Safety of Oats in Children with Celiac Disease: A Double-Blind, Randomized, Placebo-Controlled Trial

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Objective To evaluate the long-term validity and safety of pure oats in the treatment of children with celiac disease.

Study design This noninferiority clinical trial used a double-blind, placebo-controlled, crossover design extended over a 15 months period of time. There were 306 children with a biopsy-proven diagnosis of celiac disease on a gluten-free diet for ≥2 years were randomly assigned to eat specifically prepared gluten-free food containing an age-dependent amount (15-40 g) of either placebo or purified nonreactive varieties of oats for 2 consecutive 6-month periods separated by washout standard gluten-free diet for 3 months. Clinical (body mass index, Gastrointestinal Symptoms Rating Scale score), serologic (IgA antitransglutaminase antibodies, and IgA anti-avenin antibodies) and intestinal permeability data were measured at baseline, and after 6, 9, and 15 months. Direct treatment effect was evaluated by a nonparametric approach using medians (95% CI) as summary statistic.

Results After the exclusion of 129 patients who dropped out, the cohort included 177 children (79 in the oats–placebo and 98 in the placebo–oats group; median, 0.004; 95% CI, −0.0002 to 0.0089). Direct treatment effect was not statistically significant for clinical, serologic, and intestinal permeability variables (body mass index: median, −0.5; 95% CI, −0.12 to 0.00; Gastrointestinal Symptoms Rating Scale score: median, 0; 95% CI, −2.5 to 0.00; IgA antitransglutaminase antibodies: median, −0.02; 95% CI, −0.25 to 0.23; IgA anti-avenin antibodies: median, −0.0002; 95% CI, −0.0007 to 0.0003; intestinal permeability test: median, 0.004; 95% CI, −0.0002 to 0.0089).

Conclusions Pure nonreactive oat products are a safe dietary choice in the treatment of children with celiac disease. *(J Pediatr 2017;■■:■■-■■).*

Trial Registration ClinicalTrials.gov NCT00808301

Celiac disease is a systemic immune-mediated disorder caused by the ingestion of gluten-containing grains in genetically susceptible persons.[1] The only available treatment for celiac disease is the gluten-free diet (GFD), which consists in the dietary exclusion of grains containing gluten (ie, wheat, rye, barley, triticale, semolina or durum wheat, spelt, and kamut).[2] The need to exclude oats from the GFD has been long a matter of debate and it remains controversial.[3] Early feeding experiments suggested that oats, like wheat and barley, were toxic for celiacs.[4,5] However, it is now recognized that the oat products used in early studies may have been heavily contaminated with other gluten-containing cereals.[3] A large body of evidence has so far suggested that the consumption of pure oats is safe in the vast majority of patients with celiac disease.[6-25] Nonetheless, some concerns persist regarding the tolerance and the safety of oats for all patients with celiac disease. The purity of oat products cannot always be guaranteed, and the contamination of oats with other gluten-containing cereals during harvesting and milling is known to occur.[26,27] A small subset of patients with celiac disease experience more abdominal symptoms while consuming an oat-containing diet as compared with a conventional GFD[28,29]; some oats varieties show toxicity in vitro, suggesting that there

AB	Group A→B
BA	Group B→A
AGA	Antigliadin deamidated antibodies
ELISA	Enzyme-linked immunosorbent assay
GFD	Gluten-free diet
GSRS	Gastrointestinal Symptom Rating Scale
IPT	Intestinal permeability test
L/M	Ratio of lactulose percent to mannitol percent
TGA2	Antitransglutaminase antibodies

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are differences between oat varieties in relation to their safety or toxicity for people with celiac disease.[30] Finally, 3 patients have been described so far who developed villous atrophy after oat challenge.[28,30]

Previous studies were limited by (1) small sample sizes, (2) short follow-up periods, (3) the absence of any detail about the variety of oat used, or (4) not being ruled out that oat products were free of contamination by other gluten-containing cereals. To the best of our knowledge, there has been only 1 double-blind, randomized, placebo-controlled clinical trial.[13] Therefore, we aimed to evaluate the clinical, serologic, and mucosal safety of uncontaminated and nonreactive varieties of oats in the treatment of Italian children with celiac disease in a large, long-term, randomized, double-blind, crossover, placebo-controlled, noninferiority, multicenter clinical trial.

Methods

This noninferiority intervention trial (ClinicalTrials.gov: NCT00808301) used a crossover design. The study protocol has been described previously.[31] All children (range, 4-14 years of age) with a biopsy-proven diagnosis of celiac disease, on a GFD for ≥2 years, were recruited at 8 pediatric gastroenterology centers in Italy (Ancona, Bari, Catania, Monza, Palermo, Roma, and Cava de' Tirreni) between 2008 and 2012. Patients who (1) had other chronic conditions (including type 1 diabetes or inflammatory bowel disease) or (2) did not adhere to the GFD (as demonstrated by elevation of serologic markers at enrollment) were excluded. The random allocation sequence was generated by 2 investigators with no clinical involvement in the trial, the enrollment and the assignment of participants to interventions were performed in each center by the principal investigators). All investigators, staff, and participants were blinded to the allocation. On the basis of a stratified randomization, children were assigned to 1 of 2 groups: those in group A→B (herein described as AB) received 6 months of a GFD plus A products, then 3 months of washout with a standard GFD, and eventually 6 months of GFD plus B products, and those in group B→A (herein described as BA) received 6 months of a GFD plus B products, 3 months of washout with a standard GFD, and finally 6 months of GFD plus A products. A and B products were gluten-free flour, pasta, biscuits, cakes, and crisp toasts containing either purified oats or placebo, respectively; they were provided to the patients free of charge by a company that is leader in the production of gluten-free products in Italy (Heinz Italia s.p.a, Italy), and were identical in form and appearance. Products contained the oats varieties "Irina" and "Potenza" *Avena sativa*, which never presented the immune reactivity associated with toxic prolamins in vitro.[32] Oats were specially grown, milled, and packaged so as not to become contaminated with wheat, rye, or barley. Gluten contamination was double checked by the RIDASCREEN ELISA (R-Biopharm AG, Darmstadt, Germany).

