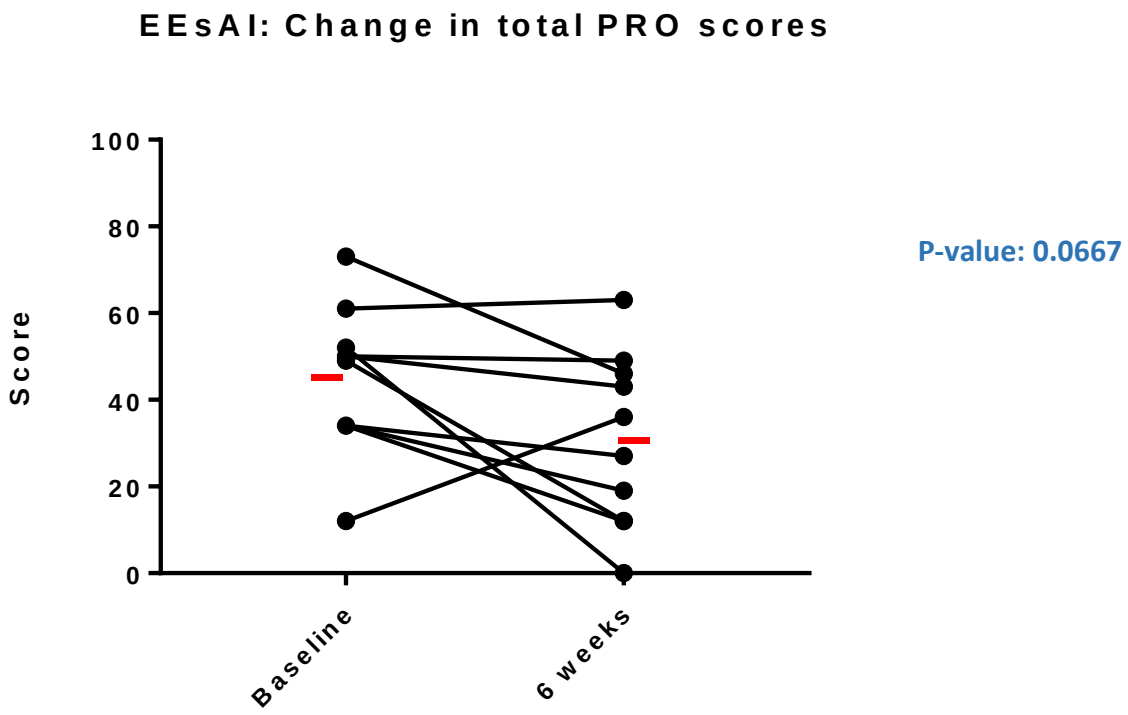

Figure 9: Change in Total PRO scores for each individual from baseline to six weeks. Red line indicates mean.

4.4 Quality of life: SF-36

The PCS (summary of physical QOL) is scored on a scale ranging from 0 (low HRQOL) to 100 (high HRQOL). The graph below shows that our patient cohort exhibited rather high MCS and PCS scores compared with mean summary scores in the general Norwegian population (dashed lines).

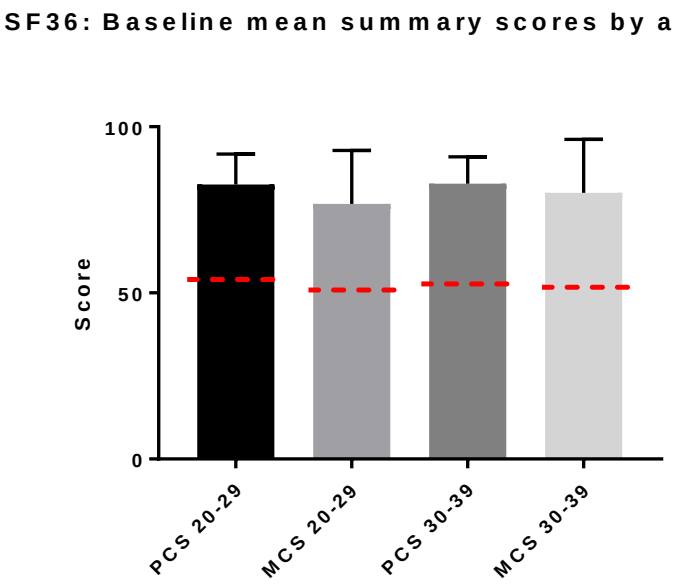

Figure 10: Mean PCS and MCS scores at baseline, by age-groups: 20-29 years and 30-39 years. Dashed lines show mean PCS and MCS scores derived from a general population sample (normative data). Based on data from Garratt et al. (139).

A paired-samples t-test was conducted to compare PCS scores at baseline and after the SFED-intervention for the total study population. The obtained p-value shows that there was not a statistically significant change/improvement in physical health-related QOL from baseline (mean=82.72 SD=7.84) to six weeks (mean=84.22 SD=8.58).

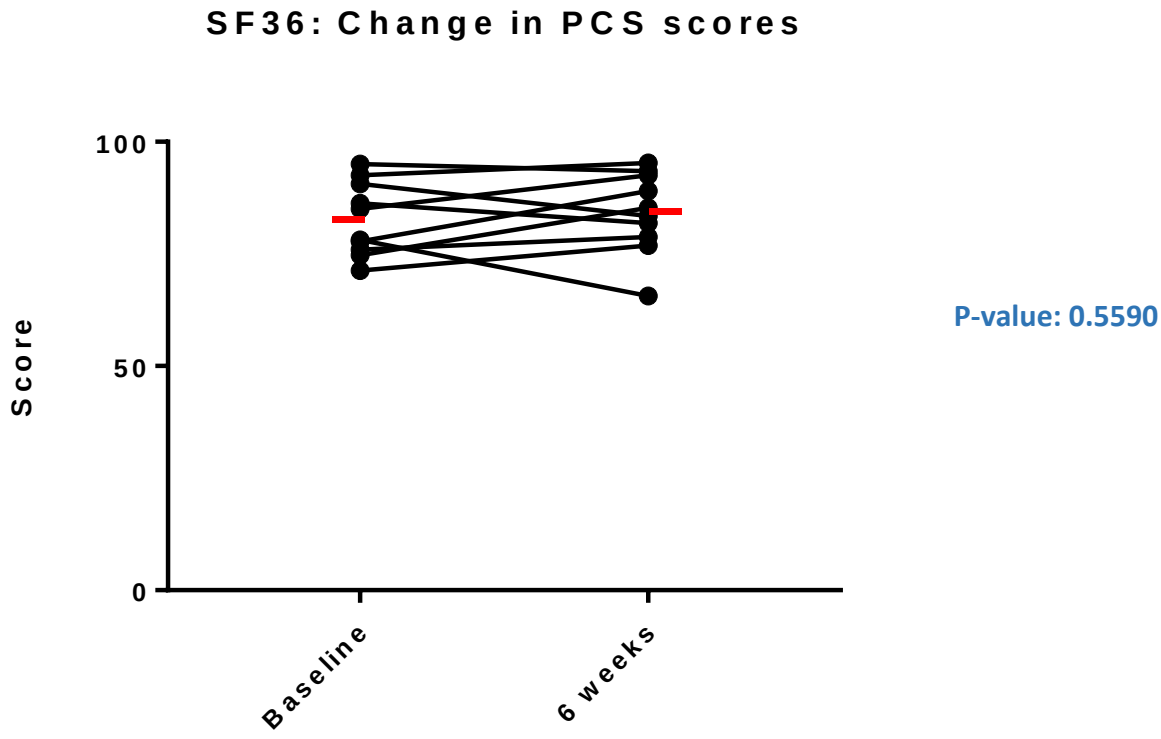

Figure 11: Change in PCS scores for each individual from baseline to six weeks. Red line indicates mean.

The MCS (summary of mental health-related QOL) is scored on a scale ranging from 0 (low HRQOL) to 100 (high HRQOL).

A paired-samples t-test was conducted to compare MCS scores at baseline and six weeks. The obtained p-value shows that there was not a statistically significant change/improvement in mental health-related QOL from baseline (mean=78.10 SD=14.51) to six weeks (mean=74.95 SD=13.34).

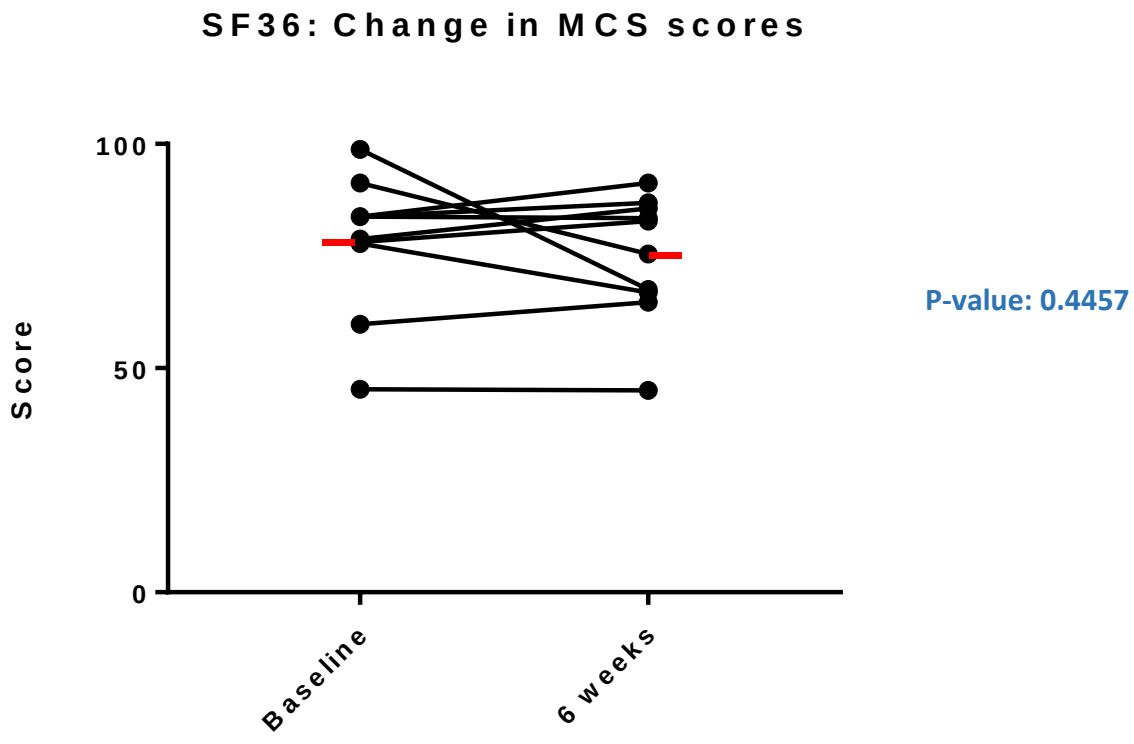

Figure 12: Change in MCS scores for each individual from baseline to six weeks. Red line indicates mean.

The PCS and MCS are comprised of four subscales each. The difference from baseline to six weeks varies, being negative for some and positive for some subscales. A more marked score difference from baseline to after the SFED intervention can be seen in GH and SF than the other subscales. Differences in each subscale score before and after the SFED have not been tested for statistical significance, as the PCS and MCS were found to not be significantly changed.

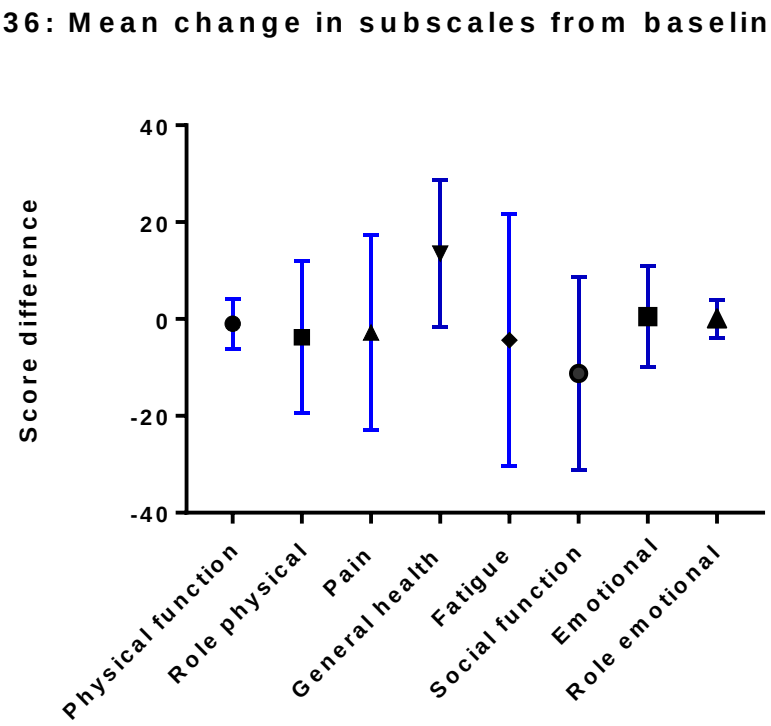

Figure 13: Mean change in each of the eight subscale scores from baseline to end of SFED-intervention. Blue bars show 95% CI for each subscale.

4.5 Relationship EEsAI and SF-36

It is logical to assume that an overall improvement in symptoms, as shown by a decreased PRO score from the EEsAI is followed by an improvement in HRQOL, as shown by increased MCS and PCS scores. Theoretically, the change in PRO variable should therefore be inversely correlated with the change in MCS and PCS variables.

A Pearson product-moment correlation coefficient was computed to assess the relationship between the change in symptoms (PRO) and the change in physical quality of life (PCS) from baseline to end of the SFED-intervention. There was a negative correlation between the two variables (r= -0.11), although this correlation was not statistically significant (p= 0.7623). The R^2 for this correlation analysis is 0.01209, meaning that only 1.21% of the variation in PCS score change can be explained by variation in PRO score change.

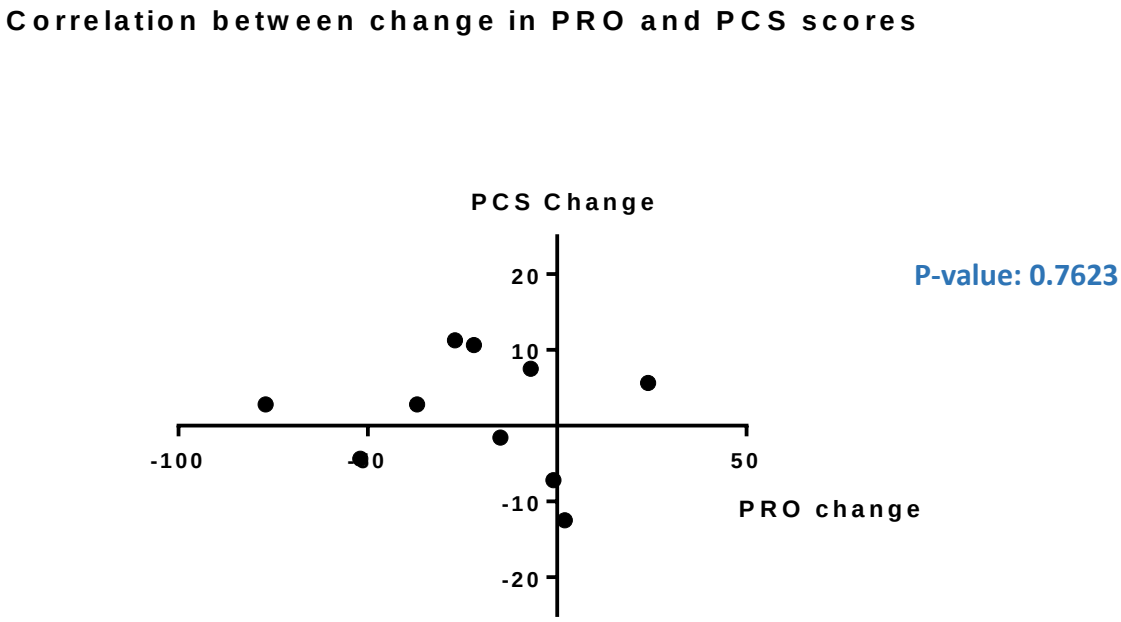

Figure 14: Scatter plot showing the relationship between change in overall PRO score (symptoms) and the change in PCS score (physical quality of life) from baseline to end of the SFED-intervention) for each individual. The inverse correlation is not statistically significant.

