

ORIGINAL COMMUNICATION

Adult coeliac patients do tolerate large amounts of oats

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Objective: The aim of the present study was to investigate whether adult patients with coeliac disease in remission could include large amounts of oats in their daily gluten-free diet for an extended period of time without adverse effects.

Design, subjects and methods: Twenty adult coeliac patients in remission included large amounts of uncontaminated rolled oats in their daily diet for a prolonged period. The examinations, performed four times during the study period, included small bowel endoscopy with biopsies, blood samples (nutritional status, serological analysis), height and body weight, gastrointestinal symptoms and dietary records. Gastrointestinal symptoms and diet were also investigated through unannounced telephone interviews once a month during the study period.

Results: No adverse effects of a large intake of oats were seen in small bowel histology, serology nor in nutritional status in the 15 subjects who completed the whole study period. Two of the subjects dropped out because of gastrointestinal symptoms and three for non-medical reasons. The median intake of oats was 93 g/day and the compliance to the oat diet was found to be good. Examinations of the patients after drop-out did not show any deterioration in small bowel histology or nutritional status nor raised levels of antibodies.

Conclusion: Results from this study indicate that adult patients with coeliac disease in remission can include large amounts of controlled wheat-free rolled oats for an extended period of time without adverse effects.

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Introduction

Since Dicke's classic work the conventional treatment for coeliac disease in most countries has been a gluten-free

diet, implying a complete exclusion of wheat, rye, barley and oats (Dicke, 1950; Dicke *et al*, 1953). Compliance to the diet results in relief of the symptoms and malnutrition, as healing of the intestinal mucosa occurs (Trier, 1991). Lifelong adherence to this diet is generally promoted, not only to control symptoms but also to prevent future health risks, including osteopenia (Valdimarsson *et al*, 1996), decreased fertility and malignancy (Holmes *et al*, 1989). However, the evidence that oats are toxic is equivocal. Studies from the 1950s reported raised levels of faecal fat or reduced xylose excretion in a few patients who consumed large amounts of oats (> 60–70 g/day; Dicke *et al*, 1953; Moulton, 1959; Baker & Read, 1976). Recent research, however, suggests that moderate amounts of oats, ie about 50 g/day, can be safely consumed by adult coeliac patients as well as subjects with dermatitis herpetiformis (Janatuinen *et al*, 1995, 2000; Srinivasan *et al*, 1996; Hardman *et al*, 1997; Reunala *et al*, 1998; Picarelli *et al*, 2001).

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Contributors: SS, RAL, AK and MO were responsible for the study design. SS was coordinator for the study, collected the dietary and symptom data, performed the statistical analyses, and drafted and wrote the manuscript. MO and AK were responsible for subject recruitment, medical examination and collation of the results. RAL participated in discussion, analyses and drafting of the manuscript. LÅN was responsible for collection and collation of the serological analyses, and also participated in drafting the manuscript. ON evaluated the mucosal morphology. All authors assisted in the writing of the paper.

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Administration of oats to the gluten-free diet has only been studied for short periods of 2 weeks to 6 months, except for the 5 y follow-up of 23 of the participants in the Finnish study (Janatuinen *et al*, 2002).

As the amount of prolamine, the potentially toxic protein fraction in oats, is small compared with wheat, rye and barley (Brohult & Sandegren, 1954), it has been argued that oats given in large quantities may still be toxic in patients with coeliac disease.

The aim of the present study was to investigate whether adult patients with coeliac disease in remission could include large amounts of controlled wheat-free rolled oats in their daily gluten-free diet for an extended period of time without adverse effects.

Materials and methods

Subjects

Adult patients with coeliac disease were recruited during 1996–1997 from the Gastrointestinal clinic at Sahlgrenska University Hospital in Gothenburg, Sweden. All of the patients were 18 y or older, and had an established diagnosis of coeliac disease, based on the presence of partial or subtotal villous atrophy of the duodenal mucosa before the initiation of a gluten-free diet, and clinical and histological improvement after gluten exclusion. The participants had normal or almost normal duodenal villous architecture after treatment with gluten-free diet for at least 12 months and were motivated for the study. Subjects should be eating a strict gluten-free diet, allowing industrially purified wheat starch-based gluten-free flours in their daily diet. Patients having any other serious medical condition were not included in the study. The Ethics Committee of the Sahlgrenska University Hospital approved the study protocol. All patients received written and oral information concerning the study before they gave their consent.