The required oat intake (calculated as 1 g/kg/day) was 15 g/day in children aged 3-6 years, 25 g/day in children between 7 and 10 years of age, and 40 g/day in children aged 11-16 years.

Clinical, serologic, and mucosal parameters were measured at baseline (B_1), at the end of the first 6-month period (T_6), at the end of the 3-month washout (B_2) and at the end of the second 6-month intervention period (T_{15}). At each time point, the daily intake of oat was assessed by means of a 3-day food diary and symptoms and/or side effects related to the ingestion of the products under investigation were promptly recorded.

Clinical Assessment

At every timepoint, all children were interviewed to recall gastrointestinal symptoms and the following data were collected: (i) body mass index, (ii) the 15-item Gastrointestinal Symptom Rating Scale (GSRS) score to assess severity and frequency of symptoms,[33] and (iii) questions to assess other variables that may have affected study results (ie, infections, life events). The following symptoms were investigated specifically: epigastric burning and/or pain, abdominal pain, acid regurgitation, heartburn, sucking sensation in the epigastrium, nausea, vomiting, bloating, abdominal distension, eructation, increased flatus, disorders of defecation (decreased/increased passage of stools, consistency of stools [loose/hard], urgency, feeling of incomplete evacuation), lack of appetite, halitosis, and taste disturbance. The questionnaire was completed by a parent–child team approach. In detail, the symptoms were scored on a 4-point scale by the child together with a family member after a simple explanation of the questions by physicians: mild (not interfering with daily activities), moderate (slightly interfering with daily activities), severe (interfering with daily activities), and very severe (continuous). Stool consistency was graded from hard (0) to watery (4). Severe side effects related to the ingested products were recorded at each timepoint of follow-up.

All serum samples were kept frozen at −20°C until analysis in a single laboratory at Buccheri-La Ferla Hospital (Palermo, Italy). Serum antitransglutaminase antibodies (TGA2) were measured by means of a commercial enzyme-linked immunosorbent assay (ELISA; Menarini Diagnostics, Winnersh, UK). More than 20 arbitrary units indicated a positive result. Deamidated gliadin antibodies (AGA IgA and IgG) were measured by means of ELISA with the use of a commercial kit (Menarini Diagnostics), and >15 arbitrary units indicated a positive result. IgA anti-avenin antibodies were measured by ELISA, developed and validated by one of our team members, and >0.1 arbitrary units indicated a positive result.

The mucosal integrity was evaluated by a noninvasive procedure, the intestinal permeability test (IPT), as described previously.[32,34] Briefly, after an overnight fast and bladder emptying, an oral solution containing 5 g of lactulose and 2 g of mannitol was administered. Urine was collected over the following 5 hours. An aliquot was preserved at −20°C with sodium azide. Urinary excretion of each sugar was assessed using a high performance anion exchange chromatography (Dionex DX-500). The ratio of recovered to ingested sugar was reported as the ratio of lactulose percent to mannitol percent (L/M). According to our own reference values, a urinary L/M ratio of >0.08 was considered abnormal (data not published). All

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IPTs were performed in the Laboratory of the Department of Pediatrics, Università Politecnica delle Marche (Ancona, Italy).

We aimed to evaluate the noninferiority of a GFD plus pure nonreactive oats as compared with a standard GFD in maintaining remission of celiac disease in children. The primary response variable was IPT, as a marker of mucosal integrity. A difference in direct treatment effect between the 2 diets of 0.01 as maximum was considered not significant clinically. Secondary outcome measures were difference in direct treatment effect between the 2 diets in clinical and serologic variables.

The Institutional Review Board of the Coordinating Center (Università Politecnica delle Marche, Ancona, Italy) and of each participating center approved this study protocol. Written, informed consent was obtained from the parents or guardians of the children.

Statistical Analyses

The sample size for a noninferiority assessment was estimated using IPT as the primary response variable and calculating a 95% CI for the mean difference of the primary response in the 2 diets. One hundred seventy-seven patients ensured to estimate a 95% CI considering a clinical difference between the 2 diets (Δ) of 0.01 as maximum, a standard deviation of 0.025, a level of significance of 2.5%, and a power of 80%.

Because data were not distributed normally, a nonparametric approach was used for all the statistical analysis. Subjects' general characteristics were summarized using descriptive statistics: median, first and third quartiles for quantitative variables, and absolute and percent frequencies for qualitative variable. Comparisons between the 2 groups were performed by means of Wilcoxon rank-sum test and χ^2 test, respectively.

For descriptive purposes, absolute variations in clinical and anthropometric variables between T_6 and B_1 and T_{15} and B_2, respectively, in the first and second periods of treatment were calculated and graphically represented by boxplots. The 95% CI for median values were calculated and comparisons between diet groups in each treatment period were performed using the Wilcoxon rank-sum test. A positive variation indicated an increase in the variable that was considered statistically significant when the 95% CI did not contain zero value.

A first-order carryover effect, direct-by-period interaction, (θ, λ), and direct treatment effect (τ) were evaluated using a nonparametric approach using medians as summary statistic.[35] The CIs for each effect (θ, λ, τ) were estimated using a probability of 0.90 for the first 2 and of 0.95 for the third. A probability of 0.05 was chosen to assess the statistical significance; the R program was used for statistical analysis.

Results

Unmasking of the blind showed that products A contained oats and products B placebo. The flow diagram of the study is shown in (**Figure 1**; available at www.jpeds.com). Of 306 randomized children, 129 withdrew from the study. Overall, there was a significantly higher frequency of withdrawals in the group AB as compared with group BA; in detail, the percentage of dropouts at T_3 was not different between the 2 groups; however, at T_6 there was a significantly higher percentage of dropouts in group AB (ie, at the end of the A period), that remained significantly higher at B_2, and at T_{12} and T_{15} (ie, during the B period). **Table I** (available at www.jpeds.com) shows the reasons for withdrawal. There was no difference between the 2 groups in the number of children withdrawn for the presence of symptoms related to the protocol; the most common reasons for giving up in both groups were inability to ingest the assigned amount of intervention food or to attend the follow-up visits. All dropouts were TGA2 and IPT negative at the time they withdrew from the study.

