AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: coeliac disease and hypertransaminasaemia

A. Sainsbury*, D. S. Sanders† & A. C. Ford*,‡

*Leeds Gastroenterology Institute, Leeds General Infirmary, Leeds, UK.
†Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield, UK.
‡Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK.

Correspondence to:
Dr A. C. Ford, Leeds Gastroenterology Institute, Room 230, D Floor, Clarendon Wing, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK.
E-mail: alexf12399@yahoo.com

Publication data
Submitted 11 March 2011
First decision 13 April 2011
Resubmitted 13 April 2011
Accepted 15 April 2011

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr P. Collins.

SUMMARY

Background
There may be a positive association between coeliac disease and serum hypertransaminasaemia but evidence is conflicting.

Aims
To conduct a systematic review and meta-analysis to determine the prevalence of coeliac disease in adults presenting with cryptogenic serum hypertransaminasaemia and the prevalence of hypertransaminasaemia in patients with newly diagnosed coeliac disease.

Methods
MEDLINE and EMBASE were searched up to August 2010. Case series and case–control studies recruiting adults with either cryptogenic hypertransaminasaemia that applied serological tests for coeliac disease and/or distal duodenal biopsy to participants or newly diagnosed biopsy-proven coeliac disease that assessed serum transaminases were eligible. The pooled prevalence of coeliac disease in individuals presenting with abnormal serum transaminases and the pooled prevalence of hypertransaminasaemia in newly diagnosed coeliac disease were calculated with 95% confidence intervals (CI).

Results
Eleven eligible studies were identified. Pooled prevalences of positive coeliac serology and biopsy-proven coeliac disease in cryptogenic hypertransaminasaemia were 6% (95% CI 3% to 10%) and 4% (95% CI 1% to 7%) respectively. Pooled prevalence of abnormal serum transaminases in newly diagnosed coeliac disease was 27% (95% CI 13% to 44%). Exclusion of gluten led to normalisation of serum transaminase levels in 63% to 90% of patients within 1 year.

Conclusions
Undetected coeliac disease is a potential cause for cryptogenic hypertransaminasaemia in 3% to 4% of cases. More than 20% of individuals with newly diagnosed coeliac disease may have abnormal serum transaminases and these normalise on a gluten-free diet in the majority of cases.

doi:10.1111/j.1365-2036.2011.04685.x

INTRODUCTION

Coeliac disease is a chronic immune-mediated enteropathy, characterised by T-cell sensitisation to gluten in genetically predisposed individuals.[1] The disorder is common, with a population prevalence of around 1% in genetically susceptible populations.[2–5] The spectrum of presentation ranges from asymptomatic disease detected incidentally to severe intestinal malabsorption, with complications that may include osteoporosis, iron deficiency anaemia and infertility.[6]

A number of hepatic abnormalities have been described in association with coeliac disease. These include auto-immune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis.[7] For over three decades, an isolated elevation of hepatic transaminases has also been noted in coeliac disease, often as a presenting feature of the condition.[8, 9] Such cases have been associated with a mild nonspecific hepatitis on liver biopsy.[8]

This so-called 'coeliac hepatitis'[10] may normalise on gluten withdrawal,[8] but the pathogenesis of liver injury remains obscure. It has been suggested that the metabolic sequelae of malnutrition in coeliac disease lead to hepatic dysfunction and steatosis.[11] However, coeliac disease presenting with malnutrition is now uncommon. Intestinal mucosal permeability is increased in coeliac disease[12] and it has been hypothesised that this facilitates absorption of antigens and cytokines directly into the hepatic portal venous system, leading to hepatic inflammation.[13]

Despite this, severity of intestinal histological changes does not appear to correlate with transaminase levels.[14] Furthermore, hepatic involvement is not a feature of tropical sprue, a condition which produces a similar histological picture to coeliac disease.[15] More recently, it has been suggested that tissue transglutaminase (tTG), the target antigen recognised by antiendomysial antibody (EMA), may play a role in hepatic dysfunction.[16] This is supported by the finding of extracellular immunoglobulin (Ig) A-class tTG antibodies in liver biopsy specimens from patients with coeliac hepatitis.[17]

Despite the well-recognised association between coeliac disease and hepatobiliary disorders, screening for coeliac disease in patients with deranged liver biochemistry is not advocated routinely.[18] Furthermore, studies investigating the prevalence of coeliac disease in patients with cryptogenic hypertransaminasaemia have reported conflicting results. To date, there has been no systematic evaluation of the relationship between hypertransaminasaemia and coeliac disease. We therefore conducted a systematic review and meta-analysis to determine, firstly, the prevalence of coeliac disease in adults presenting with cryptogenic hypertransaminasaemia, and secondly, the prevalence of hypertransaminasaemia in adults presenting with newly diagnosed coeliac disease.