Design of the study

After a baseline examination to record the nutritional status, gastrointestinal symptoms, antibodies and dietary habits as well as status of intestinal mucosa by endoscopy, the dietary intervention started, implying a daily intake of 100 g of rolled oats. Compliance with the diet was checked by monthly unannounced telephone interviews throughout the study period of 2 y. Gastrointestinal symptoms were also recorded at the interviews. The baseline examinations were repeated at fixed intervals as shown in Figure 1.

Diet intervention

Before the inclusion of oats in the diet the participants were given oral instructions about the diet by a clinical nutritionist/dietician. They received rolled oats (Kungsörnen AB, SE-15381 Järna, Sweden) which was free from wheat, rye and barley as judged by results obtained using enzyme-linked

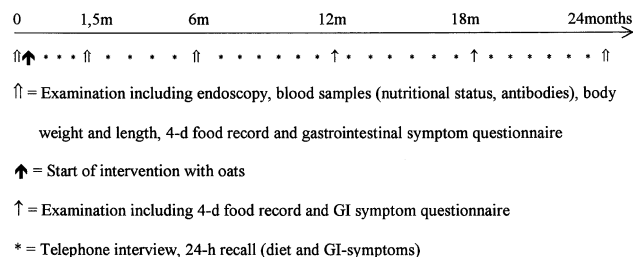


Figure 1 Study design of time and kind of examinations.

immunosorbent assay, performed at the National Food Administration, Uppsala, Sweden. In this method a specific monoclonal antibody to omega-gliadin detecting any prolamine contamination from wheat, rye and barley was used. The oat prolamine avenin is not detected by this method (Transia gluten lab-test (ref. GL-301), Transia-Diffchamb S.A. Lyon, France). The method is quantitative with a detection limit of 20 ppm (Skerrit & Hill 1991). The rolled oats was delivered to the participants free of charge during the study period. The aim for the daily intake of oats was 100 g. This amount corresponds to three servings of hot oatmeal or 10–12 slices of oat-enriched bread per day. The participants were free to choose how to include the rolled oats in their daily diet, and they were provided recipes with gluten-free food including rolled oats.

The calculations concerning the fibre content of the diet, defined as non-starch polysaccharides, indigestible by the enzymes of the small intestine, were done using the Food Composition Table—Energy and Nutrients (Swedish National Food Administration, 1993) and the computer program MATs (Rudans Lättdata, Västerås, Sweden). Data on the nutrient content of the gluten-free products and gluten-free oat recipes were added to the database.

Histopathology

Mucosal biopsies were obtained at baseline and at 6 weeks and 6 and 24 months, using the Olympus videoendoscope SIF-100 (Olympus Optical AB, Solna, Sweden). Three biopsies were obtained from the proximal part of the jejunum (below the ligament of Treitz) and three from the descending part of the duodenum. Biopsies were fixed in neutral buffered formalin and embedded in paraffin wax and plastic resin. Sections (1–3 μ thick) were stained by haematoxylin and eosin and PAS (periodic acid-Shiff stain). Mucosal morphology was evaluated blindly and randomly on coded sections by one observer. Villous architecture was graded as normal, partial or subtotal/total villous atrophy. Mucosal inflammation was graded as none, mild, moderate or severe. Grading of inflammation was based on an evaluation of the number of inflammatory cells in the lamina propria and the number of intraepithelial lymphocytes.

BMI, blood chemistry and serology

Body mass index (BMI) was calculated as body weight (kg)/height² (m). Nutritional status was checked by a blood sample after overnight fast, and serum concentrations of haemoglobin, ferritin, vitamin B₁₂, zinc, folate, albumin and alkaline phosphatase were measured. The analyses were performed using routine clinical laboratory methods.