After exclusion of the 129 dropouts, the cohort included 177 children (79 in group A and 98 in group B). There were 124 girls (70%), and the median age of the cohort at study entry was 9.1 years of age (IQR, 6.9-11.6). **Table III** shows the patient's main anthropometric and clinical characteristics at baseline. No differences were found between the 2 groups. Ninety-seven percent of patients achieved the required oats intake.

The absolute differences observed in the first and second treatment period in the 2 groups in clinical, serologic, and IPT parameters are shown in **Table II** (available at www.jpeds.co) and in **Figures 2-4**. A significant increase in body mass index was observed in the 2 treatment periods for both diet sequences, probably related to the high intake of commercial gluten-free products required for the protocol. A significant decrease was found in GRSR score in group BA in the first period; AGA IgA significantly increased in the second period in the AB group. No differences were found between the 2 groups in the 2 treatment periods for all the variables of interest.

Table III shows the results of crossover analysis. The differences in treatment carryover at the time of the second baseline measurement (first-order carryover [θ]) and differences in treatment carryover at the time of the second treatment measurement (second-order carryover or direct by period interaction [λ]) were not statistically significant for all the variables, because all the 90% CIs included a zero value. A direct treatment effect (τ) was found not statistically significant for all clinical, serologic, and mucosal variables studied. The upper limit of 95% CI of IPT direct treatment effect was found lower than the highest difference considered clinically relevant ($\Delta = 0.01$).

The number of children that tested positive at serologic and IPT assessment at T_6 and T_{15} of follow-up according to treatment groups is shown in **Table IV** (available at www.jpeds.com). There was no difference in the percentage of children testing positive for AGA, TGA2, anti-avenin, or IPT test between the 2 groups in the 2 treatment periods, suggesting that the occasional positivity was not related to the type of intervention food, but to poor adherence to the GFD. No severe side effects related to the ingestion of the products under investigation were recorded in the 2 groups during the 2 treatment periods.

Discussion

In this double-blind, placebo-controlled study, the long-term introduction of pure nonreactive oats-based products in

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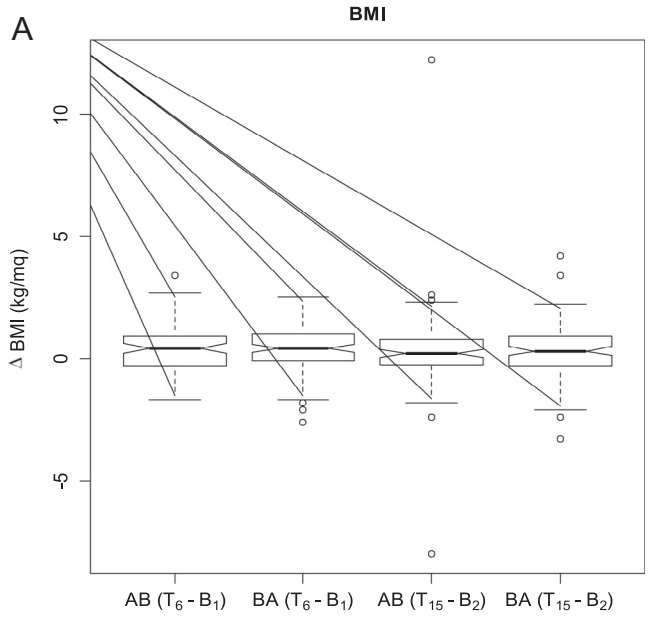


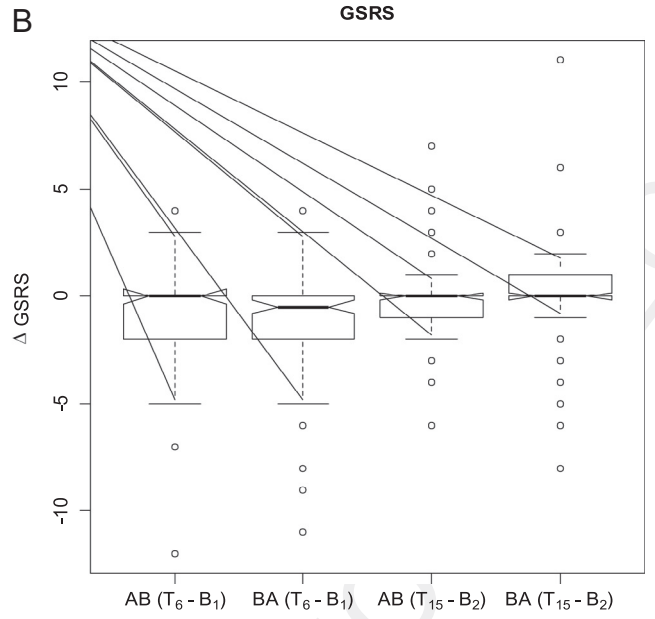
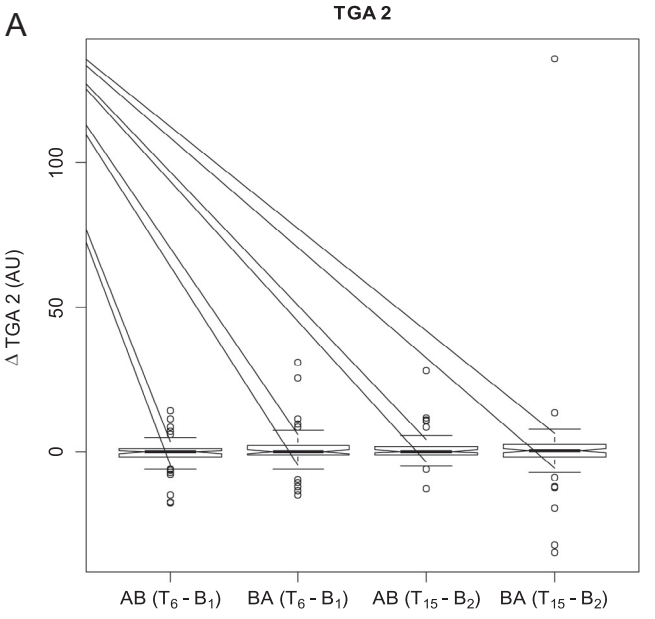


Figure 2. **A, B,** Absolute variation (Δ) in median body mass index (BMI) **(A)** and GSRS **(B)** in the 2 treatment periods according to treatment groups.