METHODS

Search strategy and study selection

A search of the medical literature was conducted using MEDLINE (1950 to 1st August 2010) and EMBASE (1980 to 1st August 2010) to identify case series and case–control studies that recruited unselected adults (over 90% of participants aged over 16 years) with either cryptogenic hypertransaminasaemia that applied serological tests for coeliac disease and/or distal duodenal biopsy to participants, or with newly diagnosed biopsy-proven coeliac disease that assessed serum transaminases.

Hypertransaminasaemia was defined as any value above the upper limit of normal for the individual investigating laboratory. IgA-class anti-EMAs and tTG were considered valid serological markers of coeliac disease. Studies were only eligible for inclusion if they contained 90 or more individuals, because of *a priori* concerns about statistical handling of rare events. First or senior authors of studies were contacted to provide additional information on studies where required.

Potentially eligible studies were identified using the following medical subject headings and free text terms: *coeliac*, *celiac*, *sprue*, *gluten sensitive enteropathy*, *villous atrophy*, *antigliadin*, *endomyseal*, *tissue transglutaminase* or *duodenal biopsy*. These were combined using the set operator 'AND' with studies identified with the following terms: *transaminase*, *transaminitis*, *hypertransaminasaemia*, *hypertransaminasaemia*, *alanine aminotransferase* or *aspartate aminotransferase*. There were no language restrictions. All abstracts of the identified articles were evaluated and potentially relevant articles were obtained and evaluated independently by two investigators (AS and ACF) according to the prospectively defined eligibility criteria, using predesigned eligibility forms. Any disagreement between investigators was resolved by consensus.

Data extraction

Data were extracted independently by two reviewers (AS and ACF) onto a Microsoft Excel spreadsheet (XP Professional Edition; Microsoft Corp., Redmond, WA, USA) and discrepancies were resolved by consensus. The following data were collected for each study: type of study,

year(s) conducted, country, setting (primary, secondary or tertiary care), number of centres, total number of subjects recruited, mean age of subjects and proportion of male subjects. In studies investigating subjects with cryptogenic hypertransaminasaemia, the number of individuals testing positive using either serum anti-EMA or tTG, or having biopsy-proven coeliac disease, was expressed as a proportion of the total number of subjects with cryptogenic hypertransaminasaemia. In studies reporting serum transaminase levels in subjects with newly diagnosed biopsy-proven coeliac disease, the number of individuals with abnormal serum transaminases was expressed as a proportion of the total number of subjects with newly diagnosed coeliac disease. For the latter group of studies, we also extracted the proportion of individuals whose serum transaminases normalised following the institution of a gluten-free diet, where individual studies reported these data.

Data synthesis and statistical analysis

In studies investigating subjects with cryptogenic hypertransaminasaemia, the proportion of individuals testing positive using serum anti-EMA or tTG, or having biopsy-proven coeliac disease, was combined for all studies to give a pooled prevalence of positive coeliac serology, or biopsy-proven coeliac disease, in cryptogenic hypertransaminasaemia, with 95% confidence intervals (CI). In studies reporting serum transaminase levels in subjects with newly diagnosed biopsy-proven coeliac disease, the proportion of individuals with abnormal serum transaminases was combined for all studies to give a pooled prevalence of hypertransaminasaemia in newly diagnosed coeliac disease with 95% CIs.

Data were pooled using a random effects model, to give a more conservative estimate of the prevalence of positive coeliac serology or biopsy-proven coeliac disease in cryptogenic hypertransaminasaemia and the prevalence of hypertransaminasaemia in newly diagnosed coeliac disease.[19] Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50%,[20] and the chi-squared test with a P value <0.10, used to define a statistically significant degree of heterogeneity. STATSDIRECT version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, UK) was used to generate Forest plots of pooled prevalences with 95% CIs.

