

## ABSENCE OF TOXICITY OF OATS IN PATIENTS WITH DERMATITIS HERPETIFORMIS

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### ABSTRACT

**Background** People with gluten sensitivity should avoid foods containing wheat, rye, and barley, but there has been debate about whether they should avoid oats. Although patients with celiac disease have recently been shown to tolerate oats, less is known about the effects of oats on patients with dermatitis herpetiformis.

**Methods** We studied seven men and three women (mean age, 58 years) with biopsy-confirmed dermatitis herpetiformis. They had followed a strict gluten-free diet for a mean of 15.8 years, which controlled their rash and enteropathy. The patients added oats that were not contaminated with gluten to their diets for 12 weeks (mean [ $\pm$ SD] daily intake, 62.5 $\pm$ 10.8 g).

**Results** None of the patients had any adverse effects. Serologic tests for antigliadin, antireticulin, and antiendomysial antibodies were negative before oats were introduced into the diet and after they were discontinued. Villous architecture remained normal: the mean ( $\pm$ SE) ratio of the height of villi to the depth of crypts was 3.59 $\pm$ 0.11 before the diet and 3.71 $\pm$ 0.09 afterward (normal, 3 to 5), and the mean enterocyte heights were 31.36 $\pm$ 0.58  $\mu$ m and 31.75 $\pm$ 44  $\mu$ m, respectively (normal range, 29 to 34). Duodenal intraepithelial lymphocyte counts all remained within normal limits (mean, 13.8 $\pm$ 1.03 per 100 enterocytes before the diet and 14.2 $\pm$ 1.2 per 100 enterocytes afterward; normal range, 10 to 30). Dermal IgA showed no significant changes.

**Conclusions** Patients with dermatitis herpetiformis can include moderate amounts of oats in their gluten-free diets without deleterious effects to the skin or intestine. (N Engl J Med 1997;337:1884-7.)

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**A** GLUTEN-FREE diet is the treatment of choice for patients with celiac disease and dermatitis herpetiformis.<sup>1,2</sup> Dermatitis herpetiformis is an irritating eruption characterized by blisters on the elbows, buttocks, and knees and IgA deposits in the dermal papillae.<sup>3</sup> Villous atrophy will be revealed by a single intestinal biopsy in two thirds of patients, and by multiple biopsies in 95 percent.<sup>4</sup> Even in the presence of normal villous architecture, evidence of gluten sensitivity is revealed by elevated levels of  $\gamma/\delta$  T lymphocytes in the intestinal mucosa, elevated intraepithelial lymphocyte counts, and the induction of villous atrophy on glu-

ten challenge.<sup>5-7</sup> Both the enteropathy and rash of dermatitis herpetiformis are dependent on gluten.<sup>1,8</sup> It takes an average of 2 years after gluten is withdrawn from the diet before the rash is completely controlled, although the rash invariably recurs within 12 weeks after the reintroduction of gluten.<sup>2,9</sup> IgA may disappear from the skin with a strict gluten-free diet; IgA deposits disappeared in 24 percent of patients after a mean of 13 years on a strict gluten-free diet.<sup>2</sup> On reintroduction of gluten, IgA reappears in the skin and is also present when the rash recurs.<sup>9</sup>

Avoidance of wheat, rye, barley, and oats is advocated in a gluten-free diet.<sup>10,11</sup> In an early study of oats, small numbers of children with celiac disease who were given large quantities (140 g of oats daily) had steatorrhea.<sup>11</sup> However, in a later study of children with celiac disease, even 169 g of oats daily for 23 days led to fecal fat excretion that was at the upper limit of normal.<sup>12</sup> In another study, the instillation of 100 to 150 g of oat flour into normal-appearing small bowel of patients with celiac disease did not produce histologic evidence of toxicity.<sup>13</sup> A recent study of 92 adults with celiac disease concluded that the addition of oats (mean, 49.9 g per day) to the diet did not cause adverse effects.<sup>14</sup> Two of the 92 patients had dermatitis herpetiformis and had pruritus, but no rash, after eating oats. In view of these results, we studied the effect of adding oats to a gluten-free diet in 10 patients with dermatitis herpetiformis.