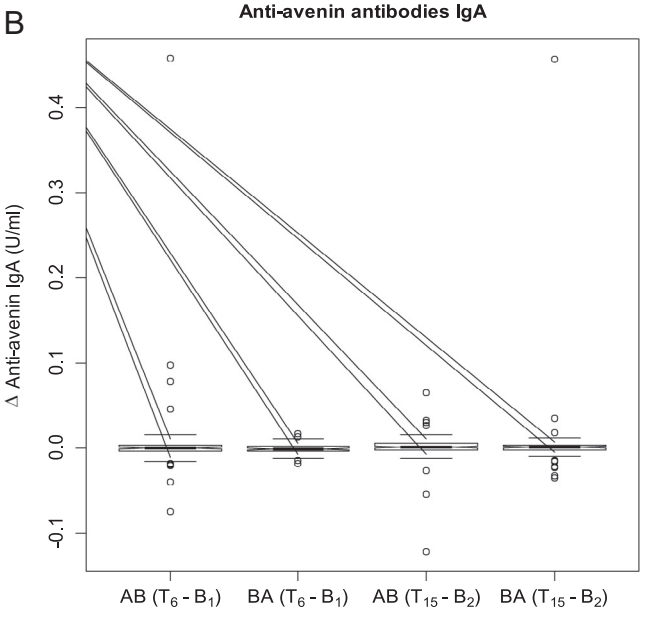


Figure 3. **A, B,** Absolute variation (Δ) in median TGA2 **(A)** and anti-avenin **(B)** results in the 2 treatment periods according to treatment groups.

children with celiac disease treated with a GFD had no deleterious effect at the clinical, serologic, or mucosal levels. The present finding is consistent with previous studies showing that medium to high amounts of gluten-uncontaminated oats can be ingested safely by patients with celiac disease.[6-25] Early short-term reports showing controversial results on oats toxicity were based on the record of gastrointestinal symptoms; however, they did not rule out that the oat products used in these studies were free of contamination with other cereals.[4,5] In 1995, Finnish investigators first compared the effect of 50-70 g/day of oats with placebo in 92 adults with celiac disease on a GFD at diagnosis or in follow-up. They found no difference in clinical and laboratory outcomes and, more important, there was no sign of histologic damage after 12 months of an oat-containing GFD.[6] There were no signs of toxicity of oats in the same group of adult patients with celiac disease participating in a 5-year follow-up study, indicating the long-term safety of oats as part of a celiac diet.[7] These data have been replicated in other clinical trials both in adults and children affected with celiac disease,[6-23] and supported by in vitro immunologic results in

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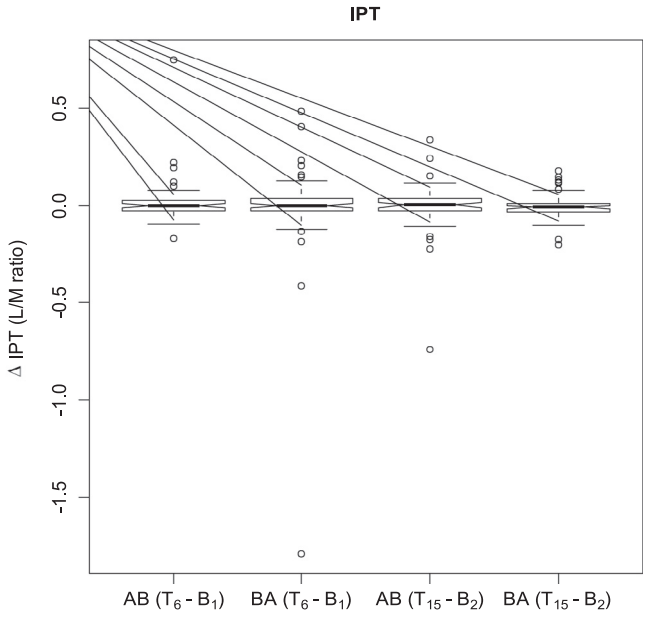

Figure 4. Absolute variation (Δ) in median IPT results in the 2 treatment periods according to treatment groups.

organ culture systems,[24,25] as summarized in systematic reviews.[3,36]

The putative nontoxic nature of oats for patients with celiac disease as compared with "toxic cereals" is mirrored by the taxonomic classification of cereals. Oats, rye, barley, and wheat are members of a subfamily of grains, the Pooidae. This subfamily is further divided into the triticae, to which wheat, rye and barley belong, and the avenae, whose only member is oats. These divisions are based on the structure of the grains' storage proteins. The prolamin fraction contains gliadin in wheat. Oats prolamin includes avenin, a protein that, although having some sequence homology with gliadin, is distinct from it and from the prolamins found in rye and barley.[3] Recent studies suggest that some oat varieties may show a degree of residual toxicity in vitro, for the presence of a peptide with a high content of proline and glutamine, suggesting that there are differences between oat varieties in relation to their safety or toxicity for people with celiac disease.[30,32] In our study, we used the naked oats *A sativa* "Irina" and "Potenza," which never presented the significant immunoreactivity associated with toxic prolamins in previous in vitro studies.[32]

Oats avenin, although structurally different, is also present as only 5%-15% of total oat protein, as opposed to the prolamin content of the triticae subgroup, which is as high as 50%. It has been argued that, in large quantities, avenin may still be toxic, suggesting the concept of an exposure threshold, which needs to be exceeded before symptoms occur. If this is the case, a greater amount of oats may need to be consumed before a toxic threshold is reached.[3] In the present study, a moderate to high amount of daily oats (1 g/kg up to 40 g/day for older children) seemed not to be harmful.

