Conference on 'Malnutrition matters'
Nutrition Society Cuthbertson Medal Lecture

Emerging concepts: from coeliac disease to non-coeliac gluten sensitivity

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The rise in gluten consumption over time has led to the increasing recognition of coeliac disease (CD) with associated complications. However, only recently has there been an appreciation that the spectrum of gluten-related disorders is greater than just CD, which may explain the growing global popularity in gluten-free products. Current literature suggests that a newly recognised clinical entity in the form of non-coeliac gluten sensitivity (NCGS) may be the most common gluten-related disorder encountered by healthcare professionals, although its exact prevalence is as yet unknown. This article will review the historical relationship between mankind and gluten as well as the progressive recognition that it is possible for gluten to have a deleterious effect on our health. To this effect we discuss the prevalence, diagnosis and complications of CD including the benefits derived from a gluten-free diet (GFD). Finally, we discuss our current understanding of NCGS, in addition to highlighting the need for further research to determine the extent, clinicopathological features and serological biomarkers to help recognise this emerging condition in clinical practice.

Non-coeliac gluten sensitivity: Coeliac disease: Gluten-related disorders

What effect has gluten had on mankind?

Although mankind may have existed in some progressive form for 2·5 million years it is only in the last 10 000 years that we have been exposed to wheat. Wheat was originally cultivated in the Fertile Crescent (South Western Asia) with a farming expansion that lasted from approximately 9000 to 4000 BC. Thus, it could be considered that wheat and therefore gluten is a relatively novel introduction to man's diet[1]. Gluten is a high molecular weight heterogeneous compound (which occurs not only in the endosperm of wheat but also in rye and barley) that can be fractionated to produce α, β and γ peptides.

Prior to 1939 (and the outbreak of World War II) the rationing system had already been devised. This led to an imperative to try to increase agricultural production. Thus, it was agreed in 1941 that there was a need to establish a Nutrition Society. A meeting of workers interested in nutritional problems was convened by Sir John Orr and was held at the Royal Institution[2]. The main objective of the new Society was to provide a common meeting place for workers in various fields of nutrition. The very roots of the Society were geared towards necessarily increasing the production of wheat[2]. This goal was achieved and by the end of the twentieth century, global wheat output had expanded 5-fold[3].

Coeliac disease (CD) or gluten sensitive enteropathy is a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals. CD was uncommon with the estimated incidence in the UK in 1950 being reported as one in 8000[4]. However, we and others have reported in the last decade that CD affects 1% of all adults[5]. Adult presentations are now more frequent than paediatric (9:1). Contemporary patients with adult CD rarely present with symptoms suggestive of malabsorption, more commonly now describing subtle gastrointestinal symptoms (e.g. irritable bowel type symptoms)[6,7]. Any gastrointestinal presentation of CD is now termed

the typical form. However, patients presenting with no gastrointestinal symptoms but alternatively extra-intestinal manifestations and/or recognised associated conditions (e.g. neurological symptoms or reduced bone mineral density)[8–16] are called the atypical form.

Delays in CD diagnosis are common, with symptoms in patients prior to the diagnosis ranging from 4·5 to 9·0 years[17]. Furthermore, for every adult patient diagnosed approximately eight cases are still yet to be detected. These observations have led to protagonists advocating an active clinical policy for case finding and even debating whether the general population should be screened for CD. The mantra is 'if you look for CD you will find it'[18–20].

Individuals with CD may initially be recognised by using either/both endomysial antibody and tissue trans-glutaminase (tTG) antibody. The positive predictive value of these serological tests is in excess of 90%[21–23]. However, a duodenal biopsy with the demonstration of villous atrophy is still considered mandatory[24–28]. The recent interest in SNP may herald the advent of novel genetic testing[29,30].

The nutritional management of coeliac disease

Individuals with CD have a high prevalence of nutritional deficiencies, reduced bone mineral density and an increased mortality and risk of malignancy[31]. The cornerstone of treatment for CD is lifelong adherence to a strict gluten-free diet (GFD). For the majority of patients, a GFD leads to clinical and histological remission, normalisation of standardised mortality rate, a reduction in long-term health complications (i.e. osteoporosis) and in some studies, an improvement in psychological well-being and quality of life (QOL)[32,33].

