Oligo-Antigenic Diet in the Treatment of Chronic Anal Fissures. Evidence for a Relationship Between Food Hypersensitivity and Anal Fissures

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OBJECTIVES: **Patients with chronic constipation due to food hypersensitivity (FH) had an elevated anal sphincter resting pressure. No studies have investigated a possible role of FH in anal fissures (AFs). We aimed to evaluate (1) the effectiveness of diet in curing AFs and to evaluate (2) the clinical effects of a double-blind placebo-controlled (DBPC) challenge, using cow's milk protein or wheat.**

METHODS: **One hundred and sixty-one patients with AFs were randomized to receive a "true-elimination diet" or a "sham-elimination diet" for 8 weeks; both groups also received topical nifedipine and lidocaine. Sixty patients who were cured with the "true-elimination diet" underwent DBPC challenge in which cow's milk and wheat were used.**

RESULTS: **At the end of the study, 69% of the "true-diet group" and 45% of the "sham-diet group" showed complete healing of AFs ($P<0.0002$). Thirteen of the 60 patients had AF recurrence during the 2-week cow's milk DBPC challenge and 7 patients had AF recurrence on wheat challenge. At the end of the challenge, anal sphincter resting pressure significantly increased in the patients who showed AF reappearance ($P<0.0001$), compared with the baseline values. The patients who reacted to the challenges had a significantly higher number of eosinophils in the lamina propria and intraepithelial lymphocytes than those who did not react to the challenges.**

CONCLUSIONS: **An oligo-antigenic diet combined with medical treatment improved the rate of chronic AF healing. In more than 20% of the patients receiving medical and dietary treatment, AFs recurred on DBPC food challenge.**

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INTRODUCTION

It has been reported that anal fissure (AF) is present in about 10–15% of proctologic patients (1). The clinical hallmark of AF is pain during and after defecation; rectal bleeding is very often present as fresh red blood seen on the toilet tissue.

Treatment of AF consists of a trial of fiber supplementation, increased volume of daily drinks, sitz baths, and topical analgesics (2); however, most patients remain symptomatic after this treatment and, consequently, surgery is performed, usually a lateral internal sphincterotomy (3). It has been demonstrated that resting anal pressure is elevated in fissure patients (4–6) and this could therefore diminish perfusion pressure to the anal tissue and lead to ischemic ulceration. For these reasons, a number of novel, nonsurgical therapeutic options have been used successfully (2,6,7), including glyceryl trinitrate (8), diltiazem (9), nifedipine (10), and botulin toxin (11), as well as other drugs.

In previous works, we have demonstrated that chronic constipation in children can be due to food hypersensitivity (FH) (12–14), and this has also been demonstrated in a few adult cases (15). One of the pathological mechanisms of constipation due to FH is the high resting anal pressure, which normalizes on elimination diet (16,17), thus demonstrating a relationship between the elimination diet and the resting anal pressure.

On this basis, we hypothesized that a percentage of adult patients suffering from AF, including both subjects with constipation and those with normal bowel habit or diarrhea, could have

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a high resting anal pressure due to an unrecognized FH, and this study was designed to evaluate this hypothesis. The aims of the present study were (1) to evaluate the effectiveness of an oligoantigenic diet in the treatment of chronic AFs (CAFs) and (2) to search for a possible cause–effect relationship between the diet and the onset of the AF.

METHODS

We enrolled consecutive adult patients with CAF, who were referred to the Surgical Department at the University of Palermo, between January 2003 and July 2005. In this way, 223 patients were initially examined as outpatients.

CAF was defined as a fissure that was persistent for more than 6 weeks, with visible transverse internal anal sphincter fibers at the bases of the fissure and indurate edges.

Inclusion criteria were evidence of CAF evaluated by an experienced rectal surgeon and patients aged >16 years. Exclusion criteria were a diagnosis of inflammatory bowel disease, previous anal surgery or trauma, celiac disease or lactose intolerance, an ongoing steroid treatment performed for any reason, an exclusion diet followed for any reason, and pregnancy. An ileum colonscopy was performed on all subjects to exclude an inflammatory bowel disease; the H2-breath test after 50 g of oral lactose load was also performed to exclude lactose intolerance.

