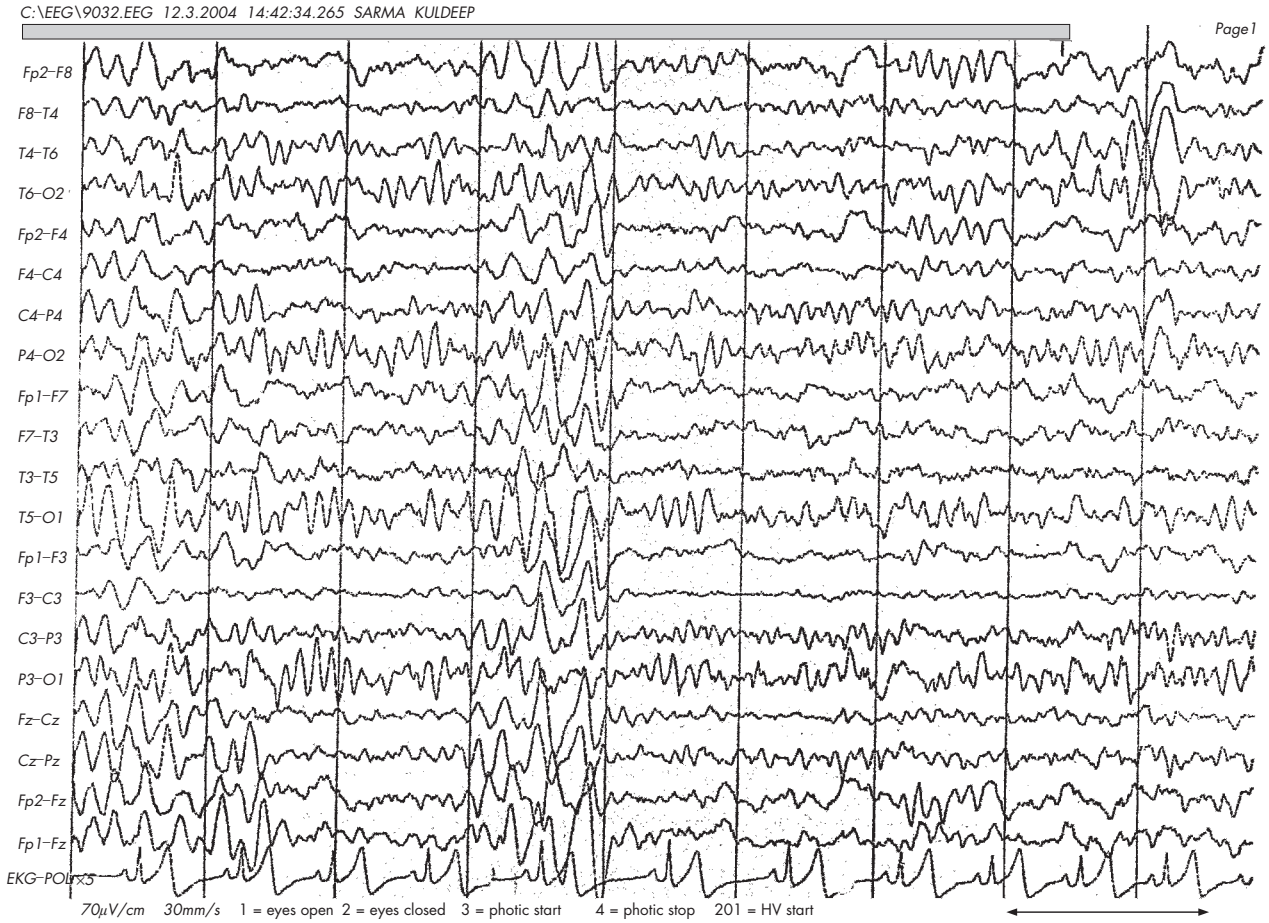

Figure 5 EEG record showing right frontal focal discharges.

correlations between mRNA levels of upregulated cytokines and effector molecules were found (data not shown). These data suggest that high levels of proinflammatory cytokines in ulcerative colitis directly trigger effector molecules, leading to a severe degree of mucosal damage.

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References

1 **MacDonald TT**. The biochemical basis of immune enteropathy. *J Pediatr Gastroenterol Nutr* 2002;**34**(Suppl 1):S27–30.
2 **Salvati VM**, MacDonald TT, Bajaj-Elliott M, *et al*. Interleukin 18 and associated markers of T helper cell type 1 activity in coeliac disease. *Gut* 2002;**50**:186–90.
3 **Nilsen EM**, Jahnsen FL, Lundin KE, *et al*. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. *Gastroenterology* 1998;**115**:551–63.