A Spearman rank correlation coefficient was computed to assess the relationship between the change in symptoms (PRO score) and the change in mental health-related quality of life (PCS score) from baseline to end of the SFED-intervention. There was a positive correlation between the two variables (r= 0.5879), however this correlation was not statistically significant (p= 0.0806).

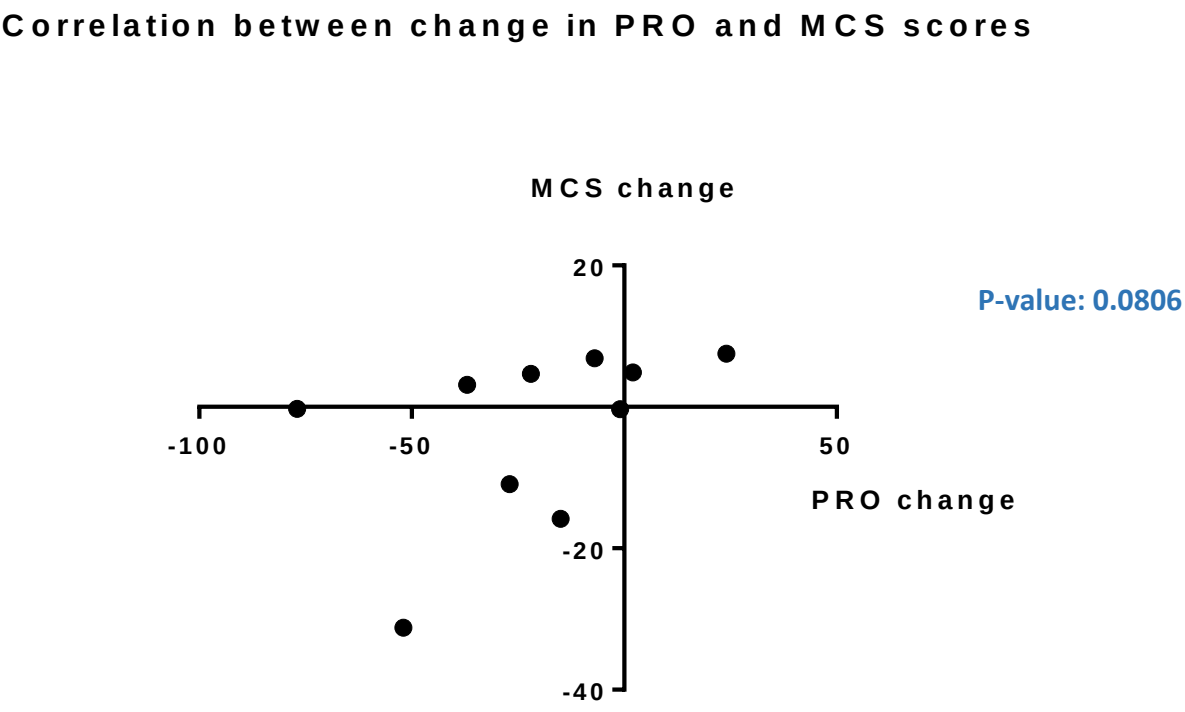

Figure 15: Scatter plot showing the relationship between change in overall PRO score (symptoms) and the change in MCS score (mental health-related quality of life) from baseline to the end of the SFED-intervention for each individual. The correlation is not statistically significant.

4.6 Histologic response

A Wilcoxon matched pairs signed rank test was carried out to compare eosinophil counts in the esophagus at baseline and after the SFED-intervention. Before the SFED intervention, our cohort of patients had a median peak eosinophil count of 80 eos/HPF (IQR=50). After the SFED intervention, peak eosinophil density significantly decreased to 10.5 eos/HPF (IQR=35.75). Hence, the SFED intervention was successful with regard to inducing histologic improvement in our group of patients.

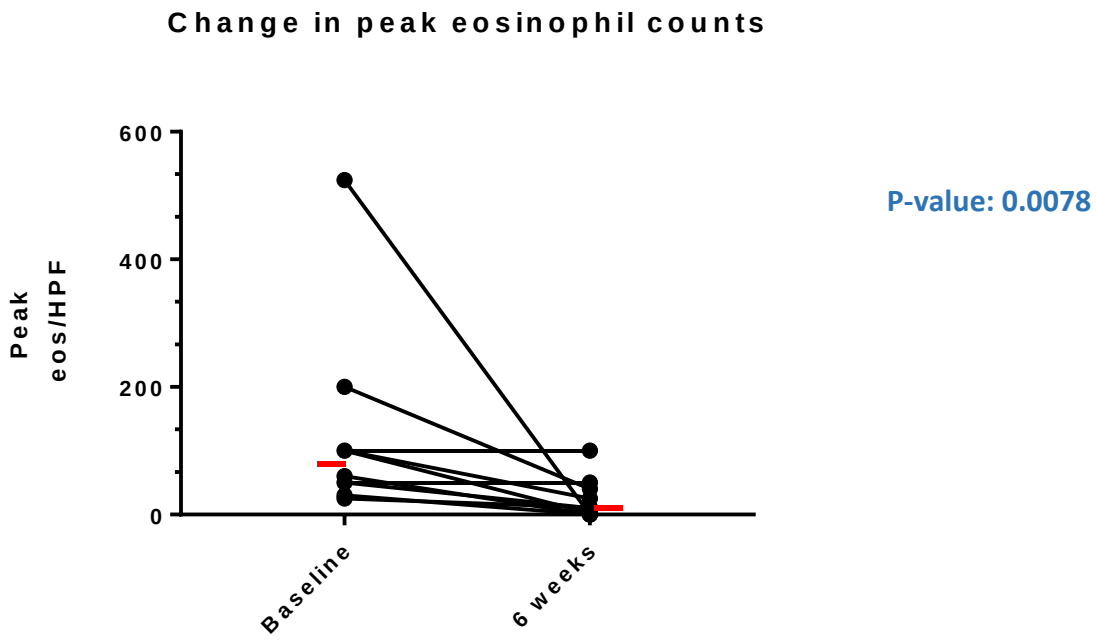

Figure 16: Change in peak eosinophil count/HPF for each individual from baseline to six weeks. Red line indicates median. Median at baseline=80 and median at six weeks=10.5.

After the 6-week SFED treatment period, no histologic change was seen in patients no. 2 and 5, with peak eosinophil counts found to be similar at baseline as well as at six weeks. However, the remaining eight patients in our cohort showed decreased peak eosinophil densities. Among the eight patients who experienced histologic improvement, complete histologic remission was seen in three patients. The other five patients exhibited between 56-98% reduction of their esophageal eosinophilia.

Table 9: Change in peak eosinophil density from baseline to six weeks for each individual patient, also expressed as percentage eosinophilia reduction.

Patient no.	Peak eos/HPF Baseline	Peak eos/HPF Six weeks	Eosinophil reduction (%)
1	30	0	100%
2	50	50	0%
3	100	2	98%
4	524	0	100%
5	100	100	0%
6	25	11	56%
7	60	0	100%
8	200	40	80%
9	100	25	75%
10	50	10	80%

At baseline, no patients presented with mild eosinophilia, eight patients presented with moderate eosinophilia while two patients were categorized as having severe eosinophilia. After the 6-week SFED intervention, six patients had mild eosinophilia, four patients had moderate eosinophilia, while no patient had severe eosinophilia.

Table 10: Overview of number of patients (n) within in each category of eosinophil density before the SFED intervention and after the SFED intervention.

Peak eosinophil count category	Baseline (n)	Six weeks (n)
<25 eos/HPF (mild)	0	6
25-100 eos/HPF (moderate)	8	4
>100 eos/HPF (severe)	2	0

4.7 Manometric findings

Table 11: Manometry results obtained at baseline and six-weeks.

	Baseline					Six weeks				
Patient	**LESP**	**IRP**	**Mean DCI**	**% IC**	**ABD**	**LESP**	**IRP**	**Mean DCI**	**% IC**	**ABD**
1	2.6	-3.8	531 5/10 failed	50%	90%	4.9	0.5	1677 0/10 failed	30%	30%
2	16.5	5.6	684 1/10 failed	45%	64%	5.0	5.5	1846 1/10 failed	0%	0%
3	1.2	-0.1	650 1/8 failed	36%	18%	7.2	1.9	704 1/4 failed	73%	45%
4	5.9	1.2	364 4/5 failed	100 %	100%	-1.4	-0.4	137 3/3 failed	100%	42%
6	12.8	6.3	739 3/10 failed	9%	73%	18.4	5.1	747 1/11 failed	0%	18%
7	26.9	2.1	1581 1/10 failed	10%	50%	7.7	3.1	1257 2/9 failed	22%	11%
9	20.0	18.6	253 6/10 failed	100%	100%	20.0	12.7	436 4/11 failed	72%	27%

LESP=Lower Esophageal Sphincter Pressure. IRP= Integrated Relaxation Pressure. DCI=Distal Contraction Integral. IC=Ineffective Contractions. ABD=Abnormal Drainage

HRM results show abnormally low resting pressures of the LES in three patients. Upon swallowing, all patients exhibited normal nadir pressures (IRP) except patient 9. Peristaltic function varied much with one (patient 4) showing almost only failed contractions (very low pressures), while others had borderline normal contractions. Patient 7 exhibited normal peristaltic function, with only one failed peristaltic wave. Abnormal drainage of saline was seen in all patients upon swallowing. Drainage was also the only parameter that improved clearly in most patients from baseline to the end of the elimination diet.

4.8 Self-reported compliance

Self-reported compliance at 3 weeks

A self-administered questionnaire was used to evaluate compliance throughout the intervention phase. When asked if they had followed the SFED during the past three weeks, eight patients responded with "yes" and two patients responded with "partly". The following table shows the response results of the items that included a VAS-scale (0-100 mm). A high-degree of self-reported adherence was reported by the study patients, with a mean of 95.50% at week 3.

Table 12: Self-reported compliance at week 3 of the SFED. Data are presented as mean ± SD.

How challenging was it to follow the SFED (0-100, where 100 is very challenging)	How carefully have you followed the SFED the past 3 weeks? (0-100, where 100 is full adherence)	How satisfied are you with the SFED for symptom relief? (0-100, where 100 is very challenging)
37.70 ± 19.14	95.50 ± 8.24	61.40 ± 35.13

The patients were requested to provide a reason for dissatisfaction with the SFED, if this was the case: one patient reported no dissatisfaction with the diet, three patients reported dissatisfaction due to lack of symptomatic effect, two patients responded that they missed foods that were not included in the SFED, whereas one patient reported the extra economic cost as the reason for dissatisfaction. Three patients reported more than one reason for dissatisfaction with the SFED: one patient responded with "time consumption" "missing

restricted foods" and "extra economic cost", one patient responded with "missing restricted foods" and "extra economic cost", while the last patient responded with "missing restricted foods" and "boring in terms of taste and variation".

Further, the patients were inquired about deviations from the diet: six patients reported "none", three patients reported "1-2 deviations during the three weeks" and one patient reported "1-2 per week". Among the four patients who had deviated from the diet, one reported consumption of milk and soy, one reported consumption of wheat and nuts, one reported consumption of milk only, while the last patient reported wheat only as their deviating food. Only one of the four patients had consumed a prohibited food on purpose, while the three others had unintentionally consumed foods not included in the SFED.

In response to how satisfied they were with the dietary guidance given prior to the start of the SFED, seven patients responded with "very satisfied", one patient responded with "satisfied" and two patients responded with "OK".

Self-reported compliance at 6 weeks

When asked if they had followed the SFED during the past six weeks, eight patients responded with "yes" and two patients responded with "partly". The following table shows the response results of the items that included a VAS-scale (0-100 mm). In similarity with the 3-week compliance evaluation, a high-degree of self-reported adherence was also reported at the end of the SFED intervention with a mean of 95.30% at week 6.

Table 13: Self-reported compliance at week 6 of the SFED. Data are presented as mean ± SD.

How challenging was it to follow the SFED (0-100, where 100 is very challenging)	How carefully have you followed the SFED the past 3 weeks? (0-100, where 100 is full adherence)	How satisfied are you with the SFED for symptom relief? (0-100, where 100 is very challenging)
41.80 ± 28.69	95.30 ± 5.68	63.90 ± 35.51

Regarding dissatisfaction with the diet, four patients responded with “not dissatisfied”, whereas three patients were dissatisfied due to lack of symptomatic improvement. Two patients reported dissatisfaction as they missed restricted foods and also found the SFED boring in terms of taste and variation. One patient responded with only “boring in terms of taste and variation”.

At this point, no dietary deviation was reported by five of the patients, while the other five patients reported deviations “1-5 times during the six weeks”. Among the five patients who had deviated from the diet, two reported consumption of soy only, one reported consumption of wheat only, one reported consumption of milk and egg, while the last subject reported consumption of multiple prohibited foods including soy, wheat, milk and nuts. Among these five patients, prohibited foods had been consumed unintentionally by all except one patient who justified his dietary deviation with “craving a food that was not included in the SFED”.

In response to how satisfied they were with the dietary guidance during the course of the study, seven patients responded with “very satisfied”, while three patients responded with “satisfied”.

4.9 Reintroduction findings

At present, a total of 10 patients have completed the SFED intervention. Three of the patients did not experience symptomatic improvement by following the SFED, and therefore did not go through the reintroduction phase. Among the remaining seven patients, two are currently going through the reintroduction phase at different stages. Out of the five patients who have completed the reintroduction phase, four patients experienced symptomatic relapse upon reintroduction of wheat. One patient reported symptomatic relapse upon reintroduction of egg. Hence, the causative food agent was found in all patients who completed the reintroduction phase.

Table 14: Overview of results from the reintroduction phase for all patients

Patient	Trigger food
1	Wheat/Gluten
2	No reintroduction
3	Wheat/Gluten
4	Egg
5	No reintroduction
6	Wheat/Gluten
7	Wheat/Gluten
8	Reintroduction ongoing
9	Reintroduction ongoing
10	No reintroduction

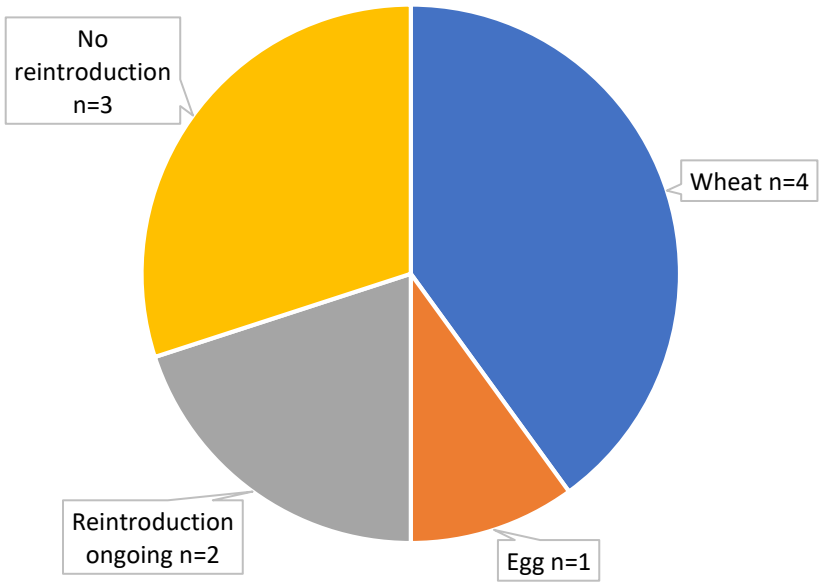

Figure 17: Preliminary results of the reintroduction phase presented as number of patients (n) within each group.