At the time of the first evaluation, a detailed clinical history with particular attention to the patients' bowel habit was obtained, and routine laboratory tests, immunology tests, rectal biopsies, and anal–rectal manometry were performed. During a 2-week prestudy period, the patients' bowel movements were recorded; constipation was defined as less than three evacuations per week.

Study design

The study has two different parts. *First part*. The aim of the first part of the study was to verify the effectiveness of the oligoantigenic diet in CAF treatment. The end point of this part of the study was the percentage of cured patients who were given an oligoantigenic diet compared with patients who were given a "normal" diet.

For 8 weeks, all patients received a treatment with sitz baths and bran supplementation (20 g of unprocessed bran daily), plus topical application of nifedipine 0.3% and lidocaine 1.5% cream three times daily. No other medications for the anal pain were allowed. Furthermore, patients were assigned randomly, and with a double-blind method, to one of the two dietary treatment groups: Group A was treated with a "sham diet" based on the elimination of rice, potato, lamb, bean, and peas; Group B received a "true-elimination diet" based on the elimination of cow's milk and its derivatives, wheat, egg, tomato, and chocolate. These elimination diets were arbitrarily chosen on the basis of our previous experience (14,18,19), as the foods eliminated in Group A were almost always tolerated, whereas the foods eliminated in Group B were those that most frequently caused symptoms in subjects with chronic constipation due to FH. The patients kept a dietary diary, and adherence to the elimination diet was evaluated by trained dieticians.

During the study period, the patients were evaluated every 2 weeks for CAF persistence or healing, by three authors unaware of the kind of diet they were undergoing; anal pain was scored on a visual analog scale ranging from 0 (absence of pain) to 10 (intolerable pain). Furthermore, the number of bowel movements per week was recorded. Lateral internal sphincterotomy was offered to all patients who were not cured by medical treatment.

Second part. The aim of the second part of the study was to search for a possible cause–effect relationship between the diet and the onset of the AF. The end point of this part of the study was to verify whether the cow's milk proteins and/or the flour, administered according to a double-blind method, could cause AF recurrence.

At the end of the treatment period, the untreated patients of Group A ("sham diet") were offered the "true diet" for 8 weeks, before potential surgery. Those who accepted and were treated with this regimen, and all the patients of Group B, who were cured after receiving the "true elimination diet," underwent double-blind placebo-controlled (DBPC) challenges for cow's milk and for wheat. During this period, the patients continued to avoid wheat, cow's milk, egg, tomato, and chocolate. The cow's milk challenge was performed before or after the wheat challenge, after randomization. DBPC for cow's milk was performed by administering capsules coded as A or B, containing milk proteins (casein from bovine milk, lactoalbumin, and lactoglobulin—daily dose 6 g, equal to about 200 ml of cow's milk) or xylose, respectively. Six capsules were given daily, which were subdivided three times daily, but not with meals.

DBPC for wheat protein was performed with capsules coded as C or D, containing flour (daily dose 12 g) or xylose, respectively. A total of 12 capsules were given daily, which were subdivided three times daily, but not with meals. Capsules A or B were given for 2 consecutive weeks, and then after 4 weeks of washout the patients received the other capsules for another 2 weeks. After 4 weeks of washout, capsules C or D were given for 2 consecutive weeks, then after another 4 weeks of washout the patients received the other capsules for 2 weeks.

FH diagnoses were based exclusively on the reappearance of painful defecation and AFs on food challenge, and its subsequent disappearance on an elimination diet. Anal–rectal manometry was repeated, both before and on the last day of the cow's milk protein challenge period.

At least 8 weeks after the DBPC challenge periods, open oral-food challenges were performed by reintroducing egg, tomato, and chocolate; these foods were reintroduced singly every 2 weeks.

All patients were invited to continue the follow-up, with regular visits every 6 months for 4 years. **Figure 1** shows the two parts of the study design.