Blood samples were also used for serological tests for antibodies to gliadin and endomysium. Antigliadin (IgA and IgG) antibodies were assessed by a modified enzyme-linked immunosorbent assay (DIG-ELISA) as described elsewhere (Kilander *et al*, 1983; Lindberg *et al*, 1985). Antiendomysial antibodies of the IgA type (EmA) were detected by the indirect immunofluorescence technique using monkey oesophagus as the substrate (Ascher *et al*, 1996).

Diet and symptoms

The participants kept a 4 day food record at the same time as the other examinations and also at 12 and 18 months. They registered everything they ate and drank during four consecutive days (Buzzard, 1998). During the same period of time the participants recorded a questionnaire concerning gastrointestinal symptoms; abdominal pain and distension, other, not specified abdominal symptoms, flatulence, and amount and appearance of the stools. The symptoms were graded from 0 to 3, from no symptoms to mild, moderate (bother but do not interrupt work) and severe symptoms (interrupt work, need to lie down). Itching and use of nutritional supplements were also recorded in the questionnaire. In addition, the subjects were free to give personal comments on the symptom questionnaire.

Once a month the clinical nutritionist/dietician interviewed the participants by telephone without prior notification. The aim was to check compliance to the diet, feasibility of the use of oats and symptoms according to the gastrointestinal questionnaire.

Statistical analysis

The results are presented as means (s.d.) and medians with range when appropriate. The data was tested and found to be normally distributed, and comparisons of variables before and after the introduction of oats in the gluten-free diet were

made, by using paired *t*-test for comparisons between means. A *P*-value < 0.05 was accepted as indicating significance.

Results

Twenty adult patients, 12 women and eight men with coeliac disease in remission were included in the study. Eighteen patients completed the study period of 6 months and 15 persons the whole period of 2 y. One woman withdrew after 1 month and one man after 6 months because of abdominal symptoms (distension and flatulence). One woman and one man left the study because of non-medical reasons (travelling a lot at work and started eating a gluten-containing diet, respectively) and one woman was excluded because of lack of cooperation concerning the diet registration.

The mean age of the patients at baseline was 41 y (range 22–71). Only one of the patients was diagnosed with coeliac disease in childhood, the rest were diagnosed in adult life. Fifty percent of the subjects had been eating a gluten-free diet for 1–5 y and 50% for more than 5 y.

Diet and compliance

Based on the food record method, the median daily intake of oats during the 2 y study period was 93 g. The median (range) daily intake of oats and fibre is seen in Table 1. Two of the subjects consumed less than 70 g/day of oats during the study period, eight included 70–100 g/day and five participants consumed more than 100 g/day, according to the written registrations and the telephone interviews. The rolled oats were mostly consumed as hot oatmeal, muesli, and baked into breads, biscuits and cakes.

As shown by the frequent telephone interviews the compliance to the gluten-free diet and to the oat intervention was good. The median daily intake of oats reported by the 24 h recalls was 88 g, range 53–97 g/day. The within-person variation was 25% and the between-person variation was 10%.

Small bowel histology

A total number of 325 biopsies from 20 patients were evaluated blindly and randomly. All patients (*n* = 20) were investigated at baseline and 6 weeks, while follow-up

Table 1 Median intake of rolled oats and fibre during the study period, g/day, based on 4 day food records

	Baseline (n = 20)	1.5 months (n = 19)	6 months (n = 18)	12 months (n = 15)	18 months (n = 15)	24 months (n = 15)
Oats						
Median	0	93	89	94	92	94
Range	0–0	46–111	27–137	52–121	54–127	50–122
Fibre						
Median	17	21*	21*	24*	23*	21*
Range	4–27	13–36	12–37	16–32	14–35	14–34