5 DISCUSSION

5.1 Main findings

We performed a prospective clinical trial, with the aim to evaluate the effect of SFED on esophageal symptoms and histopathology in adult patients with EoE. Furthermore, the effect of SFED on esophageal motility and HRQOL was assessed. All included patients followed the SFED for a minimum of six weeks.

The SFED showed a high degree of effectiveness when evaluating symptomatic response via change in troubled swallowing. A statistically significant reduction in EEsAI Item 9 score from median 27 (IQR 15) at baseline to median 7.5 (IQR 24) at six weeks was found. In total, 7 out of 10 patients reported improvement of dysphagia after the SFED-intervention and were motivated to start the reintroduction phase. There was no statistically significant reduction in dysphagia severity alone, as measured by the VDQ score. Similarly, no statistically significant change was observed in behavioral adaptation alone, measured by the AMS score. The composite PRO score derived from a combination of the VDQ, AMS and general dysphagia items, was reduced from mean 44.90 at baseline to 30.70 at six weeks although this reduction was not statistically significant ($p=0.0667$).

With regard to histopathology, our study showed a high degree of effectiveness of the SFED. In our cohort of 10 patients, eight patients achieved more than a 50% reduction in their peak eosinophil counts. No difference in peak eosinophil count was found in two patients, while the median peak eosinophil count was significantly reduced from baseline (80 eos/HPF) to six weeks (10.5 eos/HPF) in our patient cohort ($p=0.0078$).

Esophageal peristalsis, as evaluated by HRM did not change notably from baseline to six weeks, although an improvement was seen in drainage of saline. Our study did not find a statistically significant change in HRQOL, as assessed by the SF-36 questionnaire. A slight increase in physical QOL (PCS) and a slight decrease in mental health-related QOL (MCS) was seen from baseline to six weeks, although these changes were not statistically significant. Each of the eight subscales were not significance tested separately, as we deemed the relevance of single-subscale improvement to be limited in clinical settings.

Among the seven patients who experienced symptomatic response to the SFED, five patients have completed sequential reintroduction of eliminated foods. At present, the reintroduction phase has been able to identify a causative dietary trigger in all five of these patients. A single trigger food was identified by all five patients, with the most common trigger food being wheat. Reintroduction of causative foods resulted in symptom recurrence for these patients, while the remaining two patients are currently undergoing the reintroduction phase.

5.2 Discussion of findings

Symptomatic response and EoE symptom scoring

In our study, 7 out of 10 patients verbally expressed to be satisfied with the diet for symptom relief during follow-up consultations. In these seven patients, the response to the EEsAI item "*In the past 7 days, how often have you had trouble swallowing?"* accordingly improved from baseline to after the SFED intervention. Hence, these patients met the criteria for symptomatic improvement, and were subjected to subsequent reintroduction of the eliminated foods. This finding is consistent with previously conducted studies that have reported empiric elimination diets to effectively induce symptom improvement in EoE patients (120, 122, 125).

It is important to address that the scores obtained from the EEsAI did not reflect significant symptomatic improvement. We found that dysphagia severity for specific food consistencies (VDQ) and behavioral adaptation (AMS) did not change significantly after the SFED intervention when considered separately. Similarly, no significant improvement was noted in the overall PRO score which collectively considers the VDQ, AMS and general dysphagia items. Since the PRO score represents the objective measure of symptom activity derived from the EEsAI, it is reasonable to state that the SFED was not able to significantly change the degree of symptom scoring in our group of patients. Intuitively, this may seem to be in direct contrast to findings from existing studies that have reported symptomatic response rates of similar magnitude for the SFED and topical corticosteroids; the proportion of patients with symptom improvement has been found to be 97% in children (123) and 94% in adults (122). Additionally, a recent meta-regression found the proportion of patients with symptom improvement to be 87.3% for SFED in children and adults combined, indicating that food allergens play a causative role in EoE (140).

In light of the available evidence it would be reasonable to expect the SFED to cause an improvement in mean EEsAI scores to a greater extent than was seen among our patients.

However, comparability of our study with other clinical studies of the SFED is limited due to methodological differences. Firstly, none of the studies included in the meta-regression by Cotton et al. (140) used the EEsAI questionnaire for symptom assessment. Two of the studies in adult patients used a score validated for achalasia (125, 141), whereas one study used the Dysphagia Symptom Questionnaire (122). Among the remaining studies, one used the ELSA index consisting of a non-validated VAS for each of the most frequent EoE symptoms (142), while one used dichotomous patient-reported subjective improvement [yes/no] (120). The EEsAI is a comprehensive measure, inquiring into more aspects than only the presence and severity of dysphagia. Besides the VDQ and the items related to frequency and duration of dysphagia, the AMS also constitutes an important part of the EEsAI. The PRO score derived from the EEsAI thus represents a broader symptom description and is also sensitive to the presence/absence of behavioral adaptation. An improvement in dysphagia and food impaction alone does therefore not necessarily lead to an improvement in the overall PRO score. Moreover, the EEsAI uses a recall period of seven days for all the included items. The clinical presentation of EoE may vary, with some patients experiencing a relapsing and remitting course of symptoms. In such cases, the EEsAI may be unable to detect degree of dysphagia and behavioral adaptation, particularly if the patient upon completion of the questionnaire has been symptom-free for the past seven days. Perhaps, using dichotomous patient-reported symptom improvement or an instrument exclusively focused on esophageal dysfunction in our study, would yield results even more similar to those found in previously conducted studies.

Additionally, the lack of effect of SFED on EEsAI scores may be attributed to the small sample size. Comparability of our study results with results from previously conducted studies is limited, as the number of patients in our cohort is substantially lower. The low sample size may have decreased the power of the study, which includes its ability to detect a potential effect and to prevent Type II errors. Furthermore, a small sample size increases the margin of error, leading to a subsequent decrease in the confidence level of the study (143). In contrast to a large sample size, a small sample size makes it difficult to detect an effect despite its presence in the population (144). Statistical significance is dependent upon both effect size and sample size. P-values are affected by sample size, as they provide information about whether an effect exists, but do not reveal the magnitude of the effect. In our patient cohort, mean PRO score changed from 44.90 at baseline to 30.70 post-SFED, translating to an effect size of 14.20. This shows that a decrease in overall symptoms was evident in our patients, although the p-value of 0.0667 did not reflect the effect to be significant.

One may also question whether a SFED period of six weeks was sufficient with regard to inducing behavioral changes. For instance, patients who have previously experienced food impactions upon consumption of tough food consistencies will probably require a longer duration of exposure training to feel confident about reintroducing such foods in their diets. The six-week SFED period was perhaps sufficient for inducing changes in esophageal symptoms, while other factors remained unchanged. Hence, the EEsAI may be more suitable in the diagnostic phase rather than in the initial evaluation phase of EoE treatment effect. By looking at only one element in the questionnaire, we did find a significant improvement from baseline to six weeks (Item 9). Lastly, dietary consultations revealed that many patients were not aware of the extent of their own symptoms prior to the SFED. Due to this lack of awareness, there is a possibility that the EEsAI scores obtained at baseline were affected by underreporting of symptoms.

Histologic effect of the SFED

With regard to treatment of histopathology, our study showed a high degree of effectiveness of the SFED. In our study, we found that 8 out of 10 patients achieved more than a 50% reduction in their pre-SFED eosinophil counts. The reduction in median peak eosinophil count from 80 eos/HPF at baseline to 10.5 eos/HPF after six weeks in our patient cohort was further found to be statistically significant ($p=0.0078$). Among the eight histologic responders, six achieved the histologic response threshold of <25 eos/HPF while two patients achieved the histologic response threshold of 25-100 eos/HPF following the SFED.

This finding is in line with existing literature; Kagalwalla et al. found a 74% histologic response in a pediatric cohort (123). Similarly, Gonsalves et al. showed a 70% histologic response of the SFED in their adult cohort, using a treatment protocol similar to that in our study. It was also reported that 78% of patients had > 50% reduction in their peak eosinophil density (122). Recently, a mean histologic response rate of 69% was found for the SFED in a recent meta-regression analysis, with a corresponding decrease of 44.6 in eosinophil counts from baseline to six weeks (140). The histologic response found in our cohort was comparable and strengthens the idea of food allergens having a causative role in the majority of adult EoE patients.

Notably, no reduction in eosinophil count was evident in two of our study patients. This finding may suggest reactivity to potential aeroallergens as well as dietary allergens not included in the SFED, cross-contamination, low dietary compliance, or the absence of allergy.

As aeroallergens were not treated concurrently in our study, this may explain the histologic non-responders to some extent.

A high eosinophil density, as well as absence of complications at baseline seemed to increase the possibility of histologic response to the SFED. This may indicate that patients presenting with an inflammatory rather than fibrotic phenotype, are more inclined to respond to dietary treatment. Studies assessing the effect of the SFED on EoE histopathology have defined histologic response in various different ways; as an eosinophil count threshold, as a percentual difference, or as a ratio (140). In our study, three thresholds of peak eosinophil counts were used to categorize histologic response, although previous clinical studies have commonly used lower eosinophil counts of ≤ 5 eos/HPF and ≤ 10 eos/HPF to define histologic response. The rationale for this mainly lies in the rather small sample size of our study. We also considered it equally important to emphasize the percentage decrease in peak eosinophil count in each patient, as the patients who did not reach threshold levels of mild eosinophilia still showed a substantial decrease in peak eosinophil counts from baseline to post-SFED. Some of the patients also reported to be satisfied with the SFED for symptom improvement and were thus willing to enter the reintroduction phase of the study.

Despite the demonstrated effectiveness of the SFED in children and adults, it has currently not been able to attain histologic remission to the same extent as the elemental diet. In prior studies, the elemental diet has been able to achieve complete histologic remission (0 eos/HPF) in a greater proportion of patients (19). Esophageal biopsies in only two of our patients showed 0 eos/HPF after the SFED, while the remaining patients exhibited higher levels of eosinophil density. However, the restrictions placed on patients following the elemental diet may be compensated by the advantages of the SFED with regard to cost, palatability, social functioning and administration method.

Manometric effect of the SFED

Dysphagia and food impaction, the most common EoE symptoms in adults, are primarily believed to result from changes in the esophageal structure, e.g. concentric rings, furrows and strictures (145). However, dysphagia may also be experienced by patients without significant endoscopic findings. Hence, it has been proposed that esophageal dysmotility may also be involved in the pathogenesis of dysphagia (145).

A few studies have investigated the esophageal motor function in EoE patients with the aid of HRM. A case-control study using HRM found pan-esophageal pressurization to be the most common esophageal motor abnormality in EoE (48%), while peristaltic dysfunction was found in 28% of the included EoE patients. A more recent case-control study by van Rhijn et al. concluded that EoE disease duration is a risk factor for the development of abnormal esophageal motility, with reduced and failed peristalsis being more frequently present in EoE than in healthy controls (146). However, a manometric pattern characteristic for EoE has not been identified, hence the use of HRM is not deemed necessary for the diagnosis of EoE.

To our knowledge, no other studies have evaluated the effects of the SFED on esophageal motility in EoE patients. In the patients who underwent HRM in our study, peristaltic function did not seem to change from baseline to six weeks, although notable changes were evident in saline drainage. Previously, it has been found that EoE patients commonly present with a thicker esophageal wall than normal subjects, partly due to an edematous mucosa. Hence, the improvement of saline drainage seen from baseline to six weeks, may be explained by a reduction of the esophageal wall thickness which occurred secondary to the endoscopic and histologic effects of the SFED. A thinner esophageal wall, leading to an increased lumen diameter, may have facilitated the passage of saline despite the absence of peristaltic function improvement (J. Hatlebakk, unpublished data). The need for further research on manometric assessment of EoE patients undergoing dietary therapy is clear.

Impact of SFED on HRQOL

In our patient cohort, the SFED was not able to produce a significant change in neither physical (PCS) nor mental health-related QOL (MCS). This was somewhat expected, as the patients included in our study already exhibited rather high PCS and MCS scores prior to the SFED-intervention.

Recently, a study presented revised normative data to aid interpretation of SF-36 scores in Norwegian populations (139). Mean SF-36 subscale and summary scores for the general population were calculated by gender and age groups, estimating a mean PCS score of 53.57 and a mean MCS score of 50.85 for the age category 20-29 years. In the age category 30-39 years, a mean PCS score of 52.50 and mean MCS score of 51.52 was estimated (139).
In our patient cohort, we found a collective mean PCS score of 82.72 and mean MCS score of 78.10 at baseline. Considering that our patients were between 21-38 years of age, they

presented relatively high HRQOL compared with normative data for their age categories already at baseline. Hence, expecting a dramatic surge in HRQOL following the SFED-intervention would be rather unrealistic in this cohort.

Previously conducted studies using generic QOL instruments in adult EoE patients have reported inconsistent results. One study found no significant differences in HRQOL in EoE patients compared with control subjects (147). Another study by van Rhijn et al. did not find significantly different levels of PCS and MCS scores in EoE patients compared to a reference population, although VT and GH subscales were demonstrated to be significantly lower in young adult EoE patients (148). Additionally, a study reported EoE to have an impact on various domains related to mental health function, e.g. embarrassment, frustration and fear about disease outcomes, while physical health was described to be significantly better than that in patients with other chronic conditions. It is reasonable to assume that baseline SF-36 results in our study are in line with existing research, as our patient cohort did not show decreased levels of HRQOL compared to a Norwegian reference population. We did not focus on each subscale separately, as we deemed the value of such data to be limited in clinical settings. However, during conversations with patients, more concerns were raised regarding social function than physical function, indicating that some SF-36 subscales are likely to be more sensitive to EoE than others.

Further, in our study SF-36 summary scores did not significantly change despite symptomatic improvement being evident in 7 out of 10 patients when evaluated through the following EEsAI item: “In the past 7 days, how often have you had trouble swallowing?”. This finding coincides with existing literature in showing that treatment and subsequent symptomatic improvement does not necessitate improvements in HRQOL: previous studies using generic questionnaires have reported conflicting results on the effect of therapy on EoE patients’ HRQOL. In one study of Swedish adult patients receiving swallowed topical steroids, SF-36 scores did not change despite the presence of dysphagia improvement (149). In another study, a moderate increase in PCS and MCS scores was found in adult EoE patients following the four-food elimination diet, although this change was insignificant (147). Similarly, dietary or pharmacological therapy did not significantly improve overall mean QOL, when assessed with the EoE-specific questionnaire EoE-QOL-A (150).

The inability of the SFED to affect HRQOL in our study may be attributed to our choice of instrument for HRQOL assessment. Firstly, one may question the ability of the generic SF-36 to capture EoE-specific challenges. Symptoms are primarily limited to the esophagus, suggesting that EoE patients' HRQOL can only moderately be explained by their health condition, especially when measured with a generic instrument. During dietary consultation, several social and emotional concerns related to EoE were verbally expressed by patients. The challenges addressed by patients were mostly linked to dietary avoidance and other meal-related situations. The generic SF-36 does not sufficiently inquire about such sentiments, indicating that EoE-specific QOL instruments may be more appropriate to use in this category of patients.

While an insignificant increase was seen in mean PCS from baseline to six weeks, an insignificant decrease was seen in mean MCS. Among mental component subscales, the most prominent change from baseline to post-SFED was seen in social functioning. During the six-week SFED intervention, patients were encouraged to avoid eating at restaurants and to prepare meals to bring to work and social gatherings in order to minimize the chances of cross-contamination. Perhaps, the SFED may have been experienced as particularly limiting in social settings, consequently affecting social well-being to a greater extent than physical aspects of QOL.