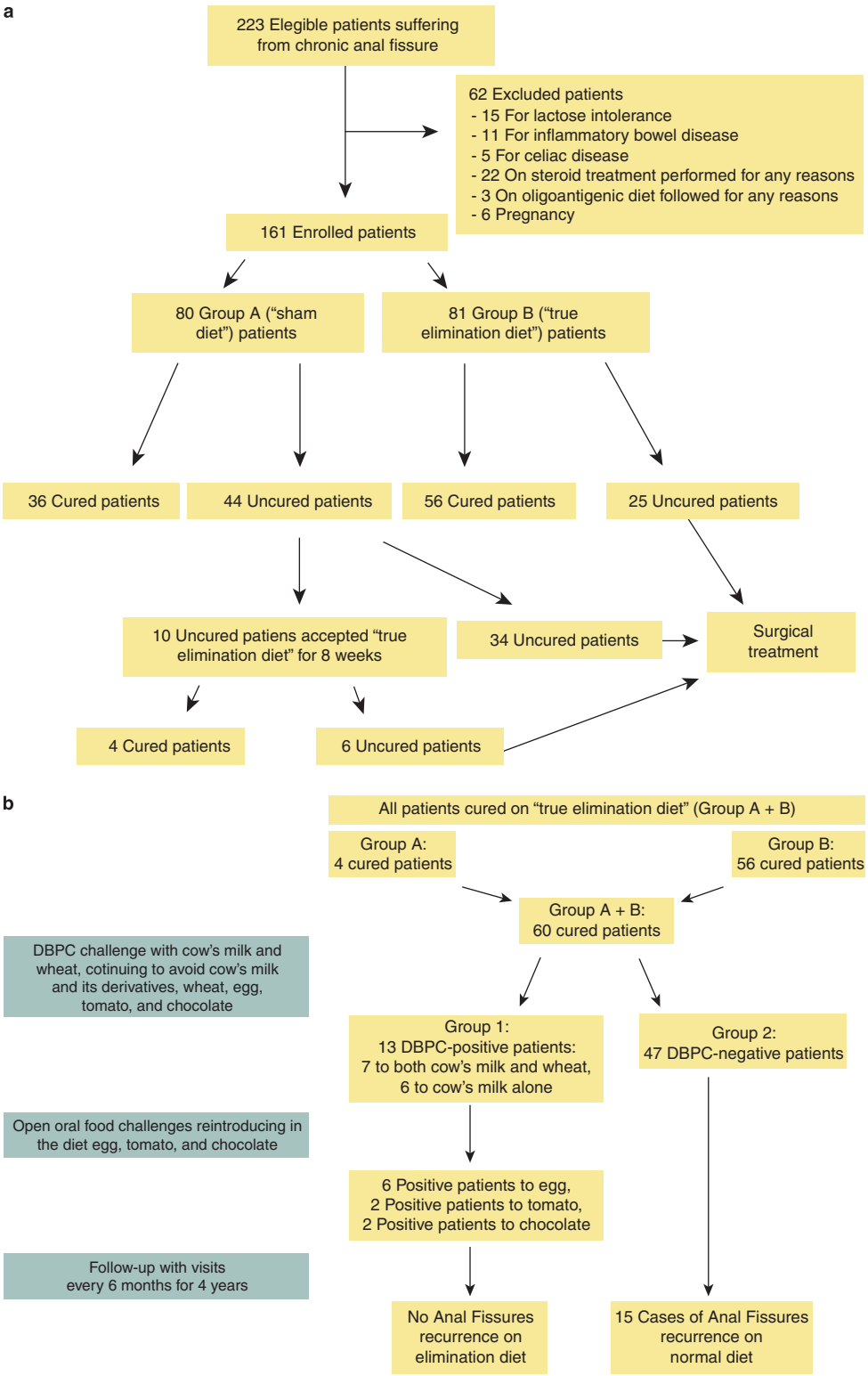

Figure 1. Study design and main results of the first and second part of the study.

Anal–rectal manometry

Manometry was performed with bowel preparation, when required, using an open perfuse catheter; sedation was not necessary. The catheter had a 4.8-mm external diameter and three radial ways with bearing point. It was supplied with water by a nitrogen infusion pump, and rectal distension was produced

with a compliant, distending rectal balloon attached to the end of the catheter. Data were recorded by an autocalibrating polygraph (Narco Bio System MMS 200) connected to a computer with dedicated software for automatic analysis of the acquired data. In all patients, data recording was begun 5–10 min after catheter positioning. Anal sphincter resting pressure was measured at the end of the manometry procedure and was calculated as the mean of a 3-min period.