QOL improves after 1 year on a GFD and may be sustained in the long term. Patients with CD on a GFD have a reduced QOL compared with healthy controls but this is still an improvement from their undiagnosed state. This benefit is particularly noticeable in patients who have presented with typical symptoms. Furthermore, we recently observed that patients with CD may report a worse QOL than patients with ulcerative colitis[34].

A GFD can be a major and initially overwhelming undertaking. Compliance to a GFD may be compromised by a lack of education, social restrictions[35], limited medical support (doctors and dietitians), the absence of symptoms at the time of diagnosis or in screen detected patients. If symptoms persist while on a GFD the most common reason is inadvertent non-adherence. However, there are a number of other conditions associated with CD that can cause persisting symptoms[36]. We have reported associations with pancreatic exocrine insufficiency[37] and co-existing inflammatory bowel disease[38].

Exploration of the putative biological disadvantages of coeliac disease

Three novel publications suggest an alarming progression in the prevalence of CD with a rise of 2% (since the initial screening studies)[39–41]. What possible mechanism could be involved? The suggestion that increased wheat consumption may play a role is highly plausible and is supported by internationally observed trends. Another alternative is that the rise in CD is in line with increasing prevalence and trends reported for other autoimmune diseases[39]. Gluten consumption may also have a bearing on the likelihood of coeliac patients developing complications and gastrointestinal malignancy[42].

In an obesogenic environment it has been suggested that undetected CD may confer a benefit to individuals. We have recently shown that the mean total cholesterol was 4·84 mM (SD 1·2) in newly diagnosed adults with CD (n 100). Males had 21% lower and females had 9% lower mean total cholesterol in comparison with the general population (difference in age-adjusted mean total cholesterol −1·09 (95% CI −0·97, −1·21) mM; −0·46 (95% CI −0·24, −0·68) mM, respectively). There was no change in mean total cholesterol following a GFD. However, there was a small but statistically significant increase of 0·12 mM (95% CI 0·05, 0·18) in the mean HDL-cholesterol. Thus, there appears to be little benefit conferred to patients with undetected CD[43].

Our most recent work pertains to the role of detecting CD in adult patients with Type 1 diabetes. We showed that at diagnosis adult Type 1 diabetes patients with undetected CD had worse glycaemic control (8·2% v. 7·5%, P = 0·05), lower total cholesterol (4·1 v. 4·9, P = 0·014), lower HDL-cholesterol (1·1 v. 1·6, P = 0·017), a higher prevalence of retinopathy (58·3% v. 25%, P = 0·02), nephropathy (45% v. 5%, P = 0·009) and peripheral neuropathy (42·9% v. 15%, P = 0·11). However, there was no difference in QOL (all P > 0·1) after 1 year on a GFD, and only the lipid profile improved[44]. This suggests that the institution of a GFD in patients with an already complex diabetic diet does not adversely affect QOL[44].

The spectrum of gluten-related disorders

Until recently, the terms gluten sensitivity and CD were used synonymously in the literature[45]. Gluten was associated only with CD and wheat allergy; therefore, patients with gluten-induced gastrointestinal symptoms who produced normal values of tTG, IgE and showed normal histology were advised to continue integrating gluten foods into their diet, as gluten was not regarded as the cause for their condition[46].

However, the majority of those seeking medical attention for gluten-induced gastrointestinal symptoms do not have CD or wheat allergy. Kaukinen and co-workers reported in a study with ninety-four adults affected by abdominal symptoms after cereal ingestion, a prevalence of 9% with CD, 8% with latent CD and 20% with cereal allergy. In total 63% of the study subjects could not be classified as CD or as allergic, but were yet affected by gluten foods and clinically benefited from a GFD[47].