The strengths of the present study are the study design (ie, a placebo-controlled intervention with a crossover), the large sample size, the long duration of the study (15 months), and the type of products containing selected nonreactive varieties of oats. We provided commercially available gluten-free products, routinely consumed by patients with celiac disease, with added oats, that were identical in form and appearance to gluten-free products containing placebo. Only 1 study has been performed so far giving gluten-free products with and without oats in a double-blind fashion and, interestingly, it showed results comparable with our findings.[13]

Based on a literature review of the studies including the histologic assessment,[6,8-10,13-15,28] only 1 patient developed villous atrophy after consuming oats[28]; the same patient was included in another uncontrolled study by the same investigators in which 2 more patients developed villous atrophy.[30] We are aware that the lack of the small intestinal mucosa histology is a weakness of our study; however, we decided to avoid the histologic assessment because performing repeated follow-up small intestinal biopsies was deemed unethical in children. Nonetheless, we evaluated the mucosal integrity by a noninvasive procedure, that is, the IPT, that is a sensitive tool for both triage of active celiac disease, as well as for monitoring patients with celiac disease on a GFD.[37] In patients with active celiac disease, a sugar "paradox" pathway is usually observed: the amount of urinary recovered mannitol is decreased owing to the reduced absorptive surface of the small intestine (villous atrophy), and urinary recovered lactulose is

Table III. Results from the crossover analysis*

Median (1-α/2 % CI)†	θ First-order carryover effect	λ Direct-by-period interaction	τ Direct treatment effect
BMI	0.084 (–0.05; 0.20)	0.05 (–0.15; 0.20)	–0.5 (–0.12; 0)
BMI class	0.50 (–1.0; 1.50)	0.50 (–1.0; 2.0)	–0.25 (–1.0; 0.25)
GRSR score	0 (0; 0)	0 (–0.5; 0)	0 (–2.5; 0)
AGA IgA	0.29 (–0.35; 0.90)	0.14 (–0.70; 1.05)	–0.15 (–0.50; 0.25)
AGA IgG	0.29 (–0.35; 0.90)	0.15 (–0.70; 1.05)	–0.15 (–0.50; 0.25)
TGA2	0.4 (–0.05; 0.95)	0.30 (–0.25; 0.80)	–0.02 (–0.25; 0.23)
IPT	**0.001 (–0.01; 0.01)**	**–0.003 (–0.014; 0.007)**	**0.004 (–0.0002; 0.0089)**
Anti-avenin	0.0005 (–0.0005; 0.0014)	–0.0005 (–0.0019; 0.0005)	–0.0002 (–0.0007; 0.0003)

BMI, Body mass index.
*First-order carryover effect, direct-by-period interaction, direct treatment effect according to the sequences AB, BA. Differences are 15 vs 9 months' measurements.
†The 90% CI for θ and λ; 95% CI for τ.

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increased because of damage to the tight junctions and consequent widening of paracellular spaces. For these reasons, an increased disaccharide/monosaccharide excretion ratio is the usual finding associated with celiac disease damage of the small intestinal mucosa. In adults with celiac disease, the IPT has been shown to be more sensitive than serologic methods in monitoring patients during follow-up and detecting minimal changes related to gluten ingestion.[38,39] In the present study, we did not find significant changes in the urinary L/M ratio either in group AB or BA, and the upper limit of 95% CI of IPT direct treatment effect was found to be lower than the greatest difference considered clinically relevant, showing that a GFD including oats was not inferior to a standard GFD in maintaining mucosal remission, as assessed by the IPT test, in children with celiac disease under treatment.

During our prolonged follow-up, we also tested the humoral response to transglutaminase-2, which is highly sensitive for active celiac disease. We found no difference in the percentage of children testing positive at TGA2 between the 2 groups, confirming the safety of prolonged oats ingestion.

According to the current literature, some patients with celiac disease experience gastrointestinal symptoms more often on an oats-containing diet than with a traditional GFD.[7,8] By using a cross-over study design, we excluded the role of oats in inducing symptoms and/or withdrawal. Indeed, we found a higher frequency of withdrawals in the group AB during the first treatment period, which included oats, as compared with group BA during diet B (ie, placebo); however, after the crossover, we still found a higher frequency of withdrawals in the group AB during diet B (ie, placebo) as compared with group BA, which was consuming diet A (ie, oats), therefore excluding that the withdrawal was caused by the oats. Moreover, there was no difference between the 2 groups with regard to the number of children withdrawn for the presence of symptoms at all time points of follow-up. The major reason for withdrawal was the long duration of the study, with several visits of follow-up that had an unfavorable impact on the family daily life, leading to an inability to complete the study.

Finally, the addition of nonreactive, noncontaminated oats had no significant impact on the GSRS score, a validated questionnaire for the assessment of gastrointestinal complaints. Indeed, we found no differences between the 2 groups in the 2 treatment periods regarding absolute variations in the GSRS score, and the direct treatment effect on GSRS score was also not statistically significant.

In contrast, a Norwegian research group demonstrated that some patients with celiac disease may have gastrointestinal symptoms while ingesting an oats-containing diet because they are intolerant to oats owing to the presence of avenin-reactive T cells in the small bowel mucosa.[22] In our study, there was no difference between the 2 groups in direct treatment effect as regard the anti-avenin antibodies titers, suggesting that oats do not produce a significant humoral response in patients with celiac disease.

The inclusion of oats in a GFD would have several potential benefits for patients with celiac disease. First, oats are a good source of fiber, especially beta-glucan, which is important in human nutrition for its outstanding functional properties, such as the attenuation of postprandial plasma glucose and insulin responses, high transport of bile acids toward lower parts of the intestinal tract, and high excretion of bile acids, thereby lowering serum cholesterol levels.[40] Oats are also a good source of B complex vitamins, iron, and thiamine. They have a higher satiety value than other gluten-free cereals,[40] and increase the palatability and variety of the GFD, thus improving compliance and reducing the risk of accumulating possible contaminants (ie, arsenic or mycotoxins).