According to the reference values of our laboratory, derived from anal–rectal manometry data in healthy subjects, anal sphincter resting pressure between 45 and 70 mm Hg was considered normal. The medical staffs who performed the anal–rectal manometry were unaware of the clinical and laboratory data of the patients, including the response to the elimination diet, histology data, and the immunology study.

Histology study

All patients underwent rectoscopy with random biopsies. Endoscopy and histology methods have been described previously (14). Three to five biopsies were taken. Intraepithelial lymphocytes (normal limit in our laboratory: <70 lymphocytes/10 high-power field ×40) and eosinophil infiltration of the lamina propria (normal limit in our laboratory <60 eosinophils/10 high-power field ×40) were evaluated.

Statistical analysis

Statistical analysis was carried out using the χ^2-test for clinical outcomes; the Mann–Whitney test for intergroup comparison and the Wilcoxon test for intragroup comparison were used for data showing a nonGaussian distribution. To determine the advantage of "true-elimination diet" over "sham diet" in CAF treatment in the first part of the study, power calculation was made based on 80% power and a significance level of $P<0.05$, assuming a success rate in "true-elimination diet" and "sham diet" of 80% and 55%, respectively. A P-value of less than 0.05 was considered statistically significant.

The study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association Declaration of Helsinki 1989) and Good Clinical Practice (European Agency for the Evaluation of Medicinal Products 2002). The Ethics Committee of the University Hospital of Palermo approved the study, and all patients gave their informed consent to participate.

RESULTS

First part of the study

One hundred and sixty one patients were included and randomized to one of the treatment groups and 62 patients were excluded (**Figure 1a**). **Table 1** shows the characteristics of the patients of each group; constipation was very frequent in both groups. Hemoglobin levels, white blood cell count, serum C reactive protein, and erythrocyte sedimentation rate were normal in all patients. The evaluation of the dietary diary showed a full adherence to the elimination diet in both groups.

Table 1. Patient characteristics in Group A (sham-elimination diet) and in Group B (true-elimination diet)

	Group A (*n*=80)	Group B (*n*=81)	*P* value
Age (median and range)	38 years (18–52)	36 years (18–54)	Not significant
Sex	30 M/50 F	28 M/53 F	Not significant
Symptom duration (median and range in months)	12 (8–24)	12.5 (7–28)	Not significant
Pain score (VAS)	7.2±2.4	6.9±2.3	Not significant
Bleeding	60 (75%)	57 (70%)	Not significant
Site of fissure			
Posterior midline	72 (90%)	74 (92%)	Not significant
Anterior midline	8 (10%)	7 (8%)	
Mean (±s.d.) anal sphincter resting pressure (mm Hg)	88±10	90±11	Not significant
Coexistent constipation (number of cases)	70 (87%)	68 (84%)	Not significant
Coexistent hemorroids and/or rectal prolapse	45 (56%)	50 (62%)	Not significant
Multiparity	25	26	Not significant
Rectal histology			
Median (range) IEL number	30 (10–120)	33 (10–100)	Not significant
Median (range) lamina propria eosinophils number	20 (11–90)	22 (10–85)	Not significant
Immunology data			
Number of patients with positive-specific IgE	4 (5%)	6 (7%)	Not significant

F, female; IEL, intraepithelial lymphocyte; IgE, immunaglobin E; M, male; VAS, visual analog score.

Notes: Constipation was defined as the presence of two or more of the following: (a) straining during defecations, (b) lumpy or hard stools, (c) sensation of incomplete evacuation, (d) < 3 evacuations per week.

Intraepithelial lymphocytes and lamina propria eosinophils were counted in 10 high-power field—40× (IEL normal limits <70 lymphocites; eosinophil normal limit <60). Normal limits for anal sphincter resting pressure were between 45 and 70 mm Hg.