**P* < 0.05 compared with baseline.

biopsies were obtained from 17 patients at 6 months (sub-optimal preparation of biopsies in one patient) and from 14 patients at 24 months (one patient declined to undergo the final endoscopic investigation). The biopsies obtained at the 6 weeks examination were not evaluated on coded sections. However, no changes were seen in the routine examination compared with baseline. Duodenal and jejunal biopsies were evaluated with identical findings in each individual patient. During the study period there was no change in the villous architecture and grade of inflammation in 13 patients. At baseline seven of them had no villous atrophy with no inflammation, three had no villous atrophy with mild inflammation and three had partial villous atrophy with mild inflammation. Three patients improved in their villous architecture from partial to no villous atrophy during the study period, while mucosal inflammation was unchanged or changed from moderate to mild in two respective one patient. One patient had a slight increase in mucosal inflammation at 24 months, from none to mild. Three patients were only evaluated at baseline and 6 weeks, two drop-outs and one with suboptimal preparation of the biopsies. However, there was no change in the second evaluation com-

pared with baseline. A summary of the histopathological findings is given in Table 2.

BMI and nutritional status of the participants

The BMI and nutritional status are shown in Table 3. Two of the participants did not want to give blood samples. They also declined to measure their body weight because of previous eating disorders.

There were no statistically significant changes in the nutritional status or BMI for the participants at any examination as compared with baseline. Multiple nutritional supplementation was registered for one person only, while three others coincidentally supplemented with vitamins A, D, B₁₂ and C and/or iron.

Serology

Antibodies to gliadin or endomysium could not be demonstrated in any of the participants at any examination time, except for one person who had demonstrable anti-endomysium antibodies (EmA) at 6 months. She was negative at baseline. This might correspond an accidental consumption of gluten before the examination at 6 months. The patient also had a 1 week episode with diarrhoea prior to the examination. She continued eating oats and at the next control EmA were not longer demonstrable in this person.

Symptoms

Fifty percent of the participants reported one or several symptoms at the baseline examination and 33% at the final examination (Table 4). The symptoms were recorded as mild, and in a few cases as moderate. Flatulence, the most pronounced reported symptom, increased during the beginning of the study period compared with baseline, with the maximum at 6 months. The median (range) number of stools increased from 1.0 (0.3–2.0) at baseline to 1.3 per day (0.6–2.1) during the intervention period. The increase

Table 2 Histopathology of duodenal biopsies (number of patients)

	Baseline (n = 20)	6 months (n = 17) ^a	24 months (n = 14) ^b
<i>Villous architecture</i>			
Normal	13	13	11
Partial atrophy	7	4	3
Subtotal/total atrophy	0	0	0
<i>Mucosal inflammation</i>			
None	8	8	6
Mild	10	8	8
Moderate	2	1	0
Severe	0	0	0

^aOne patient excluded due to suboptimal preparation of the biopsies.

^bOne patient refused to be examined.

Table 3 BMI and nutritional status, mean (s.d.)^a

	Baseline (n = 20)	1.5 months (n = 20)	6 months (n = 18)	24 months (n = 15)	Reference values ^b	CV
BMI (kg/m ²)	24.0 (2.6)	24.2 (2.6)	24.5 (2.8)	25.1 (2.4)	20–25	—
Haemoglobin (g/l)	135 (14)	137 (12)	140 (11)	136 (12)	Men: 132–166 Women: 116–149	4
s-Ferritin (µg/l)	65 (62)	69 (75)	69 (52)	49 (25)	Men: 25–400 Women: 11–120	11
Alk P ^c (ukat/l)	2.3 (0.6)	2.7 (0.9)	2.3 (0.5)	2.5 (0.7)	< 5	7
Albumin (g/l)	44 (4)	43 (8)	44 (4)	43 (3)	36–50	7
s-Vitamin B ₁₂ (pmol/l)	363 (166)	399 (237)	316 (158)	418 (267)	150–700	9
p-Folate (nmol/l)	19 (7)	19 (8)	18 (10)	14 (9)	6–35	16
b-Folate (nmol/l)	307 (70)	331 (105)	327 (68)	288 (115)	200–520	^d

^aNo changes are statistically significant.

^bSahlgrenska University Hospital, C-lab.

^cAlk P, alkaline phosphates.

^dNot accredited.