In conclusion, based on this and previous studies, selected uncontaminated and nonreactive varieties of oats can be safely included in the GFD used to treat children affected with celiac disease. As there are several potential benefits of including oats in the GFD and there will be a possible market demand for oat products among patients with celiac disease; celiac societies and the industry should make an effort to promote the production and sale of safe oat products free of gluten contamination. ■

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References

1. Fasano A, Catassi C. Celiac disease. N Engl J Med 2012;367:2419-26.
2. Lionetti E, Catassi C. New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. Int Rev Immunol 2011;30:219-31.
3. Garsed K, Scott BB. Can oats be taken in a gluten-free diet? A systematic review. Scand J Gastroenterol 2007;42:171-8.
4. Moulton ALC. The place of oats in the coeliac diet. Arch Dis Child 1959;34:51-5.
5. Baker PG, Read AE. Oats and barley toxicity in coeliac patients. Postgrad Med J 1976;52:264-8.
6. Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma VM, Järvinen RM, Uusitupa MI, et al. A comparison of diets with and without oats in adults with celiac disease. N Engl J Med 1995;333:1033-7.
7. Janatuinen EK, Kemppainen TA, Julkunen RJ, Kosma VM, Mäki M, Heikkinen M, et al. No harm from five year ingestion of oats in coeliac disease. Gut 2002;50:332-5.
8. Srinivasan U, Leonard N, Jones E, Kasarda DD, Weir DG, O'Farrelly C, et al. Absence of oats toxicity in adult coeliac disease. BMJ 1996;313:1300-1.
9. Hardman CM, Garioch JJ, Leonard JN, Thomas HJ, Walker MM, Lortan JE, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. N Engl J Med 1997;337:1884-7.
10. Reunala T, Collin P, Holm K, Pikkarainen P, Miettinen A, Vuolteenaho N, et al. Tolerance to oats in dermatitis herpetiformis. Gut 1998;43:490-3.
11. Kemppainen TA, Heikkinen MT, Ristikankare MK, Kosma VM, Sontag-Strohm TS, Brinck O, et al. Unkilned and large amounts of oats in the coeliac disease diet: a randomized, controlled study. Scand J Gastroenterol 2008;43:1094-101.
12. Hollen E, Holmgren PK, Sundqvist T, Grodzinsky E, Hogberg L, Laurin P, et al. Coeliac children on a gluten-free diet with or without oats

display equal anti-avenin antibody titers. Scand J Gastroenterol 2006;41:42-7.
13. Högberg L, Laurin P, Fälth-Magnusson K, Grant C, Grodzinsky E, Jansson G, et al. Oats to children with newly diagnosed coeliac disease: a randomised double blind study. Gut 2004;53:649-54.
14. Storsrud S, Olsson M, Arvidsson Lenner R, Nilsson L, Nilsson O, Kilander A. Adult coeliac patients do tolerate large amounts of oats. Eur J Clin Nutr 2003;57:163-9.
15. Hoffenberg EJ, Haas J, Drescher A, Barnhurst R, Osberg I, Bao F, et al. A trial of oats in children with newly diagnosed celiac disease. J Pediatr 2000;137:361-6.
16. Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. J Pediatr Gastroenterol Nutr 2009;48:559-65.
17. Holm K, Mäki M, Vuolteenaho N, Mustalahti K, Ashorn M, Ruuska T, et al. Oats in the treatment of childhood coeliac disease: a 2-year controlled trial and a long-term clinical follow-up study. Aliment Pharmacol Ther 2006;23:1463-72.
18. Guttormsen V, Lovik A, Bye A, Bratlie J, Morkrid L, Lundin KE. No induction of anti-avenin IgA by oats in adult, diet-treated coeliac disease. Scand J Gastroenterol 2008;43:161-5.
19. Sey MS, Parfitt J, Gregor J. Prospective study of clinical and histological safety of pure and uncontaminated canadian oats in the management of celiac disease. JPEN J Parenter Enteral Nutr 2011;35:459-64.
20. Kaukinen K, Collin P, Huhtala H, Maki M. Long-term consumption of oats in adult celiac disease patients. Nutrients 2013;5:4380-9.
21. Sjoberg V, Hollen E, Pietz G, Magnusson KE, Fälth-Magnusson K, Sundström M, et al. Noncontaminated dietary oats may hamper normalization of the intestinal immune status in childhood celiac disease. Clin Transl Gastroenterol 2014;5:e58.
22. Tjellström B, Stenhammar L, Sundqvist T, Fälth-Magnusson K, Hollén E, Magnusson KE, et al. The effects of oats on the function of gut microflora in children with coeliac disease. Aliment Pharmacol Ther 2014;39:1156-60.
23. Tapsas D, Falth-Magnusson K, Hogberg L, Hammersjo JA, Hollen E. Swedish children with celiac disease comply well with a gluten-free diet, and most include oats without reporting any adverse effects: a long-term follow-up study. Nutr Res 2014;34:436-41.
24. Picarelli A, Di Tola M, Sabbatella L, Gabrielli F, Di Cello T, Anania MC, et al. Immunologic evidence of no harmful effect of oats in celiac disease. Am J Clin Nutr 2001;74:137-40.
25. Kilmartin C, Lynch S, Abuzakouk M, Wieser H, Feighery C. Avenin fails to induce a Th1 response in coeliac tissue following in vitro culture. Gut 2003;52:47-52.
26. Hernando A, Mujico JR, Juanas D, Méndez E. Confirmation of the cereal type in oat products highly contaminated with gluten. J Am Diet Assoc 2006;106:665.
27. Ellis HJ, Ciclitira PJ. Should coeliac sufferers be allowed their oats? Eur J Gastroenterol Hepatol 2008;20:492-3.
28. Lundin KEA, Nilsen EM, Scott HG, Løberg EM, Gjøen A, Bratlie J, et al. Oats induced villous atrophy in coeliac disease. Gut 2003;52:1649-52.
29. Peraaho M, Kaukinen K, Mustalahti K, Vuolteenaho N, Mäki M, Laippala P, et al. Effect of an oats-containing gluten-free diet on symptoms and quality of life in coeliac disease. A randomized study. Scand J Gastroenterol 2004;39:27-31.
30. Arentz-Hansen H, Fleckenstein B, Molberg O, Scott H, Koning F, Jung G, et al. The molecular basis for oat intolerance in patients with celiac disease. PLoS Med 2004;1:e1.
31. Gatti S, Caporelli N, Galeazzi T, Francavilla R, Barbato M, Roggero P, et al. Oats in the diet of children with celiac disease: preliminary results of a double-blind, randomized, placebo-controlled multicenter Italian study. Nutrients 2013;5:4653-64.
32. Ballabio C, Uberti F, Manferdelli S, Vacca E, Boggini G, Redaelli R, et al. Molecular characterisation of 36 oat varieties and in vitro assessment of their suitability for coeliacs' diet. J Cereal Sci 2011;54:110-5.
33. Svedlund J, Sjodin I, Dotevall G. GSRS: a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129-34.
34. Generoso M, De Rosa M, De Rosa R, De Magistris L, Secondulfo M, Fiandra R, et al. Cellobiose and lactulose coupled with mannitol and determined using ion-exchange chromatography with pulsed amperometric detection, are reliable probes for investigation of intestinal permeability. J Chromatogr B Analyt Technol Biomed Life Sci 2003;783:349-57.
35. Jones B, Kenward MG. Design and analysis of cross-over trials, Vol. 34. Monograph on statistics and applied probability. New York: Chapman and Hall; 1989.
36. La Vieille S, Pulido OM, Abbott M, Koerner TB, Godefroy S. Celiac disease and gluten-free oats: a Canadian position based on a literature review. Can J Gastroenterol Hepatol 2016;2016:1870305.
37. Vogelsang H, Schwarzenhofer M, Oberhuber G. Changes in gastrointestinal permeability in celiac disease. Dig Dis 1998;16:333-6.
38. Duerksen DR, Wilhelm-Boyles C, Parry DM. Intestinal permeability in long-term follow-up of patients with celiac disease on a gluten-free diet. Dig Dis Sci 2005;50:85-90.
39. Vilela EG, Ferrari ML, de Gama Torres HO, Martins FP, Goulart EM, Lima AS, et al. Intestinal permeability and antigliadin antibody test for monitoring adult patients with celiac disease. Dig Dis Sci 2007;52:1304-9.
40. Sadiq Butt M, Tahir-Nadeem M, Khan MK, Shabir R, Butt MS. Oat: unique among the cereals. Eur J Nutr 2008;47:68-79.