After beginning the medical and dietary treatments, the patients receiving the "true-elimination diet" (Group B) showed a significantly higher rate of CAF healing than those receiving the "sham diet" (Group A) from the fourth week of treatment. At the end of the study, 69% of Group B and 45% of Group A patients showed complete healing of CAF ($P=0.0002$; **Table 2**). Furthermore, patients receiving the "true diet" showed a significantly higher number of evacuations per week than those receiving the "sham diet" from the fourth to eighth week of treatment. The evaluation of the dietary diary showed patients' compliance to the diet in both groups.

The 44 uncured patients of Group A, who had received the "sham-elimination diet," were offered the treatment option of

Table 2. Part 1 of the Study

	Cured at 2 weeks	Cured at 4 weeks	Cured at 6 weeks	Cured at 8 weeks
Group A	5/80 (6%)	24/80 (30%)	30/80 (37%)	36/80 (45%)
Group B	12/81 (15%)	42/81 (52%)	49/81 (60%)	56/81 (69%)
χ^2 and	2.4	7	8.5	9.5
P value	0.12	0.01	0.003	0.003
	Pain score at 2 weeks	**Pain score at 4 weeks**	**Pain score at 6 weeks**	**Pain score at 8 weeks**
Group A	5.1±3.5	4.8±3.4	4.4±3.2	3.6±3.4
Group B	4.2±4.0	3.4±3.1	3.0±3.1	2.4±3.3
P value	Not significant	0.004	0.008	0.04
	Bowel movements per week at 2 weeks	**Bowel movements per week at 4 weeks**	**Bowel movements per week at 6 weeks**	**Bowel movements per week at 8 weeks**
Group A	2.0±1.5	3.0±2.0	3.3±1.9	3.6±1.8
Group B	2.4±1.5	3.86±1.6	4.21±1.3	4.55±0.8
P value	Not significant	0.005	0.001	0.0001

CAF, chronic and fissure; VAS, visual analog score.
Number and percentage of patients cured (complete healing of CAF), pain score on VAS (mean±s.d.), and number of bowel movements per week (mean±s.d.), during medical and dietary treatment, in Group A (n=80) receiving the "sham diet" and in Group B (n=81) receiving the "true diet".
Note: The number of bowel movements of each patient was recorded every week.

the "true-elimination diet" before undergoing surgery; 10 of them accepted and 34 refused. Of the former 10 patients, 4 showed complete CAF healing within 8 weeks of dietary treatment.

In summary, 65 of the 161 (40%) patients remained uncured at the end of the study and underwent surgery treatment (a lateral internal sphincterotomy).

Second part of the study

Sixty patients participated in this part of the study: 56 with healed CAF on true elimination diet (Group B), plus 4 patients of Group A, who had the "true-elimination diet" at the end of the first part of the study (**Figure 1b**). The subjects consisted of 24 men and 36 women, median age 35 years (range 18–50 years). They continued on elimination diet and did not receive any medical treatment for CAF during this part of the study. Twenty-eight subjects were randomized to the cow's milk challenge first and 32 subjects to the wheat challenge.

Seven patients were positive for both cow's milk and wheat protein challenges, and six were positive only for cow's milk challenge. In total, 13 patients were positive for DBPC food challenges.

In all the patients positive for the cow's milk DBPC challenge, painful defecation reappeared after a median period of 4 days (range 1–8 days), after commencing the challenge with cow's milk or wheat proteins. AFs reappeared in all 13 patients within the 2-week challenge periods: median time 8 days. Ten of these 13 patients did not complete the cow's milk challenge period with the "active food" because of AF recurrence. None of these patients reacted on placebo administration. An identical clinical reaction was seen during the wheat challenge in the seven patients who reacted to the wheat, and four of them did not complete the challenge with the "active food" because of AF recurrence.

During the 4-week washout periods, between the administration of capsules A or B, or between capsules C or D, all patients became asymptomatic again; they underwent the same medical and dietary treatment—with the "true oligo-antigenic diet"—described for the first part of the study. AFs disappeared in all patients and defecation was painless. Similarly, it also happened between cow's milk and wheat challenges.

Figure 2 shows the mean visual analog score of painful defecation before and during the 2-week period of the cow's milk challenge. From the first week, the patients who reacted to the challenge showed a significantly higher visual analog score than the patients who did not react to the challenge.