Table 4 Gastrointestinal symptoms; number of the participants who reported one or several symptoms and percentage of the subjects without symptoms during the repeated written registrations (four consecutive days)

	Baseline (n = 20)	1.5 months (n = 20)	6 months (n = 18)	12 months (n = 15)	18 months (n = 15)	24 months (n = 15)
Pain	1	1	1	1	1	1
Distension	3	4	4	3	2	2
Flatulence	2	5	6	5	4	4
Other	3	0	0	0	0	1
Itching	2	1	0	0	1	1
Percentage without symptoms	50	50	38	60	67	67

was not statistically significant and there was no change in the appearance of the stools. Among personal comments ascertained from the symptom questionnaire the most common were 'experienced better bowel function with oats in the diet' and 'felt more satiated with oats in the gluten-free diet'.

Discussion

We found that a large daily intake of uncontaminated rolled oats during a 2y period did not cause any nutritional, morphological or serological negative effects in adult patients with coeliac disease in remission. All patients included in this study tolerated wheat starch and thus microscopic amounts of gluten. The results of this study can therefore be applied to coeliac patients usually consuming a wheat starch-containing gluten-free diet only. However, wheat starch has been a common diet component for Swedish coeliac patients and also in the north of Europe since the early 1970s. Several studies have shown that wheat starch is well tolerated among coeliac patients and does not cause damage to the small intestinal mucosa or raised antibodies (Chartrand *et al*, 1997; Kaukinen *et al*, 1999).

Even if oats *per se* are ultimately found to be safe for consumption, it may for other reasons cause problems in some patients. There are several possibilities for contamination of oats with wheat, rye and barley during harvesting, transportation, mill shipping and packaging. Whether or not the lower degree of contamination (20–200 ppm) can cause problems, especially in sensitive patients, is unknown. However, Australian and Finnish studies (Lohiniemi *et al*, 2000; Selby *et al*, 1999) report that trace amounts of gluten from wheat starch in the gluten-free diet do not affect the small intestine mucosa nor the gastrointestinal symptoms.

The 4 day food records performed six times during the study period of 2y were used to calculate the intake of oats and also to study the nutrient quality of the diet. A median intake of 93 g rolled oats per day was close to the target, which was set as 100 g/day. Women with the lowest energy requirements had the biggest problem reaching the daily amount of oats. The intake of oats as calculated from the telephone interviews correlated well with the results from the written 4 day food records, except for special occasions,

like parties, birthdays and when travelling, as can be seen by the within-person variation. The telephone interviews confirmed that compliance to the gluten-free diet was very good. The intake of fibre was of interest since the gluten-free diet is supposed to contain relatively low amounts of dietary fibre if not supplemented. The median intake of fibre increased significantly when oats were included in the diet. Subjects consuming less than 10 g fibre/day at baseline more than doubled their intake when including oats.

Abdominal distension and flatulence were expected due to the high fibre content in rolled oats (10 g/100 g; Swedish National Food Administration, 1993), and most of the participants did notice flatulence initially during the study period. This problem was most pronounced in the subjects with a large increase in the fibre intake. Vegetables that are known to cause flatulence can also be the reason for some of the symptoms, since occasional symptoms were registered after large intakes of, for example, onion, beans, peas and cabbage. The participants did not regard their symptoms, if any, as a problem, except from the two drop-outs, and many remarked a better function of the bowel compared with a conventional gluten-free diet. The two drop-outs had a fibre intake at baseline of 13 and 14 g/day, respectively, and the large increase of oat fibre could be the reason for their gastrointestinal symptoms. No adverse effects were seen in histopathology or serology in these two drop-outs, but the short duration of intake and maybe a latent period of time to histopathologic damage or increased antibodies to occur, may be the explanation. Only a continued consumption of oats despite the symptoms could have given an answer to the cause of the symptoms.

Abdominal pain and the most severe (graded as moderate and in one case severe) symptoms was noticed in three subjects only. One case can be explained by the endoscopic examination which was done on one of the four days of symptom registration. The other patient explained the symptoms as caused by food intolerance other than towards gluten, but no diagnosis of an intolerance/allergy was done in this patient. The third patient explained her symptoms by dyspepsia, however no abnormal gastro-duodenal findings were observed during endoscopy.