Furthermore, an increasing observation noted by healthcare professionals and the food industry is that the number of patients consuming a GFD seems greatly out of proportion to the projected number of CD patients. Although official data are lacking, the growing popularity
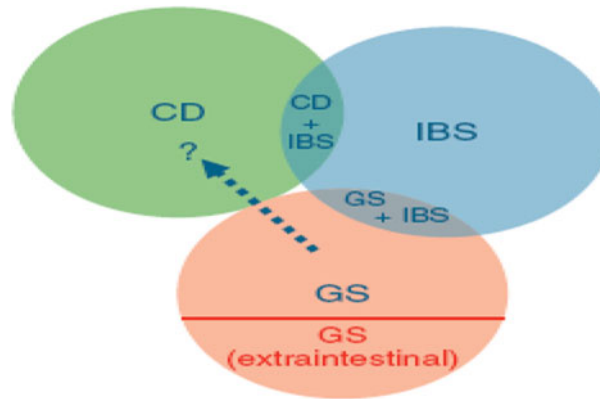
Fig. 1. (colour online) A model for the relationship between coeliac disease (CD), irritable bowel syndrome (IBS) and gluten sensitivity (GS)[52].

Table 1. Symptoms and associations in gluten sensitivity

Symptoms	Bloating
	Abdominal discomfort or pain
	Diarrhoea or constipation
Extraintestinal symptoms like	Headaches and migraines, lethargy and tiredness
Associations with	Attention deficit syndrome
	Autism
	Muscular disturbances as well as bone and joint pain

in the gluten-free market was estimated at \$2·5 billion in the US alone for the year 2010[48], with marketers estimating that up to 15–25 % of the American consumers want gluten-free foods[49].

Subsequently, this has led to the development of a consensus document on new nomenclature and classification of three gluten induced and heterogeneous conditions: CD, wheat allergy and non-coeliac gluten sensitivity (NCGS), a form of gluten intolerance that neither meets the diagnostic criteria for CD nor those for wheat allergy[48]. The diversity of these gluten-induced conditions indicates that the immune system handles gliadin in different ways, with the mechanism underpinning NCGS currently poorly understood and of great research interest. In CD, there is increased small intestinal permeability allowing for aberrant passage of antigens and the activation of both an innate and adaptive immune response, ultimately manifesting as small intestinal damage and concurrence of tTG autoantibodies. In contrast, NCGS patients show normal intestinal permeability and have been proposed to fulfil the criteria to stimulate only an innate immune response, but seemingly fall short of triggering the adaptive immune response, presumably, as they lack the associated machinery to do so, such as epithelial permeability and the susceptible genetic markers human leucocyte antigen (HLA) DQ2 or DQ8 pattern. As a result the inflammatory small bowel response is halted and mucosal manifestations absent, in addition to negative tTG and endomysial antibodies[50].

NCGS is an umbrella term and can incorporate a wide range of symptoms including abdominal discomfort, bloating, pain or diarrhoea; or it may present with a variety of extraintestinal symptoms; these may include headaches and migraines, lethargy and tiredness, attention deficit syndrome and hyperactivity, autism and schizophrenia, muscular disturbances as well as bone and joint pain (Table 1).

In an article by Verdu *et al.*, NCGS is defined by 'one or more of a variety of immunological, morphological, or symptomatic manifestations that may also be shared by CD and irritable bowel syndrome (IBS)' and thus in some quarters referred to as 'no man's land' between these two conditions[51].

There is a growing body of information that suggests patients may experience IBS symptoms related to gluten ingestion, yet in the absence of overt CD. Our group has previously reported that antigliadin antibodies were present in approximately 12 % of the general population and approximately 17 % in IBS (both in the presence of a normal small bowel biopsy)[5,7]. Kaukinen *et al.* noted that the majority of patients with cereal-induced gastrointestinal symptoms complained of bloating (83 %), diarrhoea (63 %) and abdominal discomfort (34 %), symptoms seemingly consistent with the ROME diagnostic criteria for IBS: of those in whom CD was excluded, antigliadin antibodies were present in 40 %[47]. This further supports the hypothesis of GS-IBS (Fig. 1)[51,52]. What this may suggest is that in susceptible individuals the consumption of gluten results in an immune response that is manifested by the production of antigliadin antibodies.