Table 3 shows the anal sphincter resting pressure, before and at the end of the cow's milk challenge, and the rectal mucosa histology data. At the end of the challenge, anal sphincter resting pressure significantly increased in the patients who showed AF reappearance ($P<0.0001$; Wilcoxon's rank sum test), compared with the baseline values, whereas no difference was observed in the patients who did not react to the challenge.

Regarding the rectal mucosa histology, the evaluation performed at the time of entry (first part of the study) showed that the patients who reacted to the challenges had a significantly higher number of eosinophils in the lamina propria ($z=17.7$, $P<0.0001$, Mann–Whitney's test) and intraepithelial lymphocytes ($z=23.1$,

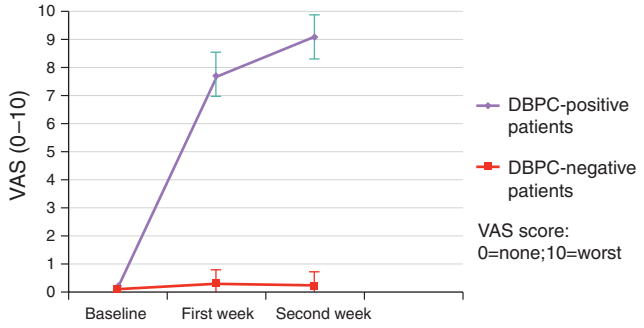

Figure 2. Visual analog score (VAS) values (mean+s.d.) of pain on defecation on cow's milk double-blind placebo controlled (DBPC) challenge in 13 patients positive to the challenge (Group A) and in 47 negative to the challenge (Group B).

Table 3. Part 2 of the study

	Group 1, *N*=13	Group 2, *N*=47	*P* value
Anal sphincter resting pressure (mm Hg)			
Before challenge	82±7	80±8	Not significant
At the end of challenge	99±5	83±7	0.0001
Rectal histology			
IEL number	70 (40–120)	30 (10–90)	0.0001
Lamina propria Eosinophil number	50 (10–90)	20 (10–80)	0.0001

CAF, chronic and fissure; VAS, visual analog score.

Mean values (±s.d.) of anal sphincter resting pressure before CM challenge and at the end of the challenge. Median and range values of lamina propria eosinophils and IEL in the rectal mucosa. Group 1 consisted of patients who became symptomatic (recurrence of anal fissures) on challenge. Group 2 consisted of patients who remained asymptomatic on challenge.

Notes: Anal sphincter resting pressure was recorded the day before the beginning of the cow's milk protein challenge, when all patients were asymptomatic and had no anal fissure, and was reevaluated at the end of the cow's milk challenge.

Normal limits for anal sphincter resting pressure were between 45 and 70 mm Hg. Rectal histology was evaluated at entry to the first part of the study, when all patients were symptomatic and had CAF. Intraepithelial lymphocytes and lamina propria eosinophils were counted in 10 high-power field—HPF×40 (IEL normal limits <70 lymphocytes; eosiniphil normal limit<60).

$P<0.0001$, Mann–Whitney's test) than those who did not react to the challenges. Specific IgE for food antigens were found elevated at the time of entry (first part of the study) in 2 of the patients who reacted positively to the challenges (2/13, 15%) and in 2 of the patients who did not react (2/47, 4%; not significant).

The 13 patients with positive DBPC challenges to cow's milk and/or wheat proteins were diagnosed with FH. In these patients, open challenges showed hypersensitivity to other foods: egg (six cases), tomato (two cases), and chocolate (two cases); the ingestion of these foods caused painful defecation and the appearance of AF.

Out of the whole group of 161 patients with CAF, 13 subjects (8%) had a final diagnosis of FH, and in these subjects a causal relationship between FH and CAF was demonstrated. The percentage of FH causing AF, among the patients who received medical treatment plus elimination diet, was 22% (13/60 patients).

During the 4-year follow-up period, all patients with AF due to FH continued to consume an elimination diet, and none of these 13 patients experienced recurrence of AF. Among the other 47 patients who suffered from AF, which was not due to FH, there were 15 cases of AF recurrence (32%; $P<0.05$).

Among the 65 patients who underwent surgery, there were six cases of AF recurrence (9%) and five cases of incontinence (7%).