Weight loss induced by orlistat reverses fatty infiltration and improves hepatic fibrosis in obese patients with non-alcoholic steatohepatitis

Non-alcoholic steatohepatitis (NASH) may cause progressive hepatic fibrosis and cirrhosis.[1 2] To date, treatment has been restricted to diet and weight loss, but without compelling results. Orlistat (Xenical) is a natural lipase inhibitor, which reduces the absorption of dietary fat by 30%[3] and improves insulin resistance and lipid profile.[4 5] Whether or not orlistat reverses hepatic fibrosis and inflammation in obese patients with NASH has not been assessed.

A total of 14 obese patients with NASH underwent liver biopsy before and after 6 months treatment with orlistat (120 mg thrice daily). Patients were also provided a moderate calorie-restricted diet with a median daily intake of 25 kcal/kg body weight/day. Parameters of oxidative stress, insulin resistance, lipids and liver histology were measured. All patients signed informed consent. Of 22 recruited patients, 14 (10 women and 4 men, mean (SD) age of 42 (3) years, and body mass index of 31.5 kg.m^2) completed the study. In all, four patients had mixed hyperlipidaemia, five had diabetes mellitus type 2 and five had obesity alone.

Orlistat reduced fatty infiltration in 10 patients (70%, $p<0.01$), 3 of whom had normal liver fat content after treatment. Orlistat improved inflammatory activity by 2 grades in 28% and by 1 grade in 50% of patients and effected no change in 22% of patients. A total of 5 (35%) patients returned to normal inflammatory activity. Orlistat improved hepatic fibrosis by 2 grades in 3 (21%) patients and by 1 grade in 7 (50%) patients. There was no change in 4 (28%) patients. The mean (SD) weight decreased from 94.1 (15.5; median 93.5) kg pretreatment to 89 (15.1; median 87.0) kg post treatment (–5.3% change). One patient did not lose weight. Of the patients who lost weight, the percentage of body weight lost ranged from (–2.3% to –16.3%, median –5%, mean (SD) 5.4 (4.3)%). Seven patients lost at least 6% of their body weight. The weight loss correlated only with the extension of fat ($r = 0.5$), but not with the changes in fibrosis or in inflammation. A significant improvement in serum levels of alanine aminotransferase, aspartate aminotransferase and lipids occurred

Table 1 Baseline histological features and changes after 6 months of treatment with orlistat

Patient	Fat extension before treatment	Fat extension after treatment	Inflammation before treatment	Inflammation after treatment	Fibrosis before treatment	Fibrosis after treatment	Weight change (%)
1	Severe	Severe	A2	A0	F2	F0	−2.9
2	Severe	Mild	A2	A1	F2	F1	−4.5
3	Mild	Normal	A4	A2	F2	F3	−8.4
4	Mild	Normal	A2	A2	F1	F1	−2.4
5	Severe	Mild	A2	A0	F2	F0	−8.2
6	Severe	Severe	A2	A1	F2	F1	−2.3
7	Moderate	ild	A1	A1	F1	F0	−5.5
8	Severe	Severe	A2	A1	F2	F1	+3
9	Severe	Mild	A2	A1	F1	F0	−16.3
10	Severe	Moderate	A2	A2	F2	F1	−3.3
11	Severe	Severe	A3	A2	F3	F1	−7.3
12	Mild	Normal	A1	A0	F1	F1	−6.3
13	Moderate	Mild	A1	A0	F1	F0	−4.1
14	Severe	Mild	A2	A0	F2	F2	−6.9

Fat extension: normal = <10%, mild = <30%, moderate = 30–60%, severe = >60%. Fibrosis scale: 0 = none, F1 = portal, F2 = portal +septa, F3 = bridging, F4 = cirrhosis. Portal & periportal inflammatory activity (A): 0 = normal, 1 = mild, 2 = moderate, 3 = severe.

at the end of treatment with orlistat (alanine aminotransferase 84 (10) IU/l vs 43 (5) IU/l, p<0.001; aspartate aminotransferase 72 (11) IU/l vs 32 (4) IU/l, p<0.001; total cholesterol 229 (12) mg/dl vs 194 (13) mg/dl, p<0.001), triglycerides 238 (23) mg/dl vs 163 (10) mg/dl, p<0.001) and LDL 143 (11) mg/dl vs 120 (5) mg/dl, p<0.003). Similarly, insulin resistance index and malondialdehyde (MDA) levels improved significantly after orlistat treatment, whereas HbAIc remained unchanged (homeostatic model assessment index, normal 0.8–5.4; 6.5 (2.5) vs 3.3 (1.2), p<0.05; MDA normal <0.3 nmol/ml; 0.47 (0.03) nmol/ml vs 0.37 (0.02) nmol/ml; p<0.01), and (HbAIc normal 3.8–6.4%, 7.1 (3.1)% vs 7.5 (2.6)%, p>0.05).