Reintroduction phase - The role of SPT and allergy blood testing

The marked reduction of esophageal eosinophilia that we found in our patients, as well as the identification of causative triggers in all five patients who completed the reintroduction course, provide support to the idea that the EoE disease response is highly driven by food allergens. Among these five patients, wheat was found to be the most common trigger food. Similar observations have been made in other studies that have found milk and wheat to be the most frequently identified trigger foods in pediatric (123) as well as adult cohorts (122). Furthermore, all five patients experienced symptomatic relapse within three days of reintroducing the given trigger food. Notably, none of the five patients reported food allergies and/or intolerance to the detected trigger foods at baseline.

One may argue that our preliminary reintroduction findings are consistent with other studies that have identified milk and wheat as common trigger foods, along with a rather quick recurrence of symptoms upon reintroduction of trigger foods (122). However, it is essential to

highlight the methodological differences between our study and previously conducted studies of the SFED with a resembling study design. For instance, the reintroduction phase in our study was merely based on patients' self-experience of symptoms. After completing two weeks of reintroduction for a given food, patients were contacted by a master's student in clinical nutrition and inquired about symptom recurrence. In contrast, other studies of the SFED have used upper endoscopies with biopsies following reintroduction of each/some food groups to determine the presence of disease recurrence (120, 122, 125). Repeated upper endoscopies with biopsies provide an objective measure of disease recurrence, whereas self-experience of symptoms represents a subjective measure of disease activity with a greater degree of built-in uncertainty. A study by Safroneeva et al. demonstrated that symptoms only with modest accuracy reflect endoscopic or histologic remission. Hence, lack of symptoms alone may not be used to make inferences about lack of biologic disease activity (82). Perhaps, using self-reporting of symptoms in addition to upper endoscopies with biopsies after reintroduction of all foods or foods that led to symptom recurrence only, would be a more reliable method for identifying trigger foods. On the other hand, this would be an invasive protocol requiring patients to be even more flexible and motivated, which in turn may have impeded the recruitment process.

Allergy blood testing and SPTs were performed on all included subjects, although their roles in EoE management remain uncertain. The degree of accordance between dietary triggers identified via food reintroduction and SPT results or s-IgE levels was demonstrated to be low by Lucendo et al. in a study of the SFED (125). In our study, 4 out of the 5 patients who detected a trigger food during the reintroduction phase were found to have negative SPTs to their identified trigger foods. Only one patient who reported symptom recurrence upon reintroduction of wheat, also exhibited a positive SPT to wheat. Three of the patients showed elevated levels of s-IgE against their identified trigger food, however these patients had elevated s-IgE levels against two or more other food allergens as well. Despite the low number of participants in our study, this finding may indicate that the use of SPT and allergy blood testing in adult EoE management is of limited value.

5.3 Methodological considerations

5.3.1 Dietary consultations

We conducted an uncontrolled clinical trial, which represent a potential source of selection bias in our study, as all included subjects were motivated and willing to go through the SFED. Dietary education was not provided by the same master's student in clinical nutrition during the first and latter half of the study. Although SFED education was provided individually throughout the study, we did not share a completely standardized format for the sessions. More comprehensive dietary education might have been given to some patients due to the experience that was gained along the study. Additionally, there may have been differences in how accessible the two master's students were via telephone and e-mail throughout the course of the study. As the study progressed, increased availability of allergen-free food products along with improved allergen labelling possibly facilitated the SFED period. The mentioned factors may have affected dietary adherence, which may in turn have had implications for how well patients responded to the SFED both histologically and clinically.

5.3.2 Questionnaire scoring methods

The SF-36 and EEsAI completed at baseline and six weeks were scored by a single person according to official manuals. The obtained scores were not controlled by another person, which may have increased the likelihood of calculation errors being present in our database. The presence of such errors may affect results of statistical analyses, which consequently may lead to erroneous study conclusions. As the SF-36 scores and EEsAI scores represented important parameters of interest in our study, administering a more thorough protocol for questionnaire scoring could have been appropriate. The low sample size in our study further increases the importance of precise calculations, as potential errors have a greater impact on statistical test results than in larger sample sizes.

5.3.3 Data collection

Due to logistical limitations, weight and height measurements could not be performed on all patients at baseline and/or at six weeks. For some patients, self-reported weight and/or height was recorded in our database. Although we did not aim to assess the effect of the SFED on body-weight in our study, previous studies have highlighted the importance of monitoring changes in weight and dietary habits in patients undergoing dietary management for EoE.

Performing weight and height measurements systematically would have yielded more accurate BMI estimates, that perhaps could have been used to propose an idea on how the SFED influenced this parameter in our study patients as well.

5.3.4 Duration of the SFED and compliance assessment

Based on previous prospective trials, we chose a six-week duration for the SFED phase. However, due to logistical aspects, follow-up measurements could not be performed during week seven for all patients. Thus, some patients were required to follow the SFED for a longer time period than six weeks. This in turn limits comparability within our patient cohort, and between our study and other studies with resembling study designs.

In our study, we assessed adherence three weeks into the SFED, as well as upon completion of the SFED. Some patients did report unintentional/intentional deviations, which may have affected their histological and clinical response to the SFED. Perhaps, it would be more appropriate to systematically extend the SFED period to compensate for such dietary indiscretions.

6 FUTURE ASPECTS AND CONCLUSION

Being a chronic disorder, it is essential to focus on the ability of therapeutic options for EoE to maintain disease remission. In some patients, multiple food allergens may be implicated, making it difficult to maintain a diet free of trigger foods in the long run. Although empiric elimination diets have demonstrated a high degree of effectiveness in inducing disease improvement, few studies have assessed long-term adherence and effects of empiric elimination diets, warranting further research on this subject.

We prospectively examined the value of an empiric SFED followed by sequential reintroduction of food allergens. We found that the six-week SFED phase effectively improved symptomatic and histopathologic features of EoE in a cohort of Norwegian adult patients. These findings provide support to the role of food allergens in EoE pathogenesis in adults with EoE. Systematic reintroduction has demonstrated the ability to detect dietary triggers of EoE, corroborating results from previous studies in children as well as adults. As allergy blood testing and SPT did not effectively predict dietary triggers, the SFED followed by sequential reintroduction represents the preferred method for doing so. In conclusion, an empiric SFED with subsequent reintroduction of food allergens remains an effective therapeutic option for adult EoE patients.

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8 APPENDIX

Appendix 1: Overview prevalence estimates of EoE

Appendix 2: Overview incidence estimates of EoE

Appendix 3: Written consent form and study protocol

Appendix 4: EEsAI questionnaire

Appendix 5: SF-36 questionnaire

Appendix 6: Dietary habits during the last 12 months

Appendix 7: SFED list of eliminated foods and alternatives

Appendix 8: Two-week menu suggestion and recipes

Appendix 9: Compliance questionnaire 3 weeks

Appendix 10: Compliance questionnaire 6 weeks

Appendix 11: The Chicago Classification of esophageal motility (version 3.0)

Appendix 1: Prevalence estimates of EoE from population-based studies

Author	Location	Study Population	Time span	Estimated Prevalence (per 100 000)
Prasad et al. (34)	Olmstead County, Minnesota	Adult + Pediatric	1976 – 2005	55.0
Gill et al. (28)	Huntington, West Virginia	Pediatric	1995 – 2004	73.0
Kim S et al. (38)	South California	Adult + Pediatric	2008 – 2013	45.0
Spergel et al. (35)	USA	Adult + Pediatric	2010	52.2
Dellon et al. (31)	USA	Adult + Pediatric	2009 – 2011	56.7
Maradey et al. (36)	USA	Adult + Pediatric	2011 – 2014	50.6
Mansoor et al. (37)	USA	Adult + Pediatric	2010 – 2015	25.9
Cherian et al. (26)	Perth, Australia	Pediatric	1995, 1999, 2004	89.0
Syed et al. (32)	Calgary, Canada	Adult + Pediatric	2004 – 2008	33.7
Hruz et al. (25)	Olten County, Switzerland	Adult	1989 – 2004 1989 – 2009	23.0 42.8
Arias et al. (27)	Castilla, Spain	Adult + Pediatric	2005 – 2011	44.6
Dellon et al. **(151)**	Denmark	Adult	1997 – 2012	13.8
Van Rhijn et al. (23)	The Netherlands	Adult + Pediatric	1996 – 2010	4.1
Ma et al. **(152)**	Shanghai, China	Adult	2015	400

Appendix 2: Incidence estimates of EoE in population-based studies

Author	Location	Study Population	Time Span	Estimated incidence (per 100 000)
Prasad et al. (34)	Olmstead County, Minnesota	Adult + Pediatric	2001 – 2005	9.5
Noel et al. (40)	Hamilton County, Ohio	Pediatric	2003	12.8
Syed et al. (32)	Calgary, Canada	Adult + Pediatric	2004 – 2008	11
Giriens et al. **(153)**	Canton of Vaud, Switzerland	Adult + Pediatric	2004 – 2013	0.16 – 6.3
Dellon et al. **(151)**	Denmark	Adult + Pediatric	1997 – 2012	0.13 – 2.6
Warners et al. (4)	The Netherlands	Adult + Pediatric	1996 – 2016	0.01 – 2.07
Arias et al. (27)	Castilla-La Manch, Spain	Adult + Pediatric	2005 – 2011	6.4

Appendix 3: Written consent form and study protocol

Forespørsel om deltakelse i forskningsprosjektet:

Effekt av en eliminasjonsdiett ved eosinofil øsofagitt.

Bakgrunn og hensikt
Mange pasienter med eosinofil øsofagitt opplever liten eller ingen bedring av sykdommen ved behandling med prednisolon. Andre får tilbakefall av symptomer etter endt behandling med prednisolon, og/eller de får bivirkninger ved langvarig bruk. Eosinofil øsofagitt er en form for allergi, forårsaket av komponenter i mat eller luft. Derfor spør vi deg om du vil delta i en studie hvor vi vil forsøke diettbehandling som et behandlingsalternativ for eosinofil øsofagitt.

Vi bruker en diett som på engelsk heter «Six Food Elimination Diet». Dette er en diett hvor seks vanlige matvarer/matvaregrupper blir utelatt fra kosten i seks uker. De seks matvaregruppene er melk, egg, hvete/gluten, fisk/skalldyr, peanøtter/nøtter og soya. Etter de seks ukene, vil vi systematisk innføre en og en av disse matvaregruppene i kosten igjen. Du vil få diettveiledning av en masterstudent i klinisk ernæringsfysiologi veiledet av en klinisk ernæringsfysiolog.

Du er valgt ut til å få tilbud om å delta i studien fordi du er over 18 år og har fått diagnosen eosinofil øsofagitt. Det er kjent at «Six Food Elimination Diet» er effektiv hos barn og voksne med eosinofil øsofagitt, men dietten er enda ikke prøvd ut på den norske befolkning og vårt typiske kosthold. Vi ønsker også å finne mer ut om hva slags skade sykdommen gjør på spiserøret, ved å gjøre noen enkle målinger i spiserøret som ikke er gjort i denne sammenhengen tidligere. Vi vil derfor sammenligne måleresultater før og etter diettbehandling, for den enkelte pasient. Deretter starter vi gjeninnføring av matvarene som ble tatt bort, for å prøve å finne ut av hvilken matvare den enkelte reagerer på. Vi spør derfor om du vil være med på denne studien som kan vise oss om «Six Food Elimination Diet» og reintroduksjon er et effektivt behandlingsalternativ hos voksne med eosinofil øsofagitt. Studien utføres av overlegene Birgitte-Elise Emken og Jan Hatlebakk ved Haukeland Universitetssykehus som også er ansvarlig for prosjektet. Diettbehandlingen utføres av en masterstudent i klinisk ernæringsfysiologi og klinisk ernæringsfysiolog ved Haukeland Universitetssykehus.

Hva innebærer studien?
Studien innebærer at målinger som gastroskopier med biopsier (vevsprøve), blodprøver, prikktest, trykkmålinger og syremålinger blir gjort på deg, i tillegg til at du over en periode på seks uker vil gå på en eliminasjonsdiett, kalt «Six Food Elimination Diet». Det betyr at du må utelate seks matvarer/matvaregrupper fra kosten over en periode på seks uker. Når det kommer til selve diettbehandlingen, vil du få en detaljert oversikt over matvarer du ikke kan spise, samt alternativer til de matvarene du må kutte ut. Dersom du velger å delta i studien, vil du få en utdypende forklaring om hva som skal skje i studien. Du skal også fylle ut noen spørreskjemaer, som vil besvares ved oppstart av dietten, etter 3 uker og etter 6 uker. Dette kan gjøres hjemme og sendes til oss i posten.

Mulige fordeler
Fordelen ved å delta i studien er en mulig bedring av symptomer som svelgevansker og dermed mindre behov for behandling med medisiner, og mindre mulighet for bivirkninger av disse. En bedring av symptomer kan også medføre bedring i livskvalitet og generell ernæringsstatus.

Mulige ulemper
Det er mulig at du ikke får noen bedring av dietten og at prøvene du skal igjennom kan oppleves som ubehagelige. Komplikasjoner er svært sjeldne. I helt spesielle tilfeller kan en biopsi føre til blødning eller rift i spiserørsveggen. Dette er noe som kun er beskrevet hos færre enn 0,01% av pasientene. Sammenliknet med normal oppfølgning, vil deltakelse i prosjektet føre til en ekstra gastroskopi med biopsi, en ekstra trykkmåling og et ekstra oppmøte med poliklinisk samtale. Dietten vil ikke medføre noen bivirkninger. Dietten du skal følge fører sannsynligvis til at du må kutte ut en del matvarer du vanligvis spiser, noe som kan oppleves som vanskelig for noen. Sosiale sammenhenger kan også være en utfordring når man går på en diett.

Hva skjer med prøvene og informasjonen om deg?
Biopsier tatt ved gastroskopier og blodprøver vil lagres i en biobank som brukes til forskningen. All informasjon som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysninger og prøver i biobanken vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Prøvene vil ødelegges etter at nødvendige analyser er gjort. Ved publisering av resultatene vil identiteten din ikke komme fram.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst, uten å oppgi noen grunn, trekke ditt samtykke til å delta i studien. Dette vil ikke få noen konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side av dette skrivet. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte student i klinisk ernæringsfysiologi Zoya Sabir (Telefon: 46 93 01 54), e-post: zsa087@student.uib.no). Eventuelt kan ansvarlig lege Birgitte-Elise Grinde Emken kontaktes på telefonnummer 55972130/31 eller på e-post biem@helse-bergen.no og/eller ansvarlig lege Jan Gunnar Hatlebakk på telefonnummer 977 07 817 eller på e-post jan.hatlebakk@helse-bergen.no.

Ytterligere informasjon om studien finnes i kapittel A – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *personvern, biobank, økonomi og forsikring.*
Samtykkeerklæring følger etter kapittel B

Kapittel A – utdypende forklaring av hva studien innebærer

Kriterier for deltakelse
Vi spør deg om å delta i studien fordi du er over 18 år, du har fått diagnostisert eosinofil øsofagitt, og du har ubehag og symptomer. Diagnosen eosinofil øsofagitt har du fått på bakgrunn av biopsi av spiserøret, mens vi har utelukket refluks ved at du har negativ pH-måling i spiserøret.

Bakgrunnsinformasjon om studien
Ikke alle med diagnostisert eosinofil øsofagitt opplever bedring av sykdommen ved behandling med prednisolon. Mange opplever også tilbakefall av symptomer etter endt behandling med prednisolon, og/eller bivirkninger ved langvarig bruk. «En Six Food Elimination Diet» har vist seg å være en effektiv behandling ved eosinofil øsofagitt, men det er ikke tidligere undersøkt om dietten har en effekt ved et nordisk kosthold. Dette vil være nyttig å kartlegge. Vi ønsker også å finne ut om hva slags skade sykdommen gjør på spiserøret, og vil derfor gjøre målinger som ikke tidligere er gjort i denne forbindelsen. Kan en «Six Food Elimination Diet» med gjenintroduksjon av matvarer være effektiv på betennelse i spiserøret, muskelsammentrekninger og bevegelse i spiserøret?