RESULTS

The search identified 2705 citations. Of these, 30 studies appeared relevant and were retrieved for evaluation (Figure 1). Twelve studies were deemed eligible for inclusion initially, with excellent agreement between investigators (κ = 0.86).[14, 21–31] After contacting one author for clarification of study methodology, 1 of the 12 studies was subsequently excluded from the meta-analysis.[31] This study only reported the proportion of subjects in whom hypertransaminasaemia was the principal presenting feature of coeliac disease; the overall prevalence of hypertransaminasaemia in the study cohort was not reported. This left 11 studies eligible for inclusion.[14, 21–30]

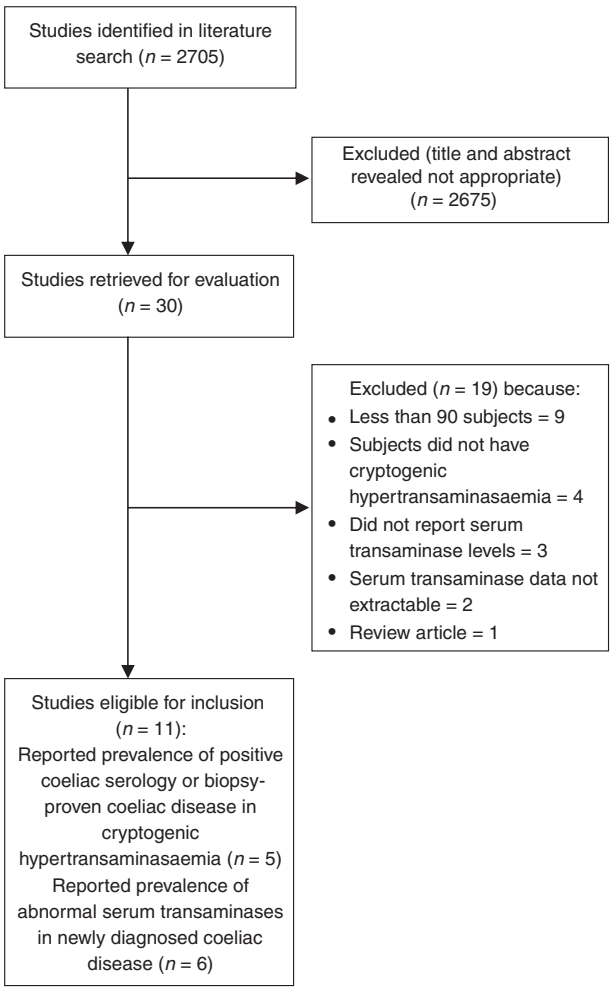

Figure 1 | Flow diagram of assessment of studies identified in the systematic review and meta-analysis.

Yield of serologic testing for coeliac disease in subjects with cryptogenic hypertransaminasaemia

Six studies, involving a total of 919 patients, reported the yield of testing for coeliac disease, using either serum anti-EMA or tTG, in patients with cryptogenic hypertransaminasaemia.[21–26] Detailed characteristics of individual studies are provided in Table 1. Two of the studies utilised a case–control design, employing blood

Table 1 | Studies reporting the prevalence of positive coeliac serology or biopsy-proven coeliac disease in patients with cryptogenic hypertransaminasaemia

Study	Country, setting, and number of centres	Other causes of abnormal serum transaminases excluded prior to coeliac testing?	Tests for coeliac disease applied	Number of participants (% male)	Number with positive coeliac serology (%)	Number with biopsy-proven coeliac disease (%)
Bardella *et al.*[21]	Italy, tertiary care, 3 sites	Yes	EMA, duodenal biopsy	140 (66)	13 (9)	12 (9)
Mugica *et al.*[22]	Spain, secondary and tertiary care, 4 sites	Yes	EMA, duodenal biopsy	147 (58)	4 (3)	2 (1)
Soresi *et al.*[23]	Italy, primary care, 1 site	Yes	tTG and EMA, duodenal biopsy	258 (64)	4 (2)	2 (1)
Volta *et al.*[24]	Italy, tertiary care, 1 site	Yes	tTG and EMA, duodenal biopsy	110 (45)	10 (9)	10 (9)
Carrocio *et al.*[25]	Italy, tertiary care, 1 site	No	tTG and EMA, duodenal biopsy	96 (68)	3 (3)	1 (1)*
Lo Iacono *et al.*[26]	Italy, tertiary care, 1 site	Yes	tTG and EMA, duodenal biopsy	168 (70)†	20 (12)	6 (4)

* The other two patients testing positive for tTG in this study had co-existent chronic hepatitis C infection and duodenal biopsy was normal histologically.

