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 15 months. Three hundred six 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 2018;194:116-22).*

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 of 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 patients with celiac disease.[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 are

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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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 a leader in the production of gluten-free products in Italy (Heinz Italia s.p.a, Latina, 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 variables 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, United Kingdom). 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, Thermo Fisher Scientific, Sunnyvale, CA). 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 IPTs were performed in the