Wahnschaffe *et al.* have suggested that serum coeliac-associated antibodies and the HLA DQ2 or DQ8 pattern may be predictive of a response to a GFD in diarrhoea-predominant IBS[53]. They investigated forty-one diarrhoea-predominant IBS patients who agreed to participate in a 6-month course of a GFD. Positive IgG antigliadin antibodies/tTG and HLA DQ2 were all independent factors for a symptomatic response to a GFD.

Conversely, an intriguing study by an Australian group adds more to the debate[54]. The investigators undertook a double-blind, randomised, placebo-controlled re-challenge trial in patients with IBS fulfilling the ROME III criteria (*n* 34). The patients were recruited through a newspaper advertisement and were already taking a self-imposed GFD

due to symptomatic gastrointestinal benefit. CD was excluded on the basis of a negative HLA DQ2 or DQ8 pattern, or a normal duodenal biopsy (on gluten challenge) in the presence of a positive HLA. Patients were randomised according to a computer-generated list of random numbers held by an independent observer to either the gluten or the placebo treatment group. Over the 6-week study period, the severity scores of pain, satisfaction with stool consistency and tiredness were significantly higher for those consuming the gluten diet compared with the placebo group. Despite this, there was no evidence of intestinal inflammation or damage while being challenged with gluten (using faecal lactoferrin and intestinal permeability). Thus, these patients could not be viewed as having latent CD. This is the first study to describe an NCGS that may cause IBS[54].

In conclusion, we have demonstrated that with the progressive increase in gluten consumption this has led to an increased prevalence of CD with the associated complications. Furthermore, we have categorised the nutritional effects of a GFD in both newly diagnosed CD patients and Type 1 diabetes patients with previously undetected CD. Our recent work suggests that adult patients either with CD alone or CD in association with Type 1 diabetes derive benefit from a GFD. Finally, the increasing global use of a GFD and our recognition of a spectrum of conditions described as gluten-related disorders has opened up further thought-provoking avenues, whereby NCGS should not be seen as a 'no man's land' but a 'fertile crescent' for further research[52]. Further work is required to understand the prevalence, clinicopathological features and serological biomarkers of NCGS, thereby potentially allowing the identification of which patients with IBS may derive benefit from a GFD.