† 121 patients were ultimately diagnosed with non-alcoholic fatty liver disease and four of these had biopsy-proven coeliac disease.

donors[23] and patients with chronic liver disease,[21] as control participants. As these control subjects were not felt to be representative of the general population, we did not extract their data for comparison. The remaining four studies were case series.

The proportion of subjects with cryptogenic hypertransaminasaemia with positive coeliac serology ranged from 2% to 12% in individual studies. The pooled prevalence of positive coeliac serology in patients presenting with cryptogenic hypertransaminasaemia was 6% (95% CI 3% to 10%), with statistically significant heterogeneity between studies (I^2 = 83%, P < 0.001) (Figure 2). Five of the six studies excluded other causes of abnormal serum transaminases prior to screening for coeliac disease, with

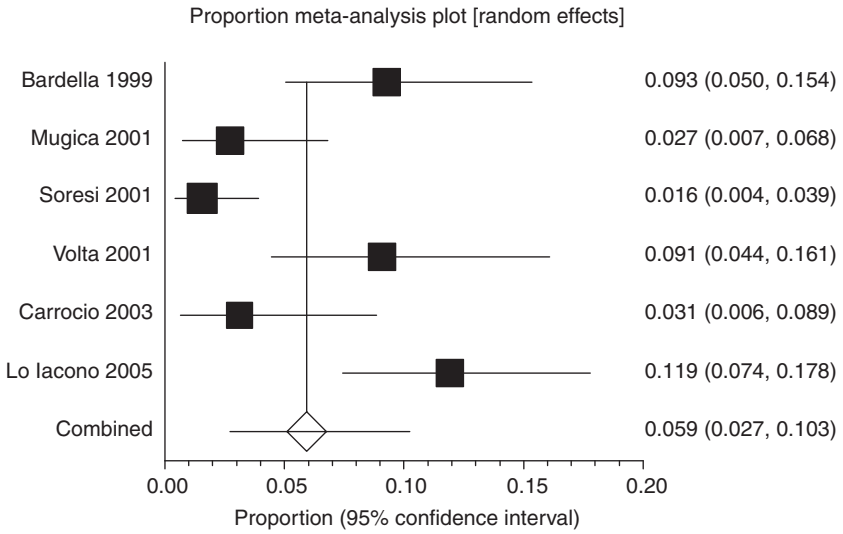

Figure 2 | Forest plot of the pooled prevalence of positive coeliac serology in cryptogenic hypertransaminasaemia.

a non-invasive liver screen for viral hepatitis, haemochromatosis and auto-immune liver disease.[21–24, 26] Four studies also screened for Wilson's disease and alpha-1 antitrypsin deficiency.[21, 22, 24, 26] When only the five studies that had performed a non-invasive liver screen were analysed, the pooled prevalence of positive coeliac serology in cryptogenic hypertransaminasaemia increased to 6% (95% CI 3% to 12%), although significant heterogeneity between studies remained (I^2 = 87%, P < 0.001).

Yield of distal duodenal biopsy following positive coeliac serology in subjects with cryptogenic hypertransaminasaemia

In all six studies that applied serological testing for coeliac disease to subjects with cryptogenic hypertransaminasaemia,[21–26] individuals with a positive serological test for coeliac disease were offered distal duodenal biopsy for histological confirmation of coeliac disease. Of the 54 patients with positive coeliac serology, 52 (96%) agreed to undergo endoscopy with distal duodenal biopsy. The proportion of subjects with cryptogenic hypertransaminasaemia with biopsy-proven coeliac disease ranged from 1% to 9% in individual studies. The pooled prevalence of biopsy-proven coeliac disease in cryptogenic hypertransaminasaemia in these six studies was 4% (95% CI 1% to 7%), with statistically significant heterogeneity between studies (I^2 = 81%, P < 0.001) (Figure 3). When only the five studies that excluded other causes of abnormal serum transaminases prior to testing for coeliac disease were included in the analysis,[21–24, 26] the pooled prevalence of biopsy-proven coeliac disease in cryptogenic hypertransaminasaemia increased to 4% (95% CI 1% to 8%), although significant heterogeneity between studies remained (I^2 = 84%, P < 0.001).