Eosinofil øsofagitt er en sykdom som kan gi spiseproblemer hos barn og svelgevansker (dysfagi) hos voksne. I løpet av de siste ti årene har man stadig funnet ut mer om sykdommen. Blant annet vet vi i dag at eosinofil øsofagitt kommer av allergi mot mat- eller luftkomponenter. Likevel, flere utfordringer gjenstår.

Ved en «Six Food Elimination Diet» med gjenintroduksjon utelates seks vanlige matvarer/matvaregrupper fra kosten i seks uker. Hensikten med dietten er å utelate det en reagerer på fra kosten. Deretter gjeninnføres en og en matvare, for på denne måten å finne ut hvilken matvare den enkelte reagerer på. Måleresultater før og etter diettbehandlingen, samt etter gjenintroduksjonen av matvaregruppene, vil fortelle om effekten av diettbehandlingen på sykdommen. Målingene vil være gastroskopier med biopsier. I tillegg vil det gjøres trykkmålinger og syremålinger, som vi forventer vil vise oss om bevegelse, muskelsammentrekninger og motstand i spiserøret vil bedres etter diettbehandling med gjenintroduksjon.

Allergispesifikke og generelle blodprøver og prikktest
Ved oppstart av studien, som er før oppstart av diettbehandlingen, skal det tas blodprøver og prikktest av deg. Dette er da snakk om allergispesifikke blodprøver, men også generelle blodprøver som viser ernæringsstatus. Blodprøvene og prikktesten tas på sykehuset i forbindelse med det første møtet. Det blir også tatt blodprøver av deg etter endt eliminasjonsdiett og etter endt gjenintroduksjon av matvaregrupper. Dette gjøres også på sykehuset i forbindelse med møter. Det er da de generelle blodprøvene som skal tas.

Spørreskjemaer
Du skal svare på 3 ulike spørreskjemaer, et skjema om symptomer av sykdommen (EEsAI), et skjema om livskvalitet (SF36) og et skjema som forteller hvordan du klarer å overholde dietten. Alle tre skjemaene skal besvares etter endt diettbehandling. Skjema om livskvalitet og symptomer skal i tillegg besvares før oppstart av dietten. Skjemaet om overholdelse av dietten

vil også besvares 3 uker ut i dietten (midt i diettbehandlingen). Det er da fullt mulig å besvare dette skjemaet hjemme og sende det til oss i posten.

Tidsskjema – hva skjer og når skjer det?
Du har blitt kontaktet og blitt spurt om å delta i studien. Dersom du er villig til å være med i studien, signerer du samtykkeskjemaet bakerst i dette skrivet.
Du skal deretter møte opp på 5-7 møter, som alle vil finne sted på Haukeland Universitetssykehus på dagtid så langt det lar seg gjøre.

1: Ved det første møtet, vil du få mer informasjon om hva studien innebærer og hva som skal skje framover. Det skal tas blodprøver og prikktest av dere før eller etter dette møtet. Det skal også tas en ny gastroskopi med biopsier av deg, så langt dette ikke er gjort relativt nylig. Resultatene fra gastroskopi med biopsier lagres i biobanken, sammen med resultatene fra blodprøvene.
2: Ved det andre møtet vil det bli tatt trykkmåling (manometri/impedans) og syremåling (pH-måling) av deg. Du vil også få utlevert skriftlig materiell i form av spørreskjemaer (SF36, symptomregistrering og overholdelse av dietten) som du må svare på underveis i studieløpet.
3: Ved det tredje møtet vil du få en samtale med student i klinisk ernæringsfysiologi, før oppstart av «Six Food Elimination Diet» som skal vare i de neste seks ukene. Du vil også få utlevert skriftlig informasjon om dietten. Dette er detaljert informasjon om matvarer du må fjerne fra kosten i de neste seks ukene og alternativer til disse matvarene. Ved dette møtet skal du også levere inn skjema om livskvalitet (SF36) og symptomregistreringsskjema til studenten i klinisk ernæringsfysiologi. Skjemaene angir hvor plaget du er av eosinofil øsofagitt og hvordan dette påvirker din livskvalitet.
3 uker ut i diettbehandlingen skal du fylle ut et skjema om overholdelse av dietten. Det utfylte skjemaet sendes i posten.
Ved spørsmål og problemer med dietten har du mulighet til å kontakte student i klinisk ernæringsfysiologi på telefon eller e-post (se kontaktinformasjon på andre side). Du kan eventuelt også kontakte de ansvarlige legene.
4: Det fjerde møtet blir etter endt elimsinasjonsdiett, hvor det nå skal testes for effekt av dietten. Det vil tas ny gastroskopi med biopsier, som vil komme i tillegg ved deltakelse i forskningsprosjektet, sammenliknet med normal oppfølgning ved Haukeland Universitetssykehus. Det skal også tas blodprøver av deg ved dette møtet. Alle måleresultatene vil lagres i biobanken. Ved dette møtet skal igjen de 3 skjemaene (om livskvalitet, symptomregistrering og overholdelse av dietten) tas med og leveres inn ferdig utfylt.
5: Ved det femte møtet, skal det gjøres trykkmåling slik du gjorde før diettbehandlingen startet. Denne trykkmålingen vil også komme i tillegg ved deltakelse i forskningsprosjektet, sammenliknet med normal oppfølgning ved Haukeland Universitetssykehus.
Dersom du opplever en effekt av dietten, sett ved resultatene fra gastroskopi med biopsier i etterkant av diettbehandlingen, vil du ha 2 møter til som også vil finne sted på Haukeland Universitetssykehus. En klinisk ernæringsfysiolog vil være tilstede ved det fjerde møtet, som vil informere om gjenintroduksjon av matvarer, hvor en og en av de utelatte matvarene/matvaregruppene nå blir gjenintrodusert med 14 dagers mellomrom. Under selve gjenintroduksjonen vil det ikke bli oppsatte møter ved Haukeland Universitetssykehus for hver enkelt matvare/matvaregruppe som gjenintroduseres. I stedet avtales for den enkelte enten et personlig møte eller møte pr. telefon for hver gjenintroduksjon. Etter gjenintroduksjonen skal du møte opp på Haukeland Universitetssykehus for de to siste møtene.

6: Det sjette møtet vil være 14 dager etter avsluttet gjenintroduksjon av matvarer/matvaregrupper. Da skal det tas en ny gastroskopi med biopsier og nye blodprøver.
7: Ved det syvende og siste møtet, skal det gjøres syremåling og trykkmåling slik du gjorde før og etter diettbehandlingen.
Dersom du ikke opplever noen effekt av diettbehandlingen, sett ved resultatene av biopsiene ved gastroskopi etter endt eliminasjonsdiett, vil det ikke være nødvendig med systematisk gjenintroduksjon av de matvarene du har utelatt fra kosten, og de to siste møtene ved Haukeland Universitetssykehus vil falle bort.

Alternative prosedyrer dersom du ikke velger å delta i studien
Dersom du underveis i studien ønsker å avslutte diettbehandlingen og/eller ikke ønsker å delta i studien, vil du få tilbud om tradisjonell behandling med medisiner og oppfølgning på poliklinikken på vanlig måte. Om du ønsker å trekke deg kan du ta kontakt når som helst. Da vil du bli invitert til en samtale, og eventuelle problemer vil bli diskutert. Du har selvfølgelig fortsatt rett til å slutte i studien når som helst uten å oppgi grunn.

Studiedeltakerens ansvar
Som deltaker i denne studien ber vi om at du setter deg inn i informasjon om prøver og målinger, samt følger dietten. Tid og dato for møtene og prøvene skal avtales slik at det passer for begge parter. Med tanke på at det noen ganger vil være flere studiedeltakere og behandlere ved et møte, ber vi om at du er fleksibel på tid og dato for møtene og prøvene som skal bli tatt. Du må også møte opp til avtalt tid, eventuelt ringe i god tid dersom timen ikke passer. Du har også ansvar for å fylle ut skjemaene som avtalt, ta dem med på møtene og sende dem i posten før avtale frister. På det første møtet med oss vil du få mer nøyaktig informasjon enn det som står i dette skrivet.

Endringer i planen
Dersom det skjer endringer i planen eller ved tidligere avslutning av dietten, vil du bli informert om dette så raskt som mulig. Du vil også bli informert dersom ny informasjon blir tilgjengelig som kan føre til at du ikke lenger ønsker å delta i studien. Dersom det oppstår en uforutsett hendelse som gjør at studien må avsluttes, vil du bli kontaktet snarest mulig.

Kapittel B – personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er informasjon om symptomer og livskvalitet fra forskjellige skjemaer som du vil fylle ut. Resultater fra gastroskopier med biopsier, blodprøver og andre målinger vil også bli registrert. Kontaktinformasjon (navn og telefonnummer) om deg vil bli lagret. Det er kun vi som holder på med studien som har tilgang til opplysninger om deg. Disse vil bli lagret innelåst.

Biobank
Vi har en biobank for lagring av blodprøver og biopsier fra gastroskopi.

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger brukes til denne studien ved Haukeland Universitetssykehus. Avidentifiserte opplysninger skal ikke sendes til andre foretak eller foretak i andre land.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi og Haukeland Universitetssykehus' rolle
Studien er finansiert gjennom driftsmidler ved Helse Bergen og forskningsmidler fra gastroenterologisk seksjon ved Klinisk Institutt 1 ved Universitetet i Bergen. De vil bidra med personell til analyser av blodprøver. Det er ingen mulige interessekonflikter.

Forsikring
Forsikringsordningen som gjelder er pasientskadeerstatning, idet du som deltaker er under behandling ved Haukeland Universitetssykehus.

Informasjon om utfallet av studien
Du har som deltaker i studien rett til å få informasjon om utfallet av studien når dette er klart. En sluttrapport vil sendes til deg.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Appendix 4: EEsAI questionnaire

KONFIDENSIELT

Personnummer: _____

Dato: _____/_____/_____

EESAI Versjon 20130627
Hatlebakk Versjon 20160426

EEsAI, SPØRRESKJEMA FOR VOKSNE

Eosinophilic Esophagitis Activity Index (EEsAI)

Vi setter pris på at du vil delta i denne viktige undersøkelsen.

Vi vil gjerne stille deg noen spørsmål om sykdommen din. Det er lett å overse et spørsmål, vær snill å påse at du ikke utelater noe underveis. Takk for at du hjelper oss med denne undersøkelsen!

Du fyller ut skjemaet på en av to måter:

- Ved å krysse i ruten som passer: ☒

ELLER

- Ved å skrive på linjen: Hvis du har besvart spørsmål 2 A-H én eller flere ganger med "Vet ikke", vær snill å forklar hvorfor for hver matvare: Eksempel: Jeg spiser ikke pommes frites

PROBLEMER P.G.A. EOSINOFIL ØSOFAGITT

Vennligst legg merke til at alle spørsmålene dreier seg om dine symptomer på eosinofil øsofagitt (EoE), og ikke plager pga. sår hals (eksempel: en streptokokk-infeksjon i halsen eller kyssesyke), eller til problemer som oppstår, for eksempel, hvis et fiskebein har satt seg fast i halsen din. Vi vil gjerne spørre deg om problemer som oppstår når du spiser (spørsmål 1 - 11).

PROBLEMER SOM OPPSTÅR NÅR DU SPISER

1 **Har du problemer med å tygge?** (for eksempel fordi du trenger nye fyllinger i en tann, eller du har tannproteser, eller du har en skade i kjeven?)

☐Nei
☐Ja **Hvis ja,** hvorfor?..... _____

KONFIDENSIELT

Personnummer: _____

Dato: _____/_____/_____

2

	A	B	C	D	E	F	G	H
	 **Fast kjøtt** (biff, stek, kylling, kalkun, lam)	 **Myk mat** (pudding, gelé, mousse, fromasj, eplemos)	 **Tørr, ikke-klebrig ris eller klebrig asiatisk ris,** uten saus	 **Kjøttdeig** (hamburger, kjøttpudding, kjøttkake, karbonade)	 **Ferskt hvitt brød som ikke er ristet** (eller smultring, muffins, kake)	 **Grøt** (havregrøt, risgrøt, o.l.)	 **Rå, fiberholdig mat, ikke revet** (eple, gulrot, kålrot)	 **Pommes frites,** uten saus eller ketchup
Hvor vanskelig er det idag å svelge ned hver av de ulike matslagene vist over? Sett kun et kryss for hvert matslag eller type konsistens. *Vennligst forestill deg hva som typisk ville skje dersom du skulle spise disse matvarene akkurat nå.* *Viktig: forestill deg at du spiser maten uten å forandre den, slik som å blande den sammen, mose den, skjære den i småbiter eller bløte den opp.*								
Store problemer (eksempel: passerer ikke i det hele tatt	☐	☐	☐	☐	☐	☐	☐	☐
Moderate problemer (eksempel: må skylles ned med væske / drikke)	☐	☐	☐	☐	☐	☐	☐	☐
Milde problemer (eksempel: glir ned etter flere svelg)	☐	☐	☐	☐	☐	☐	☐	☐
Ingen problemer	☐	☐	☐	☐	☐	☐	☐	☐
Vet ikke *Vennligst forklar ved slutten av tabellen (spørsmål 2)*	☐	☐	☐	☐	☐	☐	☐	☐

3 **Hvis du har besvart spørsmål 2 A-H én eller flere ganger med "Vet ikke", så vær snill å forklare hvorfor for hver matvare.**

KONFIDENSIELT

Personnummer: _____

Dato: _____ / _____ / _____

A	B	C	D	E	F	G	H
							
Fast kjøtt (biff, stek, kylling, kalkun, lam)	**Myk mat** (pudding, gelé, mousse, fromasj, eplemos)	**Tørr, ikke-klebrig ris eller klebrig asiatisk ris,** uten saus	**Kjøttdeig** (hamburger, kjøttpudding, kjøttkake, karbonade)	**Ferskt hvitt brød som ikke er ristet** (eller smultring, muffins, kake)	**Grøt** (havregrøt, risgrøt o.l.)	**Rå, fiberholdig mat, ikke revet** (eple, gulrot, kålrot)	**Pommes frites,** uten saus eller ketchup

4 Hvor mange måltider har du inntatt i løpet av den siste uken? *Måltider er frokost, lunsj eller middag, regelmessig mat eller mat ved en festlig anledning. Et måltid inkluderer den mengde mat som er typisk for deg til den spesifikke tiden av dagen eller anledningen og omfatter vanligvis flere matvarer. For eksempel, kaffe, brødmat og frokostblanding som du kanskje spiser til frokost, eller grønnsaker, ris og et stykke fisk som du kanskje spiser til lunsj, utgjør tilsammen et måltid. Snacks, for eksempel et eple eller en sjokolade, som du kanskje spiser mellom måltidene, blir ikke ansett som måltider.*

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 eller flere

→ *Hvis du intok 0 måltider i løpet av den siste uken, vennlist gå rett til neste side.*

Nå vil vi gjerne vite om du, i løpet av den siste uken... *vennligst fortell oss om dine hverdagslige spisevaner.*

5 ...har unngått slik mat helt pga din EoE? (eksempel fordi den ikke ville passere i det hele tatt)	☐ Ja (hvis ja, gå videre)	☐ Ja (hvis ja, gå videre)	☐ Ja (hvis ja, gå videre)	☐ Ja (hvis ja, gå videre) →	☐ Ja (hvis ja, gå videre) →	☐ Ja (hvis ja, gå videre) →	☐ Ja (hvis ja, gå videre) →	☐ Ja (hvis ja, gå videre) →
	☐ Nei	☐ Nei	☐ Nei	☐ Nei	☐ Nei	☐ Nei	☐ Nei	☐ Nei
6 ...spiste slik mat?	☐ Nei (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →	☐ Nei, (hvis nei, gå videre) →	☐ Nei (hvis nei, gå videre) →
	☐ Ja	☐ Ja	☐ Ja	☐ Ja	☐ Ja	☐ Ja	☐ Ja	☐ Ja
7 ... endret slik mat? (for eksempel, puttet den i en blender, kuttet den i små biter, bløtet den opp, moste den)	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei
8 ...spiste slik mat saktere enn andre mennesker som spiste samme mat (for eksempel fordi du tygde den lenge)	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei	☐ Ja ☐ Nei

KONFIDENSIELT

Personnummer:_____

Dato: _____ / _____ /_____

9 Siste 7 dager, hvor ofte har du hatt problemer med å svelge (ikke forbundet med forkjølelsessytomer, slik som sår hals)

- ☐ Aldri
- ☐ En til 3 ganger per uke
- ☐ Mer enn 3 ganger per uke
- ☐ Daglig

10 Siste 7 dager, hvor lenge har en episode med svelgvansker typisk vart?

- ☐ I mindre enn 15 sekunder
- ☐ 16 til 59 sekunder
- ☐ 1 til 5 minutter
- ☐ Lengre enn 5 minutter
- ☐ I løpet av den siste uken har jeg ikke hatt problemer med å svelge
- ☐ Jeg har ikke prøvd å svelge noe den siste uken (slik som før en undersøkelse, eller pga en religiøs høytid)

11 Siste 7 dager, har det vært smertefullt å svelge?

- ☐ Ja
- ☐ Nei
- ☐ Jeg har ikke prøvd å svelge noe den siste uken (slik som før en undersøkelse, eller pga en religiøs høytid)

Takk for at du fylte ut dette spørreskjemaet!