Mucosal biopsies from the small intestine did not reveal any deterioration during the study period. In fact, histological improvement was found in three subjects having partial

villous atrophy at inclusion. This may be explained by an extended time on a gluten-free diet and a close dietary supervision during this period.

Concerning oats there has been a long-running debate about the toxicity and whether or not this grain can be consumed as part of the gluten-free diet. Wheat, rye, barley and oats contain approximately the same amount of total protein, ie ca 8–13 g/100 g (Swedish National Food Administration, 1993), but they contain different amounts of prolamin, probably the major injurious constituent. The prolamin fractions of the various cereals have been given names: gliadin (wheat), secalin (rye), hordein (barley) and avenin (oats). Avenin makes up for only 10–15% of the total protein, whereas gliadin, hordein and secalin account for 35–50% (Brohult & Sandegren, 1954). It has been argued that the apparently non-toxic nature of oats may be due to the presence of a low percentage of oat prolamin, or more important, the different amino acid composition in oats compared with wheat. The prolamines of wheat contain a high content of glutamine (>30%) and proline (>15%), and the nontoxic prolamines of rice and maize have a low content. The prolamines of oats have an intermediate amino acid composition (Cornell *et al*, 1992; Wieser, 1995; De Vincenzi *et al*, 1996). Large quantities of oats are therefore suggested to be harmful (Thompson, 1997; Schmitz, 1997). The total daily amount of avenin corresponding to 100 g of oats used in the present study would be 1.3–2.0 g. Different amounts of gluten have been used for provocation with gluten for diagnostic purposes in patients with treated coeliac disease. A gliadin challenge of 0.1–0.5 g daily for 4–6 weeks resulted in histological evidence of relapse, positive antibody tests or an increased intraepithelial lymphocyte count (Catassi *et al*, 1993; Srinivasan *et al*, 1996). The lack of response to oats in the present study was probably not due to a relatively small amount of the potentially active amino acids in the protein fraction. One can speculate whether the latent time before the symptoms and adverse effects occur is longer on an oat diet than on a gliadin challenge, however Finnish coeliac patients consuming oats have been followed for 5 y without any deterioration (Janatuinen *et al*, 2002).

Compliance with a gluten-free diet is generally supposed not to be very high, with only 17–65% of coeliac disease patients adhering to a strict gluten-free diet (Kluge *et al*, 1982; Kumar *et al*, 1988; Mayer *et al*, 1991). Allowance of oats can increase compliance to the diet by providing patients with more food alternatives and can also improve the quality of life for coeliac disease patients. The participants explained that they found the diet more varied and tastier. Incorporating oats into the gluten-free diet resulted in a general increase in fibre intake. Three of the patients expressed a 'more normal function of the bowel after including oats' and five patients felt 'more satiated when eating oats for breakfast'. A higher fibre intake will not only help avoid constipation, but several studies have shown that the soluble fibre found in oats (β -glucans) is effective at lowering serum

cholesterol, particularly in subjects with hypercholesterolaemia (Ripsin *et al*, 1992).

This is the first study to show that oats, guaranteed to be free from wheat, rye or barley, in large amounts are well tolerated in adult coeliac patients in remission. Five of the participants had a mean intake of over 100 g/day during the 2 y study period, which is much more than is normally consumed. However, the amount would not be unrealistic in subjects with a high energy requirement. Some patients may consume large quantities of oats in order to improve a restricted diet. The statement from earlier studies (Janatuinen *et al*, 1995, 2000, 2002; Srinivasan *et al*, 1996; Hardman *et al*, 1997; Reunala *et al*, 1999; Picarelli *et al*, 2001) that a 'moderate quantity of oats is safe', may lead to misinterpretation and confusion. Results from this study on 20 adult coeliac patients in remission indicate that there is no reason to state that intake of uncontaminated oats in adults must be limited to small or moderate amounts.

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