The mechanism underlying the effect of orlistat remains unknown. Orlistat reduces the absorption of dietary fat and modulate insulin action by changing not only the amount of fat delivered to the liver, but also by changing the type of fat. Saturated fatty acids increase insulin resistance, whereas unsaturated fat, particularly monounsaturated fat, improves insulin sensitivity.[6] Patients with hypertriglyceridaemia have raised tumour necrosis factor-α, which induces systemic inflammation.[7] Whether the reduced levels of postprandial triglycerides induced by orlistat lowers the inflammatory component associated with NASH remains to be determined. MDA may reflect the process of lipid peroxidation occurring in the liver.[8] However, it could be an expression of an enhanced production of free radicals in the circulation as documented in obese patients and patients with diabetes.[9] In our patients, MDA levels were reduced with orlistat treatment, which may be due to the lowering of plasma low density lipopritein (LDL) levels, which may increase cellular LDL receptors synthesis. This will shorten the time of residence of LDL in the plasma, and thereby reduces its exposure to free radicals and preserves LDL antioxidant content, which make it more resistant to oxidation.

One limitation of our clinical study is absence of a placebo group. Thus, all the changes observed could be nonspecific and do not necessarily reflect any unique property of orlistat. Therefore, trials comparing orlistat-induced weight loss against the effect of similar weight loss induced by dieting or exercise are needed before any claim that orlistat has a specific benefit can be substantiated.

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References

1 **Bugianesi E**, Leone N, Vanni E, *et al*. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;**123**:134–40.
2 **Angulo P**. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;**346**:1221–31.
3 **Kushner RF**. Medical management of obesity. *Semin Gastrointest Dis* 2002;**13**:123–32.
4 **Davidson MH**, Hauptman J, DiGirolamo M, *et al*. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 1999;**281**:235–42.
5 **Zavoral JH**. Treatment with orlistat reduces cardiovascular risk in obese patients. *J Hypertens* 1998;**16**:2013–17.
6 **Grundy SM**, Abate N. Chandalia: Diet composition and the metabolic syndrome: what is the optimal fat intake? *Am J Med* 2002;**113**(Suppl 9B):25S–29S.
7 **Jonkers IJ**, Mohrschladt MF, Westendorp RG, *et al*. Severe hypertriglyceridemia with insulin resistance is associated with systemic inflammation: reversal with bezafibrate therapy in a randomized controlled trial. *Am J Med* 2002;**112**:275–80.
8 **Albano E**, Clot P, Morimoto M, *et al*. Role of cytochrome p450 2E1-dependent formation of hydroxyethyl free radical in the development of liver damage in rats intragastrically fed with ethanol. *Hepatology* 1996;**23**:155–63.
9 **Knekt P**, Reunanen A, Jarvinen R, *et al*. Antioxidants, vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol* 1995;**142**:1269–78.

Screening for coeliac disease in patients fulfilling the Rome II criteria for irritable bowel syndrome in a secondary care hospital in The Netherlands: a prospective observational study

Irritable bowel syndrome is the most commonly diagnosed gastrointestinal condition and affects a large proportion of the population in the West.[1] Several guidelines suggest that in typical patients with no alarm symptoms or signs, apart from routine laboratory tests, no additional tests are necessary.[2] Coeliac disease, however, may present with symptoms suggestive of irritable bowel disease.[3] Several studies suggested that screening for coeliac disease in patients with symptoms suggestive of irritable bowel disease might be cost-effective.[4–7] We, therefore, started to routinely screen patients with typical irritable bowel disease symptoms for coeliac disease using antiendomysial antibodies.

All patients referred to three doctors at the outpatient gastroenterology department of our hospital between November 2002 and November 2005 for suggestive irritable bowel disease and fulfilling the Rome II criteria were included if routine laboratory tests and an endoscopy of the lower gastrointestinal tract were performed. Furthermore, all patients received standard care including an interview and physical examination. Apart from these tests, the treating physician could order any other diagnostic test as considered necessary.

In addition, serological screening for coeliac disease was carried out in all patients. Total IgA was measured to exclude IgA deficiency. Thereafter, IgA antiendomysial antibodies were measured using indirect fluorescent antibody test anti-EmA (monkey endomysial) IgA Assay (Scimedx Corporation, Denville, New Jersey, USA) according to the instructions of the manufacturer. A titre of 1:10 U/l or more was considered positive.

A total of 163 patients (108 women, 55 men, median age 35 years, range 16–75 years) fulfilled the inclusion criteria and have been included in this analysis. 154 (94%) patients were diagnosed finally with irritable bowel disease, 4 with Crohn's disease, 2 with hyperthyroidism, 1 with endometriosis, 1 with lactase deficiency and 1 with idiopathic bile salt malabsorption.

Fifteen patients were not screened with antiendomysial antibodies. In four of these patients, the treating physician ordered duodenal biopsy specimens because of predominant diarrhoeal symptoms. Histological examination of the biopsy specimens showed normal mucosa in all of them.

Therefore, in 148 evaluated patients antiendomysial antibodies were measured. IgA