KONFIDENSIELT

Personnummer:_____
Dato:_____/_____/_____

Denne siden har vi med vilje latt være tom.

Skriv gjerne kommentarer du måtte ha til dette spørreskjemaet.

Appendix 5: SF-36 questionnaire

SF-36 Norsk versjon

Vi spør deg her om hvordan du opplever din egen helse. Vi ønsker å vite hvordan du føler deg og hvordan du mestrer dine vanlige aktiviteter. Vær snill å svare på alle spørsmål. Noen av spørsmålene ligner på hverandre, men alle er forskjellige. Ta deg tid til å lese spørsmålene nøye og svar med et kryss for det alternativ som du velger!

Takk for at du svarer på disse spørsmålene!

Pasientnummer:
Dato:
Besøksnummer:

---

1. Stort sett, vil du si at din helse er:

Utmerket	**Meget god**	**God**	**Nokså god**	**Dårlig**
○	○	○	○	○

2. Sammenlignet med for ett år siden, hvordan vil du si at helsen din stort sett er nå?

Mye bedre nå enn for ett år siden	**Litt bedre nå enn for ett år siden**	**Omtrent den samme som for ett år siden**	**Litt dårligere nå enn for ett år siden**	**Mye dårligere nå enn for ett år siden**
○	○	○	○	○

3. De neste spørsmålene handler om gjøremål som du kanskje utfører i løpet av en vanlig dag. Er **din helse nå slik at den begrenser deg** i utførelsen av disse aktivitetene? Hvis ja, hvor mye?

	Ja, begrenser meg mye	**Ja, begrenser meg litt**	**Nei, begrenser meg ikke i det hele tatt**
Anstrengende aktiviteter, som å løpe, løfte tunge gjenstander, delta i anstrengende idrett	○	○	○
Moderate aktiviteter, som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	○	○	○
Løfte eller bære en handlekurv	○	○	○
Gå opp trappen **flere** etasjer	○	○	○
Gå opp trappen **en** etasje	○	○	○
Bøye deg eller sitte på huk	○	○	○
Gå **mer enn to kilometer**	○	○	○
Gå **noen hundre meter**	○	○	○
Gå **hundre meter**	○	○	○
Vaske deg eller kle på deg	○	○	○

4. I løpet av **de siste fire ukene**, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

	Hele tiden	**Det meste av tiden**	**En del av tiden**	**Litt av tiden**	**Ikke i det hele tatt**
Har du **redusert tiden** du har brukt på arbeidet ditt eller andre aktiviteter	○	○	○	○	○
Har du **utrettet mindre** enn du hadde ønsket	○	○	○	○	○
Har du vært hindret i visse **typer** arbeid eller andre aktiviteter	○	○	○	○	○
Har du hatt **vansker** med å utføre arbeidet ditt eller andre aktiviteter (for eksempel fordi det krevde ekstra anstrengelser)	○	○	○	○	○

5. I løpet av **de siste fire ukene**, har du hatt følelsesmessige problemer som har ført til vanskeligheter i ditt arbeid eller i andre av dine daglige gjøremål (for eksempel fordi du har følt deg deprimert eller engstelig)

	Hele tiden	**Det meste av tiden**	**En del av tiden**	**Litt av tiden**	**Ikke i det hele tatt**
Har du **redusert tiden** du har brukt på arbeidet ditt eller andre aktiviteter	○	○	○	○	○
Har du **utrettet mindre** enn du hadde ønsket	○	○	○	○	○
Har du ikke arbeidet eller utført andre aktiviteter **like nøye** som vanlig	○	○	○	○	○

6. I løpet av de **siste 4 ukene**, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

Ikke i det hele tatt	**Litt**	**Endel**	**Mye**	**Svært mye**
○	○	○	○	○

7. Hvor sterke **kroppslige** smerter har du hatt i løpet av **de siste 4 ukene?**

Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
○	○	○	○	○	○

8. I løpet av **de siste 4 ukene**, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt	Litt	En del	Mye	Svært mye
○	○	○	○	○

9. De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det **de siste 4 ukene**. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av **de siste 4 ukene** har du …

	Hele tiden	Det meste av tiden	Endel av tiden	Litt av tiden	Ikke i det hele tatt
følt deg full av tiltakslyst?	○	○	○	○	○
følt deg veldig nervøs?	○	○	○	○	○
vært så langt nede at ingenting har kunnet muntre deg opp?	○	○	○	○	○
følt deg rolig og harmonisk?	○	○	○	○	○
hatt mye overskudd?	○	○	○	○	○
følt deg nedfor og trist?	○	○	○	○	○
følt deg sliten?	○	○	○	○	○
følt deg glad?	○	○	○	○	○
følt deg trøtt?	○	○	○	○	○

10. I løpet av de **siste 4 ukene**, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

Hele tiden	Nesten hele tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
○	○	○	○	○

11. Hvor RIKTIG eller GAL er hver av følgende påstander for deg?

	Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
Det virker som jeg blir litt lettere syk enn andre	○	○	○	○	○
Jeg er like frisk som de fleste jeg kjenner	○	○	○	○	○
Jeg forventer at min helse vil bli dårligere	○	○	○	○	○
Min helse er utmerket	○	○	○	○	○

Appendix 6: Dietary habits during the last 12 months

Pasientnummer:_____

Kostholdet ditt siste 12 måneder

Hvor ofte spiser/drikker du (sett kryss)

a) Melk

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

b) Yoghurt

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

c) Ost (på skiven eller i revet form eller tilsvarende)

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

d) Unngår du mat som inneholder melk eller melkeprodukter?

- ☐ Ja, alltid
- ☐ Ja, som regel
- ☐ Nei

e) Egg (kokt, stekt, eggerøre, omelett eller liknende)

- ☐ Daglig
- ☐ Ukentlig
- ☐ Månedlig
- ☐ Aldri

Hvis «aldri», hvorfor:

- ☐ Allergi/overfølsomhet
- ☐ Liker ikke
- ☐ Andre grunner (forklar:_____)

f) Unngår du mat som inneholder egg?

- ☐ Ja, alltid
- ☐ Ja, som regel
- ☐ Nei

g) Brød (brødskiver, rundstykker, boller, kjeks ol.)

- ☐ Daglig
- ☐ Ukentlig
- ☐ Månedlig
- ☐ Aldri

Hvis «aldri», hvorfor:

- ☐ Allergi/overfølsomhet
- ☐ Liker ikke
- ☐ Andre grunner (forklar:_____)

h) Unngår du mat som inneholder hvete?

- ☐ Ja, alltid
- ☐ Ja, som regel
- ☐ Nei

i) Unngår du mat som inneholder gluten?

- □ Ja, alltid
- □ Ja, som regel
- □ Nei

j) Fisk (som pålegg, til middag eller liknende):

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

k) Skalldyr (som pålegg, til middag, i salat eller liknende)

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

l) Peanøtter

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

m) Andre nøtter (paranøtter, pistasj, mandelmelk ol.)

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

n) Produkter med soya (soyasaus, soyaolje, soyamelk, soyabønner o.l.)

- □ Daglig
- □ Ukentlig
- □ Månedlig
- □ Aldri

Hvis «aldri», hvorfor:

- □ Allergi/overfølsomhet
- □ Liker ikke
- □ Andre grunner (forklar:_____)

Appendix 7: SFED list of eliminated foods and alternatives

«Eliminasjonsdiett»

Kost uten

- **Melk**
- **Egg**
- **Hvete/gluten**
- **Fisk/skalldyr**
- **Soya**
- **Peanøtter/nøtter**

Dette er en testdiett som skal følges i noen uker mens du deltar i et forskningsprosjekt om eosinofil øsofagitt. Rådene i dette skrivet vil ikke nødvendigvis passe for personer med påvist allergi mot de samme matvarene/matvaregruppene (henholdsvis melk, egg, hvete/gluten, fisk/skalldyr, soya, og/eller nøtter/peanøtter).

UNNGÅ	**VELG I STEDET**
MELK OG MELKEPRODUKTER Alle typer melk (fra ku, geit eller andre pattedyr). Yoghurt Fløte, rømme, creme fraiche, kesam. Alle typer ost (brun og hvit). Prim. Iskrem.	ERSTATNING FOR KUMELKSPRODUKTER *Matlaging:* Havremelk, rismelk, vann, kraft, buljong, fruktjuice. Fruktpureer, smoothie. Fløteerstatning (havrebasert). Kokosmelk. Wilmersburger (Osteerstatning). Saftis uten sjokoladetrekk. Slush. Risbasert iskrem (Rice Dream)*.
MATFETT Meierismør, margarin, lettmargarin.	MATFETT Soft Spesial margarin uten melk og soya (blå). Matoljer (alle typer bortsett fra nøtteoljer og soyaolje).
EGG Egg i alle former (både plommen og hviten).	ERSTATNING FOR EGG *Baking:* Eggerstatning*(f eks Orgran No Egg eller Egg Replacer), linfrø-avkok eller bakepulver kan erstatte egg.
KORNVARER Hvete, rug, bygg, spelt og vanlig havre (mel, gryn, kli og kim av disse kornsortene). Semulegryn, couscous. Kli. Vanlige kornblandinger. Vanlig makaroni/spagetti.	KORNVARER Mel og gryn av ris, mais, bokhvete, hirse, quinoa, teff, amarant. Ren, glutenfri havre. Glutenfrie melblandinger uten melk/egg/soya: • Toro glutenfrie melblandinger (grov og lys) • Jyttemjøl (alle typer) • Semper Fin mix og Grov mix • Finax Gluten & mjölkfri melblandinger Potetmel, maizena. Polentagryn, sagogryn. Pofiber*, Fiber Husk*; Fibrex*, linfrø, psyllium. Puffet ris, glutenfri corn flakes*, Finax Glutenfri Frukt Müsli*, Semper Multimüsli*. Glutenfri makaroni/spaghetti uten egg/soya (f.eks. fra Schär/Semper). Ris, risnudler.

BRØD OG ANDRE BAKERVARER Vanlig brød, rundstykker, knekkebrød, kjeks, boller, kaker, vafler, pannekaker osv.	BRØD OG ANDRE BAKERVARER Glutenfritt brød/bakverk som er fritt for melk, egg, soya og nøtter (f.eks. de fleste produktene fra Fria, gluten- og melkefrie brød fra Brisk, Wasa gluten- og laktosefritt knekkebrød, mange sorter brød og knekkebrød fra Semper) Riskjeks, maiskjeks. Tacoskjell.
ØL Glutenholdig øl, med og uten alkohol (vørterøl).	ØL Glutenfritt øl (eks: Ringnes Lite, Estrella Galicia, Estrella Daura, Lammsbräu Glutenfrei, Against the Grain, Greens Blonde) Ingefærøl (brus).

* Selges i nettbutikker, helsekostforretninger og velassorterte dagligvareforretninger.

UNNGÅ	**VELG I STEDET**
KJØTT *Middagsmat:* Vanlige pølser, kjøttkaker og kjøttboller, kjøttfarse, medisterfarse. *Pålegg:* Leverpostei, servelat og annet kjøttpålegg som inneholder melk, hvetemel eller soya.	KJØTT *Middagsmat:* All slags rent kjøtt (f eks kalv/storfe, lam/får, svin, vilt, kylling/høne, kalkun), kjøttdeig, medisterdeig, skinke på boks, hjemmelagede kjøttkaker og kjøttboller (lag farse av kjøttdeig, potetmel, vann, salt og krydder). Gilde Go' og Mager pølser og kjøttkaker. Leif Vidar Wienerpølser og Grillpølser (kjøpt i butikk). *Pålegg:* De fleste kjøttpålegg som kokt skinke, bankekjøtt, spekekjøtt, fårepølse, salami, men sjekk ingredienslisten. Gilde Go'og mager: Leverpostei og Servelat. Rester av middagsmat (kjøttkaker, stek).
FISK OG SKALLDYR Fisk og skalldyr i alle former.	

POTETER OG GRØNNSAKER Potetmos, stuinger og andre potet- eller grønnsakretter hvor egg, mel eller melk inngår.	POTETER OG GRØNNSAKER Poteter og grønnsaker i ren form.
FRUKT OG BÆR Mandler og nøtter av alle slag.	FRUKT OG BÆR Alle andre typer frukt og bær.
ANNET *Sauser og supper:* Sauser og supper som inneholder melk, egg, soya og/eller gluten/hvete. Majones, remulade, majonesbaserte dressinger. *Pålegg:* Nugatti, Hapå, peanøttsmør etc. Italiensk salat og andre majonessalater. *Snacks:* Ostepop, peanøtter, diverse chips-typer. *Desserter:* Puddinger, fromasjer, iskrem. *Søtsaker:* Sjokolade, karameller, marsipan. Lakris og fylte drops kan inneholde hvete.	ANNET *Sauser og supper:* Hjemmelagede sauser og supper (jevnet med maisenna). Sjysaus. Enkelte grønnsaksauser til pasta og ris på glass (sjekk ingredienslisten). Fransk dressing (olje/eddik). *Pålegg:* Kjøttpålegg, Gilde Go' og mager leverpostei, Streich smørepålegg*, syltetøy, honning, skiver av frukt og grønnsaker. *Snacks:* Maarud potetgull med salt. *Desserter:* Kompotter, hermetisk frukt, fruktsalat, gelé, saftis. *Søtsaker:* Pastiller, drops, seigmenn, vingummi, skumgodter, marshmallows, rosiner. *Les innholdsfortegnelsen!*

* Selges i helsekostforretninger og enkelte velassortert dagligvareforretninger.

FERDIGMAT

Mange typer ferdigmat inneholder melk, egg, fisk, skalldyr, glutenholdige korn, peanøtter, nøtter og/eller soya i større eller mindre mengder. Det er derfor viktig å lese varedeklarasjonen nøye. Produsenten er pålagt å oppgi alle ingredienser og forekomst av noen av de nevte matvarene skal merkes tydelig.

Mat uten varedeklarasjon (f.eks. i ferskvaredisk, restaurant) kan inneholde uventede ingredienser. Spør alltid om innholdet og bruk ikke matvarer med ukjent sammensetning!