### METHODS

The study was approved by the Health Authority Ethics Committee. Ten patients were asked to participate, and all provided written informed consent. At the time of the original diagnosis, all the patients had had biopsies of the small intestine. Histologic evidence of celiac disease was seen in all patients, with villous atrophy and elevated intraepithelial lymphocyte counts. At that time the patients had mild gastrointestinal symptoms of bloating and frequent stools; they sought medical advice because of their skin disorder. In all 10 patients the diagnosis of dermatitis herpetiformis was confirmed by the finding of granular deposits of IgA in the dermal papillae of uninvolved skin on direct immunofluorescence.

Our policy is to offer all patients with dermatitis herpetiformis a gluten-free diet as the most appropriate treatment.<sup>2</sup> Sulfur-con-

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taining drugs, typically dapsone, are given to control the rash. In those who comply with the diet, dapsone is stopped after about two years and the strict gluten-free diet continued.<sup>3</sup> The patients were selected because of their compliance with a strict gluten-free diet. The study sample consisted of seven men and three women with a mean age of 58 years (range, 44 to 71). In all patients the disease had been controlled by a strict gluten-free diet alone (without the need for dapsone) for a mean of 15.8 years (range, 5.6 to 25.5).

A clinical nutritionist and a physician interviewed the patients and gave them advice, instructions, and gluten-free recipes incorporating oats at week 0. The nutritionist and physician interviewed the patients again at week 6, week 12, and two months after the end of the study. At each visit during the study, compliance was assessed and the patients were examined. The patients continued to follow a strict gluten-free diet during the study and were advised to eat 50 to 70 g of oats daily for 12 weeks (the average serving of porridge contains about 30 g of oats). They weighed and kept records of their daily quantity of oats.

Patients were given 10 kg of oats (Peter Kölln, Elmshorn, Germany) that were determined to be free of gluten contamination by an enzyme-linked immunosorbent assay and polymerase-chain-reaction techniques.<sup>15</sup> The mean ( $\pm$ SD) daily intake of oats was  $62.5 \pm 10.8$  g per patient (range, 47.9 to 77.5). One patient who ate 70 g of oats daily for the first half of the study volunteered to eat 95 g of oats daily for the second six weeks.

All patients underwent duodenal biopsy at the beginning of the study (before adding oats to their diet) and 12 weeks later. A wide-caliber endoscope, allowing the passage of large forceps, was used to ensure that adequate specimens were obtained. Three specimens were taken from the second part of the duodenum during each biopsy. The samples were assessed by a single histopathologist who had no knowledge of when they were obtained. Morphometric measurements of the ratio of the height of villi to the depth of crypts and the height of surface enterocytes were analyzed in three biopsy specimens from each patient.<sup>16</sup> Three adjacent villi were assessed in each specimen, and mean values determined. The number of intraepithelial lymphocytes per 100 enterocytes was determined by two independent observers as a blinded procedure; mean counts from three villi were taken. Before oats were added to the diet and after they were removed from the diet, a 3-mm specimen of skin was obtained by punch biopsy from the forearm of each patient, embedded in Optimum Cutting Temperature compound 4583 (Tissue-Tek, Miles Scientific, Elkhart, Ind.), snap-frozen in liquid nitrogen, and assessed by direct immunofluorescence for IgA deposits in the dermal papillae.<sup>17</sup> The intensity of staining for IgA was expressed as negative, weakly positive, positive, or strongly positive. Serum obtained from 10 ml of venous blood was assessed for the presence of anti gliadin (IgG and IgA) antibodies by enzyme-linked immunosorbent assay. IgA antireticulin and antiendomysial antibodies were detected by standard indirect immunofluorescence with rat kidney and monkey esophagus as the respective substrates. Serum samples were screened at a dilution of 1:10, and positive and negative controls were included in each run.