Acknowledgements

References

1. Accomando S & Cataldo F (2004) The global village of coeliac disease. *Dig Liv Dis* **36**, 492–498.
2. Copping AM (1978) The history of the Nutrition Society. *Proc Nutr Soc* **37**, 105–139.
3. International Maize and Wheat Improvement Center (1998). *CIMMYT* Available at: www.cimmyt.org.
4. Davidson LSP & Fountain JR (1950) Incidence of the sprue syndrome. *Br Med J* **1**, 1157–1161.
5. Sanders DS, Patel D, Stephenson TJ *et al.* (2003) A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* **4**, 407–413.
6. Sanders DS, Hopper AD, Azmy IAF *et al.* (2005) Association of adult coeliac disease with surgical abdominal pain: a case control study in patients referred to secondary care. *Ann Surg* **242**, 201–207.
7. Sanders DS, Carter MJ, Hurlstone DP *et al.* (2001) Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling the ROME 2 criteria referred to secondary care. *Lancet* **358**, 1504–1508.
8. Hadjivassiliou M, Kandler RH, Chattopadhyay AK *et al.* (2006) Dietary treatment of gluten neuropathy. *Muscle Nerve* **34**, 762–766.
9. Hadjivassiliou M, Grünewald RA, Kandler RH *et al.* (2006) Neuropathy associated with gluten sensitivity. *J Neurol Neurosurg Psychiatry* **77**, 1262–1266.
10. Hadjivassiliou M, Chattopadhyay AK, Grünewald RA *et al.* (2007) Myopathy associated with gluten sensitivity. *Muscle Nerve* **35**, 443–450.
11. Hadjivassiliou M, Maki M, Sanders DS *et al.* (2006) Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. *Neurology* **66**, 373–377.
12. Hadjivassiliou M, Boscolo S, Davies-Jones GA *et al.* (2002) The humoral response in the pathogenesis of gluten ataxia. *Neurology* **58**, 1221–1226.
13. Hadjivassiliou M, Davies-Jones GA, Sanders DS *et al.* (2003) Dietary treatment of gluten ataxia. *J Neurol Neurosurg Psychiatry* **74**, 1221–1224.
14. Hadjivassiliou M, Grunewald RA, Sharrack B *et al.* (2003) Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* **126**, 685–691.
15. Sanders DS, Patel D, Khan FB *et al.* (2005) The prevalence of unrecognised adult coeliac disease in patients with reduced bone mineral density: a case-finding approach. *Dig Dis Sci* **50**, 587–592.
16. Hopper AD, Hadjivassiliou M & Butt S (2007) Adult coeliac disease. *Br Med J* **335**, 558–562.
17. Sanders DS, Hurlstone DP, Stokes RO *et al.* (2002) The changing face of coeliac disease: experience of a single University Hospital in South Yorkshire. *Postgrad Med J* **78**, 31–33.
18. Richey R, Howdle P, Shaw E *et al.* (2009) Recognition and assessment of coeliac disease in children and adults: summary of NICE guidance. *Br Med J* **338**, b1684.
19. Evans K, McAllister R & Sanders DS (2009) Should we screen for coeliac disease? No. *Br Med J* **339**, b3674.
20. Azmy IAF, Hurlstone DP, Kong SC *et al.* (2004) Does surgical removal of mucosal associated lymphoid tissue protect against adult celiac disease: a case controlled study. *Dig Liver Dis* **36**, 187–190.
21. Hopper AD, Hadjivassiliou M, Hurlstone DP *et al.* (2008) What is the role of serological testing in celiac disease? A prospective, biopsy confirmed study with economic analysis. *Clin Gastroenterol Hepatol* **6**, 314–320.
22. Sanders DS, Hurlstone DP, McAlindon ME *et al.* (2005) Antibody negative coeliac disease presenting in the elderly – an easily missed diagnosis. *Br Med J* **330**, 775–776.
23. Hopper AD, Cross SS, Hurlstone DP *et al.* (2007) Pre-endoscopy serological testing for coeliac disease – an evaluated clinical decision tool. *Br Med J* **334**, 729–732.
24. Hopper AD, Cross SS & Sanders DS (2008) Patchy villous atrophy in adult patients with suspected gluten sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate? *Endoscopy* **40**, 219–224.
25. Hopper AD, Chew TS, Lewis A *et al.* (2008) Is there a case for routine duodenal biopsy at gastroscopy or is a targeted approach adequate? *Endoscopy* **40**, 727–730.
26. Höroldt BS, McAlindon ME, Stephenson TJ *et al.* (2004) Making the diagnosis of coeliac disease: is there a role for push enteroscopy? *Eur J Gastroenterol Hepatol* **16**, 1143–1146.
27. Hopper AD, Sidhu R, Hurlstone DP *et al.* (2007) Capsule endoscopy: an alternative to duodenal biopsy for the

recognition of villous atrophy in coeliac disease? *Dig Liv Dis* **39**, 140–145.

28. Hopper AD, Hurlstone DP, Leeds JS *et al.* (2006) Occurrence of terminal ileal histological abnormalities in patients with coeliac disease. *Dig Liv Dis* **38**, 815–819.

29. Van Heel D, Lude F, Hunt KA *et al.* (2007) A celiac disease genome-wide association study identifies a susceptibility variant in the IL2/IL21 region. *Nat Genet* **39**, 827–829.

30. Hunt KA, Zhernakova A, Turner G *et al.* (2008) Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet* **40**, 395–402.

31. Hopper AD, Leeds JS, Hurlstone DP *et al.* (2005) Are lower gastrointestinal investigations necessary in patients with coeliac disease? *Eur J Gastroenterol Hepatol* **17**, 617–621.

32. Zarkadas M, Cranney A, Case S *et al.* (2006) The impact of a gluten-free diet on adults with coeliac disease: results of a national survey. *J Hum Nutr Diet* **19**, 41–49.