DISCUSSION

In previous studies, we demonstrated that FH could cause chronic constipation in children and adults (12,13,15). In these patients, the anal resting pressure is higher than in subjects with chronic constipation, which was not due to FH, and it became normal on oligo-antigenic diet (16). Borrelli *et al.* (17) demonstrated that mast cell density in the rectal mucosa correlates with anal motor abnormalities and the diet positively influenced this aspect.

On this basis, we designed this DBPC prospective study in adults with CAFs, as it is known that an elevated anal resting pressure in fissure patients can diminish perfusion pressure to the anal tissue and lead to ischemic ulceration (4–6).

We tested the hypothesis that a "true oligo-antigenic diet"—with the elimination of cow's milk and its derivatives, wheat, egg, tomato, and chocolate from the diet—improves the rate of CAF healing compared with a "sham-elimination diet" (both diets combined with standard medical treatment). Our results showed that the patient group on "true-elimination diet" had a significantly higher rate of CAF healing from the fourth week of treatment (52% vs. 30%), and at the end of the 8 weeks of study they had a frequency of cured fissures of 69% vs. 45% in the group of the patients treated with a "sham diet." Pain score on defecation was also significantly lower from the fourth week in the patients on "true-elimination diet" than in the controls on "sham diet."

However, it must be noted that the percentage of healed AFs on glycerol nitrate treatment reported in the literature (24–90%) (2) is consistent with the frequency of cured patients we observed in our study groups.

In the second part of the study, we attempted to demonstrate a causal effect of FH on the appearance of AF and on anal resting pressure. Of the 60 patients who received standard medical treatment plus "true-elimination diet," 13 showed AF recurrence and severe pain on defecation on cow's milk challenge. Painful defecation reappeared very quickly—between 1 and 8 days after the beginning of the challenge—and AF recurrence prevented the conclusion of the 2-week challenge in 10 patients; all 13 patients showed AFs at the end of the challenge. After adequate medical and dietary treatment, none of these patients reacted to

the placebo administration. An identical reaction to the challenge was recorded in the seven patients who were positive to the wheat challenge, as regards the time and the severity of the clinical reaction.

During the cow's milk challenge, anal sphincter resting pressure significantly increased from 82 to 99 mm Hg in all patients who reacted with AF recurrence, whereas no significant changes were observed in those who did not react to the challenge. At the end of the challenge period, the anal resting pressure was significantly higher in patients who were positive to the challenge than in those who were negative.

The patients who were positive to the challenges showed significantly higher inflammatory infiltration in the rectal mucosa than the patients who were negative to the challenges. Both intraepithelial lymphocytes and lamina propria eosinophils were significantly higher in patients who reacted, and about half of these subjects had lymphocyte and eosinophil values above the normal limits for our laboratory. These findings are in agreement with the data recorded in patients with irritable bowel syndrome where immune cell infiltration and activation is considered a pivotal mechanism of dismotility (20,21). Future studies should clarify whether the rectal mucosa histology evaluation—establishing a threshold of inflammatory cell number—could be useful in identifying the patients with AFs, who would benefit from the elimination diet or not.

There are a number of limitations in our study. First, the choice of the foods to avoid in the elimination diet was arbitrary. We based the diets—"true diet" and "sham diet"—on our previous experience; for several decades we have studied FH and applied this experience in this study design. However, it is probable that we underestimated the number of the patients with AF due to FB, as many offending foods could not be excluded in the elimination diet prescribed to the patients. Furthermore, all patients received bran and it can contain gluten; this could determine symptoms in gluten-sensitive patients. On the other hand, it is possible that the patients we studied were preselected by their physicians who referred them to the Surgery Department that collaborated with us, a center with experience in FH. This possible selection bias could have increased the percentage of AFs due to FH. Consequently, our data do not offer a definitive conclusion about the real frequency of AF due to FH.

It is noteworthy that in our study a high percentage of the patients suffered from constipation; although constipation is commonly associated to AFs, other studies have reported a lower frequency of constipation in subjects with AFs (22,23).