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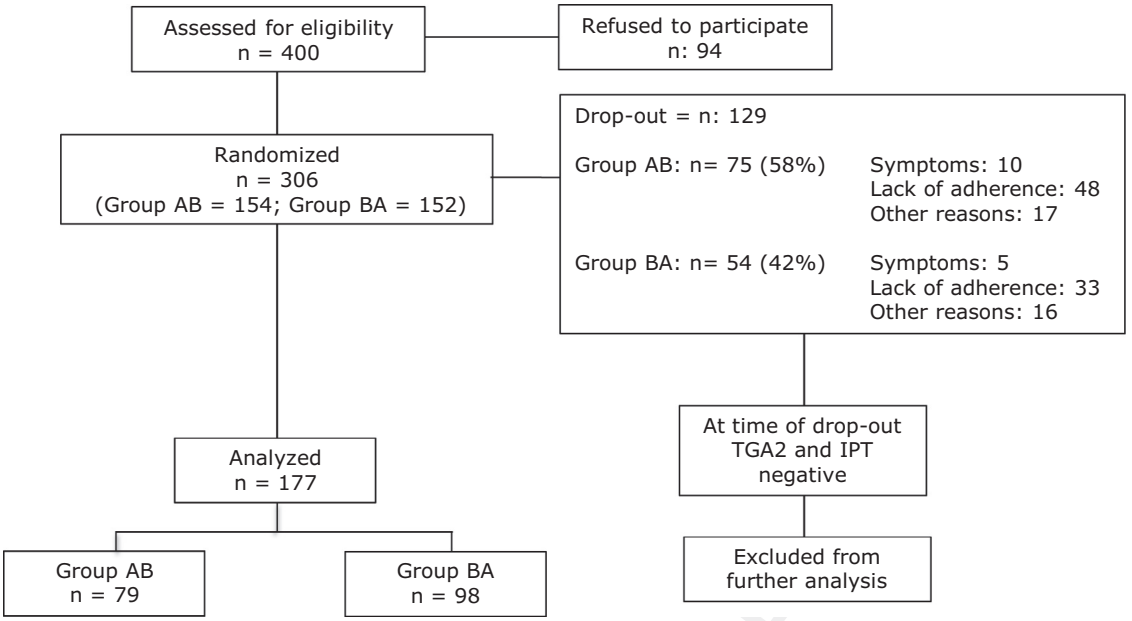

Figure 1. Flow diagram of the study.

Table I. Reasons for withdrawal at all time points of follow-up according to treatment groups

Times	Groups, n (%)		*P*
3 months (T_3)	**AB (n = 43)**	**BA (n = 29)**	
Symptoms related to the protocol	9 (20.9)	5 (17.2)	.174
Inability to attend the follow-up visit	15 (34.9)	14 (48.3)	
Inability to follow the diet	13 (30.2)	3 (10.3)	
Other reasons (parental problems, etc)	6 (14)	7 (24.1)	
6 months (T_6)	**(n = 13)**	**(n = 6)**	
Symptoms related to the protocol	0 (0)	0 (0)	1.000
Inability to attend the follow-up visit	11 (84.6)	5 (83.3)	
Inability to follow the diet	1 (7.7)	0 (0)	
Other reasons (parental problems, etc)	1 (7.7)	1 (16.7)	
9 months (B_2)	**(n = 10)**	**(n = 5)**	
Symptoms related to the protocol	1 (10)	0 (0)	.476
Inability to attend the follow-up visit	3 (30)	4 (80)	
Inability to follow the diet	1 (10)	0 (0)	
Other reasons (parental problems, etc)	5 (50)	1 (20)	
12 months (T_{12})	**(n = 6)**	**(n = 12)**	
Symptoms related to the protocol	0 (0)	0 (0)	1.000
Inability to attend the follow-up visit	2 (33.3)	4 (33.3)	
Inability to follow the diet	2 (33.3)	3 (25)	
Other reasons (parental problems, etc)	2 (33.3)	5 (41.7)	
15 months (T_{15})	**(n = 3)**	**(n = 2)**	
Other reasons (parental problems, etc)	3	2	