Melk kan deklareres som

- melk, tørrmelk eller melkepulver
- melkeprotein
- myse, mysepulver
- fløte, rømme, creme fraiche, fløtepulver
- yoghurt
- ost, ostepulver, kvarg, cottage cheese, kesam

Fett brukt til steking og baking (margarin, smør m.m.) inneholder svært ofte melk.

Egg kan deklareres som

- egg
- eggeplomme
- eggehvite
- eggpulver

Majones og majonesbaserte dressinger innholder nesten alltid egg.

Gluten kan deklareres som

- hvete, rug, bygg, havre, spelt
- hvetemel, hvetekli, hvetekim, hveteprotein, puffet hvete
- durumhvete, makaroni, pasta
- semulegryn
- couscous, bulgur
- rugmel
- byggmel, byggryn
- havremel, havregryn, havrekli, puffet havre
- triticale (en krysning mellom hvete og rug)
- spelt, dinkel, emmerhvete (gamle hvetesorter)

Strøbrød og griljering/panering inneholder som regel gluten. Godt renset hvetestivelse er tillatt ingrediens i produkter som er merket ”glutenfri”. Havre som er merket ”glutenfri” kan også inngå i glutenfri kost. Hvetestivelse i glutenfrie produkter og glutenfri havre er produkter som er tillatt.

Soya kan deklareres som

- soyabønner
- soyamel
- soyaprotein
- Soyaolje

Alt som ifølge ingredienslisten inneholder soya er ikke tillatt, med unntak av soyalecitin (E322).

Med nøtter menes

- hasselnøtt
- valnøtt
- cashewnøtt
- pekannøtt
- paranøtt
- pistasjnøtt
- macadamianøtt
- mandel
- Peanøtt (jordnøtt)

Tilsetningsstoffer

Dersom tilsetningsstoffene som er brukt i en matvare inneholder eller er utvunnet av melk, egg, hvete/glutenholdig kornsort, fisk, skalldyr, soya, peanøtter eller nøtter, skal dette framgå av varedeklarasjonen.

Forurensing/kontaminering av matvarer

Bearbeidede matvarer kan i blant inneholde små mengder tørrmelk, eggepulver, nøttestøv e.l. uten at dette framgår av innholdsdeklarasjonen. Det dreier seg da om en forurensing, som kan skyldes at mange ulike produkter tilvirkes i samme lokale eller med samme utstyr. I slike tilfeller velger enkelte produsenter å opplyse om at matvaren kan inneholde spor av melk, egg, nøtter etc. I fasteperioden er matvarer merket med «spor av» tillatt.

MENYFORSLAG

Frokost, lunsj og kvelds

- Havregrøt (tilberedt av glutenfrie havregryn og vann eller havremelk)
- Frokostblanding (Finax glutenfri frukt müsli, Semper Multimüsli eller Nestle Gluten Free Corn Flakes) med havremelk eller rismelk
- Hjemmelaget müsli av glutenfrie havregryn/cornflakes, rosiner og annen tørket frukt
- Ristet brød med Soft spesial margarin og syltetøy/marmelade
- Varme rundstykker med diverse pålegg (se forslag)
- Hjemmelagde eller kjøpte knekkebrød med pålegg
- Sprøstekt bacon med tomatbønner
- Middagsrester
- Salat

Brød/bakevarer/knekkebrød: brød fra Fria, frossenvarer fra Brisk, brød fra Schär, Semper brød eller melblandinger, Semper Grovknäcke (eks rosmarinknäcke, havreknäcke), Wasa gluten- og laktosefritt knekkebrød

Pålegg: De fleste kjøttpålegg (eks kokt skinke, kalkunfilet), produkter fra Gilde Go` og mager (servelat, leverpostei), syltetøy, honning, Wilmersburger-ost, middagsrester

Drikke: Kaffe, te, juice, havremelk, rismelk

Middag

- Glutenfri spaghetti
- Kjøttkaker
- Kyllingwok/wok
- Suppe
- Taco (uten ost og rømme)
- Lasagne (glutenfri lasagne, melkeerstaning og Wilmersburger-ost)
- Pizza (laget med glutenfri bunn og Wilmersburger-ost)

Dessert og kjeks/snacks

- Hildes sjokoladekake/gulrotkake (www.hildekaken.no)
- Gele med freia vaniljesaus til koking (tilberedes med melkeerstatning)
- Salt potetchips
- Spesialsjokolade (melkefri sjokolade)
- Gelesnop
- Semper Cookie-O`s
- Frukt (fruktsalat/fruktkompott)
- Smoothie
- Saftis uten sjokoladetrekk

HALVFABRIKATA

Toro:	Lett bearnaisesaus (tilberedes med melkeerstatning)
	Glutenfri brun saus eller glutenfri hvit saus
	Glutenfri tomatsuppe
	Glutenfri blomkålsuppe (tilberedes med melkeerstatning)
Freia:	Vaniljesaus til koking (tilberedes med melkeerstatning)

FERDIGRETTER

Eksempler på egnede produkter.

Findus:	Mexican chicken (dypfryst)
Fjordland:	Lys lapskaus (kjølevare)
	Ertesuppe med bacon (kjølevare)
	Fårikål med poteter (kjølevare)
Fria:	Pizza Prosciutto (dypfryst)
	Pizza Margherita (dypfryst)
Toro:	Thai panang curry kylllingryte (kjølevare)
Trondhjems:	Erter, kjøtt og flesk (hermetikk)

OPPSKRIFTSBØKER

Nettstedene **www.allergikokken.no og www.allergimat.no**

Ann Eli Mavrakis: **Allergikokebok for hele familien**, Cappelen Damm, 2014.

KOSTENS NÆRINGSINNHOLD

Kost uten melk, egg, fisk og glutenholdige kornsorter kan bli energifattig og gi for lite av enkelte næringsstoffer - spesielt vitamin B2 (riboflavin), vitamin D, kalsium, jern, jod, selen, omega-3-fettsyrer og fiber.

Anbefalte tilskudd:	1000 mg kalsium (2-4 tygge-eller svelgetabletter)*
	1 multivitamin- og mineraltablett (f.eks. Nycomed Multi)
	Tran eller omega-3

* Uten vitamin D dersom du tar tran og/eller vitamintilskudd med vitamin D

Ved behov for næringsdrikk fra apotek kan følgende produkter brukes:

- ProvideXtra drink (juiceliknende drikk, smaker: eple, solbær, appelsin & ananas)
- Elemental 028 Extra (juiceliknende drikk, smaker: sommerfrukt, grapefrukt, appelsin & ananas)

Appendix 8: Two-week menu suggestion and recipes

Meny og oppskrifter

Uke 1

MANDAG

- Frokost: Havregrøt med banan (av glutenfrie havregryn, laget på vann, med havremelk)
- Lunsj: Knekkebrød (eks. Semper) med smør (Soft blå), div. pålegg (kokt skinke, kalkunfilet, spekeskinke, og div. grønnsaker (agurk, paprika o.l.)
- Middag: Spagetti (glutenfri) bolognese
- Kvelds: Brødskiver med smør (Soft blå), div. pålegg og grønnsaker (agurk, paprika)
- Mellommåltid: Gulrot (-røtter)
- Husk å ta kosttilskudd ☺

TIRSDAG

- F: Frokostblanding (eks. Gluten Free Corn Flakes med havremelk/rismelk)
- L: Middagsrester
- M: Ovnsbakt kyllingfilet, potetbåter og ovnsstekte grønnsaker (løk, rotgrønnsaker), ris
- K: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, paprika)
- MM: Smoothie
- Husk å ta kosttilskudd ☺

ONSDAG

- F: Müsli (hjemmelaget *eller* Semper Multimüsli, med havremelk/rismelk)
- L: Knekkebrød med smør (soft blå) div. pålegg og div. grønnsaker (agurk, paprika)
- M: Wok med strimlet svinekjøtt
- K: Brødskiver med smør (soft blå) div. pålegg og div. grønnsaker (agurk, paprika)
- MM: Banan(er) og pære(r)
- Husk å ta kosttilskudd ☺

TORSDAG

- F: Havregrøt med blåbær (av glutenfrie havregryn, laget på vann, med havremelk)
- L: Middagsrester
- M: Suppe

- K: Rundstykker (eks fra Schär) med smør (soft blå), div. pålegg og div. grønnsaker (eks agurk, paprika)
- MM: Pære(r) og eple(r)
- Husk å ta kosttilskudd ☺

FREDAG

- F: Frokostblanding (eks. Gluten Free Corn Flakes med havremelk/rismelk)
- L: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, reddik)
- M: Taco (uten tacolefser, ost og rømme)
- K: Ristet brød med smør (soft blå), div. pålegg og div grønnsaker (agurk, paprika)
- MM: Eple(r) og banan(er)
- Husk å ta kosttilskudd ☺

LØRDAG

- F: Varme rundstykker med smør (soft blå) div. pålegg og div grønnsaker (agurk, reddik)
- L: Knekkebrød med smør (soft blå) div. pålegg og div grønnsaker (agurk, paprika)
- M: Pizza (laget med glutenfri bunn og Wilmerburger-ost)
- K: Müsli (hjemmelaget, Semper Multimüsli, med havremelk/rismelk)
- MM: Smoothie
- Husk å ta kosttilskudd ☺

SØNDAG

- F: Sprøstekt bacon med tomatbønner, agurk og ristet, glutenfritt brød
- L: Müsli (hjemmelaget, Semper Multimüsli, med havremelk/rismelk)
- M: Lasagne m/salat (glutenfri lasagne/aubergine/squash, melkeerstatning, Wilmersburger-ost)
- K: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, reddik)
- MM: Salat
- Husk å ta kosttilskudd ☺

Uke 2

MANDAG

- F: Havregrøt med banan (av glutenfrie havregryn, laget på vann, med havremelk)
- L: Pizzarester
- M: Spagetti (glutenfri) bolognese
- K: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, reddik)
- MM: Smoothie (hjemmelaget eller kjøpt)
- Husk å ta kosttilskudd ☺

TIRSDAG

- F: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, reddik)
- L: Middagsrester
- M: Kjøttkaker (Gilde go' og mager eller hjemmelagde), kokte poteter og kokte grønnsaker
- K: Müsli (hjemmelaget *eller* Semper Multimüsli, med havremelk/rismelk)
- MM: Pære(r) og nektarin(er)
- Husk å ta kosttilskudd ☺

ONSDAG

- F: Frokostblanding (eks. Gluten Free Corn Flakes med havremelk/rismelk)
- L: Salat
- M: Kyllingwok
- K: Rundstykker med smør (soft blå), div. pålegg og div. grønnsaker (agurk, tomat, reddik)
- MM: Gulrot(-røtter)
- Husk å ta kosttilskudd ☺

TORSDAG

- F: Havregrøt med blåbær (av glutenfrie havregryn, laget på vann, med havremelk)
- L: Middagsrester
- M: Suppe
- K: Knekkebrød med smør (soft blå), div. pålegg og div. grønnsaker (agurk, reddik)
- MM: Banan(er) og nektarin(er)
- Husk å ta kosttilskudd ☺

FREDAG

- F: Frokostblanding (eks. Gluten Free Corn Flakes med havremelk/rismelk)
- L: Brødskiver med smør (soft blå), div. pålegg og div. grønnsaker (agurk, tomat)
- M: Hjemmelaget hamburger (glutenfritt hamburgerbrød, uten dressing og ost)
- K: Salat
- MM: Eple(r) og pære(r)
- Husk å ta kosttilskudd ☺

LØRDAG

- F: Varme rundstykker med smør (soft blå), div. pålegg og div grønnsaker (agurk, tomat)
- L: Müsli (hjemmelaget, Semper Multimüsli, med havremelk/rismelk)
- M: Taco (uten tacolefser, ost og rømme)
- K: Knekkebrød med smør (soft blå), div. pålegg og div grønnsaker (agurk, reddik)
- MM: Smoothie
- Husk å ta kosttilskudd ☺

SØNDAG

- F: Sprøstekt bacon med tomatbønner, agurk og ristet, glutenfritt brød med smør (Soft blå)
- L: Knekkebrød med smør (soft blå) div. pålegg og div grønnsaker (tomat, reddik)
- M: Kyllingsalat med ristet, glutenfritt brød med smør (Soft blå)
- K: Frokostblanding (eks. Gluten Free Corn Flakes med havremelk/rismelk)
- MM: Banan(er) og eple(r)
- Husk å ta kosttilskudd ☺

Havregrøt av glutenfrie havregryn, laget på vann – 2 porsjoner

- 3 dl vann
- 1,5 dl glutenfrie havregryn

Serveres med et smørøye, banan, blåbær, sukker, kanel, havremelk o.l. etter ønske

Brød (1) – 1 brød

- 50 g gjær
- 4 dl melkeerstatning
- ½ dl flytende margarin (Soft blå)
- 1ss fiberhusk
- 1ss lys sirup
- 2 dl pofiber
- 1 ts salt
- 5 dl grov, glutenfri melmiks (eks fra Semper)
- 1ts anis

Smuldre gjæren i en bakebolle. Varm melken og margarin til 37 C, og hell over gjæren. Rør til gjæren er oppløst. Tilsett fiberhusk og la det stå og svelle i 10 minutter. Ha i resten av ingrediensene og arbeid deigen godt sammen. La deigen heve under plast i bakebollen i 30 minutter. Dryss melmiks på bakebordet, elt deigen og form den til et brød som legges på bakepapirkledt bakeplate. Heves i 30 minutter. Stek brødet på nederste rille i ca 45 min på 200 C

Tips: ønsker du sprø skorpe kan du sette inn en skål med 2 dl vann nederst i ovnen. Dampen som frigjøres under stekingen gjør at brødskorpen blir sprøere.
Tips: man kan også lage rundstykker av denne oppskriften.

Brød (2)

- 1L vann
- 50g gjær
- 2ss rapsolje til baking
- 2ss fiberhusk
- 1ss honning (kan sløyfes)
- 2ts salt
- 1-2 poteter, ca. 150g moste, kokte poteter
- 100 g glutenfrie havregryn
- Ca. 750g grov, glutenfri melblanding (eks. Semper grov mix)

Ha fingervarmt vann i en bakebolle, tilsett olje og fiberhusk, rør om, og la svelle i ca. 10 minutter. Tørrgjær tilsettes med det tørre, fersk gjær løses opp i den fingervarme væsken. Elt inn glutenfritt mel, havregryn, mosede poteter og salt. Bruk kjøkkenmaskin med eltekrok. Denne deigen skal være løsere enn en tradisjonell deig med hvetemel. Fordel deigen i smurte brødformer, eller form den med en slikkepott til et rundt brød på

stekebrettet. Dekk med klede, og la deigen heve 40-50 minutter. Stek ved 200 grader på nederste rille i ca. 45 minutter.
Tips: man kan også lage rundstykker av denne oppskriften.

Hjemmelaget müsli

- Glutenfrie havregryn
- solsikkefrø
- Rosiner
- Tørket frukt, eks aprikos, banan
- Glutenfrie corn Flakes

Rist havregryn og solsikkefrø i en varm og tørr stekepanne. Rør hele tiden. Bland inn andre (ønskede) ingredienser. Serveres gjerne med fersk frukt og/eller bær og melkeerstatning.

Spagetti Bolognese – 4 porsjoner

- 400g karbonadedeig
- 2ss margarin eller olje til steking
- 1 stk finhakket gulrot
- 1 stk finhakket løk
- 2 stk finhakket stilkselleri (stangselleri)
- 2ss tomatpuré
- 1 boks hermetiske tomater
- 1ts salt
- ½ ts pepper
- 400g spagetti (glutenfri)
- Ingredienser til en salat ved siden av (isbergsalat, agurk, paprika/reddiker)

Ha margarin eller olje i en varm stekepanne. Stek kjøttdeig i biter. Ha i grønnsaker, tomatpurè og hermetisk tomat. Kok opp og la denne sausen småkoke i 15-20 minutter. Smak til med salt og pepper. Kok glutenfri spagetti i en kjele med lettsaltet vann etter anvisning på pakken. Server frisk salat til.