33. Mustalahti K, Lohiniemi S, Collin P *et al.* (2002) Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Effect Clin Pract* **5**, 105–113.

34. Barratt S, Leeds JS, Robinson K *et al.* (2011) Reflux and irritable bowel syndrome are negative predictors of quality of life in coeliac disease and inflammatory bowel disease. *Eur J Gastroenterol Hepatol* **23**, 159–165.

35. Karajeh MA, Hurlstone DP, Patel T *et al.* (2005) Chefs' knowledge of coeliac disease (compared to the public): a questionnaire survey from the United Kingdom. *Clin Nutr* **24**, 206–210.

36. Evans KE & Sanders DS (2009) Symposium 1: joint BAPEN and British Society of Gastroenterology Symposium on 'Coeliac disease: basics and controversies' Coeliac disease: optimising the management of patients with persisting symptoms? *Proc Nutr Soc* **26**, 1–7.

37. Leeds JS, Hopper AD, Hurlstone DP *et al.* (2007) Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Therap* **25**, 265–271.

38. Leeds JS, Hœroldt BS, Sidhu R *et al.* (2007) Is there an association between coeliac disease and inflammatory bowel disease? A study of relative prevalence with population controls. *Scand J Gastroenterol* **42**, 1214–1220.

39. Lohi S, Mustalahti K, Kaukinen K *et al.* (2007) Increasing prevalence of coeliac disease over time. *Aliment Pharmacol Ther* **26**, 1217–1225.

40. Rubio-Tapia A, Kyle RA, Kaplan EL *et al.* (2009) Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* **137**, 88–93.

41. Catassi C, Kryszak D, Bhatti B *et al.* (2010) Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. *Ann Med* **42**, 530–538.

42. Biagi F & Corazza GR. (2010) Mortality in coeliac disease. *Nat Rev Gastroenterol Hepatol* **7**, 158–162.

43. Lewis NR, Sanders DS, Logan RF *et al.* (2009) Cholesterol profile in people with newly diagnosed coeliac disease: a comparison with the general population and changes following treatment. *Br J Nutr* **102**, 509–513.

44. Leeds JS, Hopper AD, Hadjivassiliou M *et al.* (2011) High prevalence of diabetic microvascular complications in adults with Type 1 diabetes and newly diagnosed coeliac disease: the Sheffield CD Prospective Study. *Diabetes Care* **34**, 2158–2163.

45. Hadjivassiliou M, Williamson CA & Woodroofe N (2004) The immunology of gluten sensitivity: beyond the gut. *Trends Immunol* **25**, 578–582.

46. Rostami K & Villanacci V (2009) Microscopic enteritis: novel prospect in coeliac disease clinical and immuno-histogenesis. Evolution in diagnostic and treatment strategies. *Dig Liver Dis* **41**, 245–252.

47. Kaukinen K, Turjanmaa K, Mäki M *et al.* (2000) Intolerance to cereals is not specific for coeliac disease. *Scand J Gastroenterol* **35**, 942–946.

48. Sapone A, Bai JC, Ciacci C *et al.* (2012) Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* **10**, 13.

49. Painter K (2008) Gluten-free diets gaining in popularity. *USA Today* 17 August.

50. Sapone A, Lammers KM, Casolaro V *et al.* (2011) Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med* **9**, 23.

51. Verdu EF, Armstrong D & Murray JA (2009) Between celiac disease and irritable bowel syndrome: the 'no man's land' of gluten sensitivity. *Am J Gastroenterol* **104**, 1587–1594.

52. Ball AJ, Hadjivassiliou M & Sanders DS. (2010) Is gluten sensitivity a 'No Man's Land' or a 'Fertile Crescent' for research? *Am J Gastroenterol* **105**, 222–223; author reply 223–4.

53. Wahnschaffe U, Schulzke JD, Zeitz M *et al.* (2007) Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* **5**, 844–850.

54. Biesiekierski JR, Newnham ED, Irving PM *et al.* (2011) Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* **106**, 508–514.