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Table II. Absolute variation in the 2 treatment periods according to treatment groups

	First period (T_6-B_1)					Second period (T_{15}-B_2)				
	n	AB	n	BA	*P*	n	AB	n	BA	*P*
Weight										
Median (95% CI)	102	2 (1.69 to 2.31)*	114	2 (1.67 to 2.33)*	.765	88	2 (1.59 to 2.41)*	90	1.7 (1.33 to 2.07)*	.279
First to third quartiles		1 to 3		1.0 to 3.2			1.00 to 3.45		0.8 to 3.0	
BMI										
Median (95% CI)	79	0.4 (0.19 to 0.61)*	98	0.4 (0.22 to 0.58)*	.785	79	0.2 (0.01 to 0.39)*	98	0.3 (0.11 to 0.49)*	.506
First to third quartiles		−0.3 to 0.9		−0.1 to 1.0			−0.25 to 0.80		−0.3 to 0.9	
BMI class										
Median (95% CI)	79	1 (−0.87 to 2.87)	98	0.5 (−0.46 to 1.46)	.877	79	0 (−1.6 to 1.6)	98	0 (−1.12 to 1.12)	.413
First to third quartiles		−4.5 to 6.0		−2 to 4			−5 to 4		−3 to 4	
GRSR score										
Median (95% CI)	79	0 (−0.36 to 0.36)	98	−0.5 (−0.82 to −0.18)*	.314	78	0 (−0.18 to 0.18)	97	0 (−0.16 to 0.16)	.183
First to third quartiles		−2 to 0		−2 to 0			−1 to 0		0 to 1	
AGA IgA										
Median (95% CI)	76	0.15 (−0.48 to 0.78)	92	0.3 (−0.35 to 0.95)	.984	62	0.8 (0.17 to 1.43)*	85	−0.1 (−0.99 to 0.79)	.512
First to third quartiles		−1.26 to 2.20		−1.68 to 2.30			−1.05 to 2.10		−2.5 to 2.7	
AGA IgG										
Median (95% CI)	77	0.5 (−0.27 to 1.27)	92	−0.2 (−1.12 to 0.72)	.166	62	0.3 (−0.62 to 1.22)	84	−0.39 (−0.87 to 0.09)	.095
First to third quartiles		−2.0 to 2.3		−3.45 to 2.15			−1.9 to 2.7		−1.85 to 0.92	
TTG IgA										
Median (95% CI)	76	−0.04 (−0.54 to 0.46)	93	0.1 (−0.47 to 0.67)	.103	72	0.2 (−0.32 to 0.72)	90	0.45 (−0.23 to 1.13)	.613
First to third quartiles		−1.70 to 1.09		−1.10 to 2.40			−1.05 to 1.75		−1.50 to 2.60	
IPT										
Median (95% CI)	75	0 (−0.0091 to 0.0091)	89	0 (−0.0101 to 0.0121)	.64	67	0 (−0.01 to 0.02)	77	−0.01 (−0.02 to 0)	.059
First to third quartiles		−0.0255 to 0.0245		−0.029 to 0.037			−0.03 to 0.04		−0.04 to 0.01	
Anti-avenin IgA										
Median (95% CI)	74	0 (−0.0015 to 0.0015)	93	−0.001 (−0.002 to 0)	.247	73	0.001 (−0.0005 to 0.0025)	93	0.001 (0 to 0.002)	.468
First to third quartiles		−0.004 to 0.004		−0.004 to 0.002			−0.002 to 0.006		−0.002 to 0.004	

BMI, Body mass index.
*Indicates a significant variation of the variable of interest in each group between T_6 and B_1 and between T_{15} and B_2, respectively (95% CI did not contain zero value); *P* values refer to Wilcoxon rank-sum tests for the comparisons between the 2 groups.

Table IV. Clinical and laboratory evaluation (expressed as negative = normal or positive = abnormal) at T_6 and T_{15} according to treatment groups

	T_6			T_{15}		
	AB	BA	*P*	AB	BA	*P*
GSRS score	79	98		78	97	
Negative (=0)	39 (49.4)	57 (58.2)	.31	47 (60.3)	56 (57.7)	.855
Positive (>0)	40 (50.6)	41 (41.8)		31 (39.7)	41 (42.3)	
Aga IgA	78	93		69	92	
≤20	74 (94.9)	84 (90.3)	.407	65 (94.2)	84 (91.3)	.697
>20	4 (5.1)	9 (9.7)		4 (5.8)	8 (8.7)	
Aga Ig G	78	93		69	92	
≤20	72 (92.3)	82 (88.2)	.520	65 (94.2)	84 (91.3)	.697
>20	6 (7.7)	11 (11.8)		4 (5.8)	8 (8.7)	
TGA2	78	95		76	94	
≤20	78 (100)	91 (95.8)	.128*	75 (98.7)	90 (95.7)	.382*
>20	0 (0)	4 (4.2)		1 (1.3)	4 (4.3)	
IPT	76	90		69	84	
≤0.08	55 (72.4)	60 (66.7)	.532	48 (69.6)	67 (79.8)	.206
>0.08	21 (27.6)	30 (33.3)		21 (30.4)	17 (20.2)	
Anti-avenin	75	94		74	96	
≤0.1	71 (94.7)	92 (97.9)	.409*	71 (95.9)	92 (95.8)	1
>0.1	4 (5.3)	2 (2.1)		3 (4.1)	4 (4.2)	

χ^2 test.
*Fisher exact test.

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