Kjøttkaker Gilde go' og mager

- Lag etter anvisning på pakken, kok poteter og grønnsaker (gulrot, kål, erter)

Tips: server med glutenfri, brun saus fra Toro eller hjemmelaget brun saus (jevnet med maisenna)

Wok med strimlet svinekjøtt – 2 porsjoner

- 1 gulrot, ½ rødløk, 1 paprika og purre *eller* frossen wokblanding fra eks. Findus/Eldorado
- 250g strimlet svinekjøtt stekes
- 2ss olje

- Søt chilisaus, fra eks. Eldorado
- Kokt ris

Grovriv gulrot, skjær paprika i strimler og purre i ringer. Varm oljen i woken til det ryker og brun kjøttet i små porsjoner, 2-3 minutter på sterk varme. Legg tilside. Fres grønnsakene i olje, ha kjøttet tilbake i woken og bland sammen. Smak til med salt og pepper, og la det trekke et par minutter. Server med kokt ris og chilisaus.

Kyllingwok - 4 porsjoner

- 4 stk kyllingfilet i strimler
- 2ss olje til steking
- 3 gulrøtter, 1 rødløk, ½ stk brokkoli, 1 pk frisk babymais, ½ pk sukkererter *eller* frossen wokblanding fra eks. Findus/Eldorado
- Søt chilisaus, fra eks. Eldorado
- 200g ris

Skjær kyllingfilet i strimler. Skrell gulrot og kutt opp grønnsaker. Kok ris som anvist på pakken. Varm olje i en wokpanne eller en dyp stekepanne. Stek kyllingstrimlene på høy varme i mindre porsjoner og sett til side. Varm opp olje og fres de oppdelte grønnsaker. Tilsett de harde grønnsakene først og sukkererter til sist. Ha i stekt kylling. Smak evt. til med salt og pepper. Server med kokt ris og chilisaus.

Maissuppe med sprøstekt bacon

- 2 ss olivenolje/rapsolje
- 1 gul løk, hakket
- 1/2 rød paprika, hakket
- 250 g maiskorn
- 4 dl grønnsaksbuljong, varm
- 2,5 dl Oatly iMat havrefløte
- salt og nymalt hvit pepper
- 1/2 pakke bacon,
- litt ruccola eller bladpersille

Varm opp oljen og fres løk og paprika i en romslig gryte uten at det tar farge. Ha i mais og hell i varm buljong. La det småkoke i 5 minutter. Bruk gjerne stavmikser for å få blandingen glatt og jevn. Ha i Oatly iMat havrefløte og smak til med salt og pepper. La alt bli varmt. Stek bacon sprøtt i en stekepanne og strø bacon og ruccola/bladpersille over suppen. Serveres med ristet, glutenfritt brød.

Tomatsuppe med solsikkepesto

<u>Tomatsuppe</u>

- 1 gul løk, skåret i små biter
- 3 hvitløksbåter, skåret i små biter
- 1 ss olivenolje

- 1 boks plommetomater
- 5 dl vann
- 2 ss kylling eller grønnsaksfond/buljong (sjekk at den er glutenfri)
- 1 krm salt
- 2 krm nymalt svart pepper
- 1 ts tørket basilikum
- Evt. 1 ts sukker
- 1 dl Oatly iMat havrefløte

Solsikkepesto

- 0,75 dl tørristede solsikkefrø
- 1 hvitløksbåt
- 1 potte fersk basilikum
- 1 dl olivenolje
- 0,5 ts fingersalt
- 1 krm nymalt svart pepper

Pesto: Miks tørristede solsikkefrø med de øvrige ingrediensene med en stavmikser.

Suppe: Fres løk og hvitløk i olje i en gryte. Tilsett tomatene, vann og grønnsaks- eller kyllingfond. Krydre med salt, pepper, basilikum og evt sukker (kommer an på hvor søte tomatene er). La småkoke i 15 min under lokk. Trykk på tomatene med en sleiv, slik at de sprekker. Gjør suppen glatt med stavmikseren, ha i litt fløte. Kok noen minutter og smak til. Ha suppen i skåler, ringle i pesto. Alternativt kan suppen serveres med glutenfri makaroni og/eller ristet, glutenfritt brød.

Kyllingsalat

- 1 avokado
- 1 pk ruccola
- 1 pk cherrytomater
- 1 stk kyllingbryst
- ½ - 1 rødløk
- Kokt ris/glutenfri makaroni/pasta

Forvarm ovnen til 180°C. Brun kyllingbryst på skinnsiden i varm stekepanne med olje til det er gyllent. Ha på salt og nykvernet sort pepper. Stek fileten videre i ovn i ca. 15 minutter. La kyllingen hvile i 5 minutter før servering. Vask salaten. Skjær avokado i skiver og del cherrytomater i to. Finhakk løk og bland det med salaten. Smak til med salt og nykvernet pepper. Kutt opp kyllingen og ha i salaten. Server med kokt ris/glutenfri pasta.

Ovnsbakt kyllingfilet i bacon – 4 porsjoner

- 4 stk kyllingfilet
- 1 pk bacon
- 4 stk potet
- 4 stk rødbete
- 4 stk gulrot
- 2 stk pastinakk
- Olje, salt og pepper

Stek kyllingfiletene et par minutter i stekepannen slik at den får noe stekeskorpe. Legg deretter kyllingfiletene innsurret i bacon i en ildfast form. Skrell potet, rødbeter, gulrøtter og pastinakk og del dem i biter. Legg bitene i en ildfast form og dryss med salt, pepper og olje. Bak grønnsakene og kyllingen i hver sin form i ovnen. Grønnsakene skal stå i ca. 20 minutter og kyllingen i ca. 30 minutter, begge deler ved 200 °C.

Hjemmelagde hamburgere

- 400g karbonadedeig
- 3/4 ts salt
- 3/4 ts finmalt pepper
- Tørket oregano
- Smør til steking (Soft blå)
- Glutenfrie hamburgerbrød fra Brisk/Fria
- Bacon
- Isbergsalat, agurk, tomat, løk, champinjong

Ha karbonadedeigen i en bolle sammen med krydderet. Bruk fingrene og bland alt sammen. Fordel deigen i 4 like store biter. Disse 4 deigbitene skal nå formes til stekeklare burgere, her er en enkel måte å gjøre dette på: Legg bakepapir på ei fjøl. Væt fingrene før du former en av deigene til en rund ball. Legg ballen på bakepapiret og press ned med håndflatene til denne er ca. 0,5 – 1 cm tykk. Gjenta samme prosedyre for de 3 andre deigene (væt hendene på nytt hver gang). Stek begge sider kjapt på høy temperatur i en stekepanne. Senk temperaturen og etterstek noen minutter på hver side til kjøttet er gjennomstekt. Legges på forvarmede, glutenfrie hamburgerbrød. Forslag til garnityr er bacon, løk, salat, agurk, tomat, sylteagurk.

Smoothie 1

- 3 dl appelsinjuice
- 1 avokado
- 1 kiwi
- 200g frossen mango
- Litt sitronsaft

Smoothie 2

- 1 banan
- 200 g blåbær (frosne, evt. frosne skogsbær)
- 3 dl appelsinjuice

Grønnkålsalat med quinoa, søtpoptet & eple

- 3 dl tørr quinoa
- 200 g grønnkål (5 store blader)
- 2 røde epler (gjerne crispy pink lady)
- 2 søtpoteter
- Olivenolje

Dressing:

- saften av 1/2 sitron
- 2 ss dijonsennep
- 2 ss rødvinseddik
- 4 ss olivenolje
- 1 ts honning
- salt + pepper

Kok quinoa etter anvisning på pakken, 1 del quinoa til 2 deler vann. Skrell søtpotet og skjær dem i små terninger. Ovnsbak søtpotet med et dryss av olivenolje, salt og pepper i ca 20 min, til bitene er møre. Finkakk grønnkål, og skjær eplene i tynne skiver. Bland sammen alle ingrediensene til dressingen. Vend sammen quinoa, grønnkål, eplebiter og ovnsbakt søtpotet i en stor bolle, og vend tilslutt dressingen godt inn i salaten.

Appendix 9: Compliance questionnaire 3 weeks

Overholdelse av eliminasjonsdietten 3 uker ut i diettbehandlingen

Vennligst sett strek på tvers eller kryss tydelig av.

Har du fulgt dietten de siste 3 ukene?

- O Ja
- O Delvis
- O Bare enkelte dager
- O Nei

Hvordan synes du det var å følge dietten:

Kjempelett Veldig utfordrende

0% ——————————————————— 100%

Hvor nøye har du fulgt eliminasjonsdietten gjennom de siste 3 ukene?

Ikke fulgt den i det hele tatt Kun spist etter dietten

0% ——————————————————— 100%

Hvor fornøyd er du med eliminasjonsdietten som symptomlindring?

Svært misfornøyd Svært fornøyd

0% 100%

Hvis du er misfornøyd med dietten, hvorfor:

- O For tidkrevende
- O Savner for mange matvarer
- O Opplever ingen bedring
- O For dyrt
- O Dietten er kjedelig mtp. smak/variasjon e.l.
- O Jeg er ikke spesielt misfornøyd med dietten

Hvor ofte hadde du avvik fra dietten i løpet av de 3 ukene:

- O Ingen ganger
- O 1-2 ganger i løpet av de 3 ukene
- O 1-2 ganger i uken
- O 3 eller flere ganger i uken

Hva slags type matvarer inntok du ved avvik fra dietten?

- O Jeg hadde ingen avvik fra dietten
- O Melk
- O Egg
- O Hvete/gluten
- O Fisk/skalldyr
- O Soya
- O Peanøtter/nøtter

Hvorfor spiste du mat som ikke inngår i eliminasjonsdietten:

- O Fulgt kun eliminasjonsdietten
- O Visste ikke at maten inneholdt en av de eliminerte matvarene
- O Ikke tilgang på maten som inngår i eliminasjonsdietten på restaurant/gatekjøkken
- O For tidkrevende å lage mat etter eliminasjonsdietten
- O Merket ikke noe effekt av dietten og dermed stoppet jeg
- O Hadde lyst på matvarer som ikke inngår i eliminasjonsdietten
- O Eliminasjonsdiett-maten var for dyr

Hvor lenge gikk du på dietten før du spiste matvarer som ikke inngår i dietten:

- O Jeg gikk på dietten hele tiden
- O Ingen dager
- O 1-3 dager
- O 4-7 dager
- O 2-3 uker

Hvor fornøyd er du med informasjonen du fikk om dietten:

- O Meget misfornøyd
- O Misfornøyd
- O Ok
- O Fornøyd
- O Meget fornøyd

Appendix 10: Compliance questionnaire 6 weeks

Overholdelse av eliminasjonsdietten etter 6 uker

Vennligst sett strek på tvers eller kryss tydelig av.

Har du fulgt dietten de siste 6 ukene?

- O Ja
- O Delvis
- O Bare enkelte dager
- O Nei

Hvordan synes du det var å følge dietten:

Kjempelett Meget vanskelig

0% _____ 100%

Hvor nøye har du fulgt eliminasjonsdietten gjennom de siste 6 ukene?

Ikke fulgt den i det hele tatt Kun spist etter dietten

0% _____ 100%

Hvor fornøyd er du med eliminasjonsdietten som symptomlindring?

Svært misfornøyd Svært fornøyd

0% 100%

Hvis du er misfornøyd med dietten, hvorfor:

- O For tidkrevende
- O Savner for mange matvarer
- O Opplever ingen bedring
- O For dyrt
- O Dietten er kjedelig mtp. smak/variasjon e.l.
- O Jeg er ikke spesielt misfornøyd med dietten

Hvor ofte hadde du avvik fra dietten løpet av de siste 6 ukene:

- O Ingen ganger
- O 1-5 ganger i løpet av de 6 ukene
- O 1-2 ganger i uken
- O 3 eller flere ganger i uken

Hva slags type matvarer inntok du ved avvik fra dietten?

- O Jeg hadde ingen avvik fra dietten
- O Melk
- O Egg
- O Hvete/gluten
- O Fisk/skalldyr
- O Soya
- O Peanøtter/nøtter

Hvorfor spiste du mat som ikke inngår i eliminasjonsdietten:

- O Fulgt kun eliminasjonsdietten

- O Visste ikke at maten inneholdt en av de eliminerte matvarene
- O Ikke tilgang på maten som inngår i eliminasjonsdietten på restaurant/gatekjøkken
- O For tidkrevende å lage mat etter eliminasjonsdietten
- O Merket ikke noe effekt av dietten og dermed stoppet jeg
- O Hadde lyst på matvarer som ikke inngår i eliminasjonsdietten
- O Eliminasjonsdiett-maten var for dyr

Hvor lenge gikk du på dietten før du spiste matvarer som ikke inngår i dietten:

- O Jeg gikk på dietten hele tiden
- O Ingen dager
- O 1-3 dager
- O 4-7 dager
- O 2-3 uker
- O 3-4 uker
- O 5-6 uker

Hvor fornøyd er du med informasjonen du fikk om dietten:

- O Meget misfornøyd
- O Misfornøyd
- O Ok
- O Fornøyd
- O Meget fornøyd

Appendix 11: The Chicago Classification of esophageal motility version 3.0. Reused with permission from John Wiley and Sons.

ACHALASIA and EGJ OUTFLOW OBSTRUCTION	**CRITERIA**
Type I achalasia (classic achalasia)	Elevated median IRP (>15 mmHg[‡]), 100% failed peristalsis
	(DCI <100 mmHg)
	Premature contractions with DCI values less than 450 mmHg·s·cm *satisfy criteria for failed peristalsis*
Type II achalasia (with esophageal compression)	Elevated median IRP (>15 mmHg[‡]), 100% failed peristalsis, panesophageal pressurization with ≥20% of swallows
	Contractions may be masked by esophageal pressurization and DCI should not be calculated
Type III achalasia (spastic achalasia)	Elevated median IRP (>15 mmHg[‡]), no normal peristalsis, premature (spastic) contractions with DCI >450 mmHg·s·cm with ≥20% of swallows
	May be mixed with panesophageal pressurization
EGJ outflow obstruction	Elevated median IRP (>15 mmHg[‡]), sufficient evidence of peristalsis such that criteria for types I-III achalasia are not met[*]
MAJOR DISORDERS of PERISTALSIS	*(Not encountered in normal subjects)*
Absent contractility	Normal median IRP, 100% failed peristalsis
	Achalasia should be considered when IRP values are borderline and when there is evidence of esophageal pressurization
	Premature contractions with DCI values less than 450 mmHg·s·cm *meet criteria for failed peristalsis*
Distal esophageal spasm	Normal median IRP, ≥20% premature contractions with DCI >450 mmHg·s·cm [†]. Some normal peristalsis may be present.
Hypercontractile esophagus (jackhammer)	At least two swallows with DCI >8,000 mmHg·s·cm [†§]
	Hypercontractility may involve, or even be localized to, the LES
MINOR DISORDERS OF PERISTALSIS	*(Characterized by contractile vigor and contraction pattern)*
Ineffective esophageal motility (IEM)	≥50% ineffective swallows
	Ineffective swallows can be failed or weak (DCI<450 mmHg·s·cm)
	Multiple repetitive swallow assessment may be helpful in determining peristaltic reserve
Fragmented peristalsis	≥50% fragmented contractions with DCI > 450 mmHg·s·cm

NORMAL ESOPHAGEAL MOTILITY	Not fulfilling any of the above classifications

[†]Cutoff value dependent on the manometric hardware; this is the cutoff for the Sierra device

[*]Potential etiologies: early achalasia, mechanical obstruction, esophageal wall stiffness, or manifestation of hiatal hernia

[§]Hypercontractile esophagus can be a manifestation of outflow obstruction as evident by instances in which it occurs in association with an IRP greater than the upper limit of normal