**RESULTS**

**Adverse Effects**

None of the patients reported pruritus, rash, gastrointestinal symptoms, or other adverse effects during the 12 weeks in which they ate oats. Compliance with the diet was excellent, and the mean ( $\pm$ SD) daily intake of oats was  $62.5 \pm 10.8$  g per patient (range, 47.9 to 77.5). Since the completion of the study, nine of the patients have continued to include oats regularly in their diet, and the other one eats oats occasionally.

**TABLE 1. RESULTS OF SEROLOGIC TESTS FOR ANTIGLIADIN, ANTIRETICULIN, AND ANTIENDOMYSIAL ANTIBODIES AND STAINING FOR IgA DEPOSITS IN SKIN BEFORE AND AFTER OAT CHALLENGE.\***

PATIENT No.	BEFORE OATS		AFTER OATS	
	SEROLOGIC TESTS	SKIN IgA STAINING	SEROLOGIC TESTS	SKIN IgA STAINING
1	-	+	-	+
2	-	+	-	+
3	-	-	-	-
4	-	++	-	+
5	-	+	-	++
6	-	++	-	++
7	-	-	-	+
8	-	-	-	-
9	-	+	-	++
10	-	+	-	+

\*Direct immunofluorescence was used for IgA staining. A minus sign indicates negative results, a plus sign weakly positive results, and two plus signs positive results.

**Dermal IgA and Serologic Analysis**

Three patients had no dermal IgA on biopsy before the diet (Table 1), and IgA was still undetectable in two at the end of the study. The third patient had small amounts of IgA. In the remaining seven patients, the levels of IgA did not change significantly during the study.

Antigliadin (IgA and IgG), antireticulin (IgA), and antiendomysial (IgA) antibodies were not detected before oats were added to the diet or after they were discontinued (Table 1).

**Intestinal Biopsies**

There was no evidence of any abnormality of the villous architecture before oats were added to the diet or after they were discontinued in any of the patients (Table 2). The mean ( $\pm$ SE) ratio of the height of villi to the depth of crypts was  $3.59 \pm 0.11$  before the diet and  $3.71 \pm 0.09$  afterward (normal ratio, 3 to 5). The heights of enterocytes were also normal in all patients both before and after the diet ( $31.36 \pm 0.58$   $\mu$ m and  $31.75 \pm 0.44$   $\mu$ m, respectively; normal range, 29 to 34). Duodenal intraepithelial lymphocyte counts were all within normal limits (10 to 30 per 100 enterocytes), with a mean of  $13.8 \pm 1.03$  per 100 enterocytes before the diet and  $14.2 \pm 1.2$  per 100 enterocytes afterward.

**DISCUSSION**

We found that the ingestion of moderate amounts of oats had no deleterious effects on the skin or in-

**TABLE 2.** RESULTS OF DUODENAL HISTOLOGIC ANALYSIS AND INTRAEPITHELIAL LYMPHOCYTE COUNTS BEFORE AND AFTER OAT CHALLENGE.

PATIENT No.	BEFORE OATS			AFTER OATS		
	VILLOUS HEIGHT:CRYPT DEPTH*	ENTEROCYTE HEIGHT†	INTRAEPITHELIAL LYMPHOCYTE COUNT‡	VILLOUS HEIGHT:CRYPT DEPTH*	ENTEROCYTE HEIGHT†	INTRAEPITHELIAL LYMPHOCYTE COUNT‡
		$\mu\text{m}$	per 100 enterocytes		$\mu\text{m}$	per 100 enterocytes
1	3.33	32.9	9	3.06	29.6	12
2	3.00	34.0	20	3.59	32.0	18
3	3.75	29.8	12	3.72	32.9	10
4	3.66	29.1	13	3.83	30.4	10
5	3.53	30.4	15	3.77	33.0	11
6	3.35	32.1	13	3.83	33.0	13
7	3.28	34.0	10	3.86	32.9	19
8	4.00	31.6	14	3.76	30.4	13
9	4.12	29.3	17	4.15	30.4	17
10	3.84	30.4	15	3.51	32.9	19
Mean ( $\pm$ SE)	3.59 $\pm$ 0.11	31.36 $\pm$ 0.58	13.8 $\pm$ 1.03	3.71 $\pm$ 0.09	31.75 $\pm$ 0.44	14.2 $\pm$ 1.2

\*The normal range for this ratio is 3 to 5.