We have not provided evidence of an allergic mechanism in the pathogenesis of AFs in the patients we studied, and alternative hypotheses should be considered. It has been demonstrated that the fat content in milk decreased the levels of circulating motilin and ghrelin, consequently inducing constipation (24); this could contribute to the appearance of AFs. However, it must be said that in our study the challenges were performed with capsules containing exclusively cow's milk proteins and the reaction to the challenge was rapid; this suggests a possible hypersensitivity to cow's milk proteins. Regarding other possible pathogenetic mechanisms, referring to the "gluten-sensitivity field", we would recall that in experimental model gluten was able to determine an increased acetylcholine release from the myenteric plexus and muscle hypercontractility in DQ-8 mice (25).

On the other hand, the IgE-mediated immunologic assays (PRISTs, Skin tests) have a very low accuracy in the diagnosis of most gastrointestinal manifestations due to FH (26), and this can be in keeping with the low rate of positive serum-specific IgE for food antigens that we found in our patients.

Furthermore, we did not provide any data on mast cell infiltration in the rectal mucosa, nor on the interactions between inflammatory and neural cells. It has been demonstrated that mast cells have a fundamental role in children with chronic constipation due to FH (17) and, in general, in colon dismotility (27). However, our data supported the evidence that mucosal inflammation influenced anal resting pressure and underlined a possible role of lymphocytes and eosinophil cells. It is interesting to recall that the fecal excretion of eosinophil cationic protein has recently been suggested as a possible marker of food allergy in patients with irritable bowel syndrome-like symptoms (18), and some experimental data suggest a role for eotaxin—an eosinophil-derived cytokine—in gastrointestinal dismotility (28).

In conclusion, our data demonstrated, for the first time, that an oligo-antigenic diet combined with medical treatment could improve the rate of CAF healing. Moreover, in 20% of the patients who received medical and dietary treatment, AFs recurred on DBPC cow's milk challenge and, to a lesser degree, on wheat challenge. The ingestion of these foods also increased anal resting pressure.

CONFLICT OF INTEREST

Guarantor of the article: Antonio Carroccio, MD.

Specific author contributions: Antonio Carroccio: study design, patient recruitment and follow-up, data collection and interpretation, and writing the manuscript. Pasquale Mansueto and Sebastiano Bonventre: patient recruitment and follow-up, data collection and interpretation, and revising the manuscript. Giuditta Morfino, Alberto D'Alcamo, Valentina Di Paola, and Gregorio Scerrino: patient recruitment and follow-up, data collection, and interpretation. Giuseppe Iacono, Gaspare Gulotta, and GiovamBattista Rini: data interpretation and revising the manuscript. Emiliano Maresi: histology study, data collection, and interpretation. Maurizio Soresi: statistics, data collection, and interpretation.

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Potential competing interests: None.

Disclaimer

The authors declare that they have participated in the study and have seen and approved the final version.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Chronic constipation in children can be due to food hypersensitivity (FH). One of the pathological mechanisms of constipation due to FH is the high resting anal pressure, which normalizes on elimination diet. It has been demonstrated that resting anal pressure is also elevated in patients with anal fissure (AF), and this could therefore diminish perfusion pressure to the anal tissue and lead to ischemic ulceration.
- ✓ We hypothesized that an unrecognized FH could be the cause of AFs in some percentage of the adult cases; therefore, we evaluate the effectiveness of an oligo-antigenic diet in the treatment of chronic AFs (CAFs) and search for a possible cause–effect relationship between the diet and the onset of the AFs.

WHAT IS NEW HERE

- ✓ The patient group that underwent a "true-elimination diet" had a significantly higher rate of CAF healing from the fourth week of treatment and at the end of the 8 weeks of the study, compared with the control patient group treated with a "sham diet." Pain score on defecation was also significantly lower from the fourth week in the patients on "true-elimination diet" than in the patients on "sham diet."
- ✓ About 20% of the patients who received standard medical treatment plus "true-elimination diet," showed AF recurrence and severe pain on defecation on cow's milk challenge. After adequate medical and dietary treatment, none of these patients reacted to the placebo administration. An identical reaction to the challenge was recorded in a lower percentage of the patients who were positive to the wheat challenge.
- ✓ Therefore, our data demonstrated, for the first time, that an oligo-antigenic diet combined with medical treatment can improve the rate of CAF healing; and if AFs might be etiologically related to a FH condition, then it should be studied.

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