†The normal range is 29 to 34  $\mu\text{m}$ .

‡The normal range is 10 to 30 per 100 enterocytes.

testine of patients with dermatitis herpetiformis. Early studies suggesting that oats were toxic in celiac disease were based only on the observation of steatorrhea and the results of xylose-absorption tests without intestinal biopsies.<sup>10,11</sup> Furthermore, the purity of the oats that were used was not ascertained. Conventional oats are frequently contaminated with wheat during growth (by crop rotation) or the milling process, and it is important that oats supplied to patients be free of such contamination. As in our study, more recent studies have shown an absence of toxicity of moderate amounts of oats in patients with celiac disease.<sup>14,15,18</sup>

The cereal species whose proteins are toxic to patients with celiac disease are grasses of the tribe Triticeae, which includes wheat, rye, and barley. Oats belong to a different tribe, Aveneae. The seed-storage proteins of oats differ structurally from those of grasses belonging to other species.<sup>19</sup> The toxic proteins are rich in proline and glutamine; hence, their name, prolamins. Oat prolamins (avenin) has a lower proline content than prolamins in wheat, rye, and barley (gliadin, secalin, and hordein, respectively). The sequence glutamine–glutamine–glutamine–proline–phenylalanine–proline is found in prolamins of wheat, rye, and barley, but so far has not been found in oats. This sequence may make up at least part of the toxic core sequence in gluten sensitivity.<sup>20</sup>

Avenin accounts for only 5 to 15 percent of the total protein found in oats, whereas gliadin accounts

for 40 percent of the total protein in wheat. It could be argued that since there are fewer toxic sequences per unit weight of avenin, larger daily amounts of oats (100 to 160 g) could be toxic in celiac disease.<sup>21</sup> We observed no adverse effects in the one patient who ate 95 g of oats daily for the second six weeks of the study. Since an exact toxic sequence or structural factor has not been identified in oats, it is not possible to count the number of such sequences in avenin (Kasarda D: personal communication).

In patients with celiac disease, antigliadin antibodies disappear during treatment with a gluten-free diet<sup>22</sup> but reappear when gluten is reintroduced into the diet, often before there is clinical or mucosal relapse.<sup>23</sup> Assay of antigliadin antibodies was therefore a useful means of ensuring the strictness of compliance with the gluten-free diet in our patients. Since oats do not contain gliadin, antigliadin antibodies would not be expected to develop after the consumption of oats. We did not assay antiavenin antibodies. No antigliadin antibodies were detected in our patients before oats were introduced into the diet or after they were discontinued. This finding also supports the absence of antigenic cross-reactivity of gliadin and avenin. Although antigliadin antibodies are not specific to celiac disease, tests for antireticulin and antiendomysial antibodies are highly disease specific,<sup>24,25</sup> and these tests were also consistently negative in our patients.

In about one fourth of patients with dermatitis

herpetiformis, IgA deposits in skin disappear after a mean of 13 years on a strict gluten-free diet.<sup>9</sup> This accounts for the initial absence of IgA in three of our patients. One of these three had weak IgA staining at the end of the study. This result may not necessarily be due to the formation of new IgA antibodies, since IgA does not disappear from the skin uniformly in patients with dermatitis herpetiformis, and small quantities may still be detected in some areas.<sup>18</sup>

Duodenal architecture was abnormal, with elevated numbers of intraepithelial lymphocytes, in all 10 patients at the time of the original diagnosis. With a strict diet, duodenal architecture was normal at the beginning of this study and did not change significantly after oats were added to the diet. Compliance with the gluten-free diet was only 44 percent in one study<sup>26</sup> and might be increased by the addition of oats. Although our patients were already following a strict gluten-free diet, they viewed the introduction of oats into their diet as beneficial.

In conclusion, we found that in patients with dermatitis herpetiformis, like those with celiac disease alone, the addition of moderate amounts of oats to a gluten-free diet did not produce any deleterious effects to either the skin or intestine.

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