Prevalence of abnormal serum transaminases in patients with newly diagnosed coeliac disease

Five studies, involving a total of 1136 patients, reported the prevalence of abnormal serum transaminases in newly diagnosed coeliac disease.[14, 27–30] All studies were of case series type. Detailed characteristics of individual studies are provided in Table 2. The prevalence of abnormal serum transaminases in newly diagnosed coeliac disease ranged from 11% to 42%. The pooled prevalence of abnormal serum transaminases in newly diagnosed coeliac disease was 27% (95% CI 13% to 44%), with statistically significant heterogeneity between studies (I^2 = 97%, P < 0.001) (Figure 4).

All five studies reported the degree of improvement in abnormal serum transaminases with institution of a gluten-free diet within 1 year. In four of the studies, exclusion of gluten led to normalisation of serum transaminase levels in between 63% and 90% of participants.[14, 27–29] The fifth study reported statistically significant reductions in mean transaminases levels with gluten withdrawal.[30]

DISCUSSION

The current meta-analysis has demonstrated a pooled prevalence of biopsy-proven coeliac disease of between 3.6% and 4.1% in patients found to have cryptogenic hypertransaminasaemia. This equates to an approximately four-fold risk of coeliac disease, compared with the background population risk of around 1%.[32] It is conceivable that growing numbers of patients with coeliac disease will be identified in this way, given that the classical presentation of malabsorption and failure to thrive in childhood is increasingly being replaced by more subtle gastrointestinal symptoms, or incidental

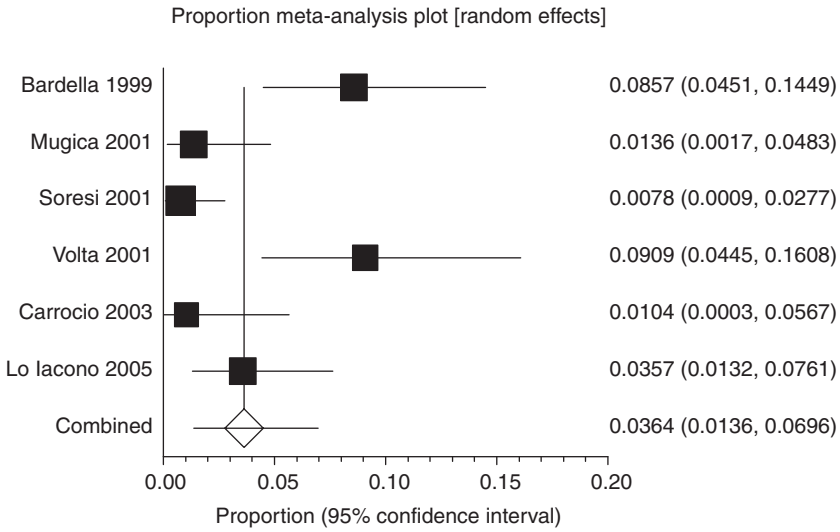

Figure 3 | Forest plot of the pooled prevalence of biopsy-proven coeliac disease in cryptogenic hypertransaminasaemia.

Table 2 | Studies reporting the prevalence of abnormal serum transaminases in newly diagnosed coeliac disease

Study	Country, setting and number of entres	Number of participants (% male)	Number with abnormal serum transaminases (%)	Number improving with institution of gluten-free diet (%)
Bardella *et al.*[14]	Italy, tertiary care, number of sites not reported	158 (20)	67 (42)	60 (90)
Dickey *et al.*[27]	Northern Ireland, secondary and tertiary care, 4 sites	129 (32)	19 (15)	15 (79)
Novacek *et al.*[28]	Austria, tertiary care, 1 site	178 (27)	72 (40)	64 (89)
Foley *et al.*[29]	Australia, tertiary care, 1 site	99 (24)	34 (34)	12/19* (63)
Lewis *et al.*[30]	United Kingdom, tertiary care, 2 sites	572 (not reported)	60 (11)	Not reported†

* Only the initial 53 study participants were followed up regularly for 12 months after gluten withdrawal, of whom 19 had abnormal liver biochemistry.

† The study reported statistically significant reductions in mean transaminases levels with gluten withdrawal but not absolute number of patients whose transaminases improved.

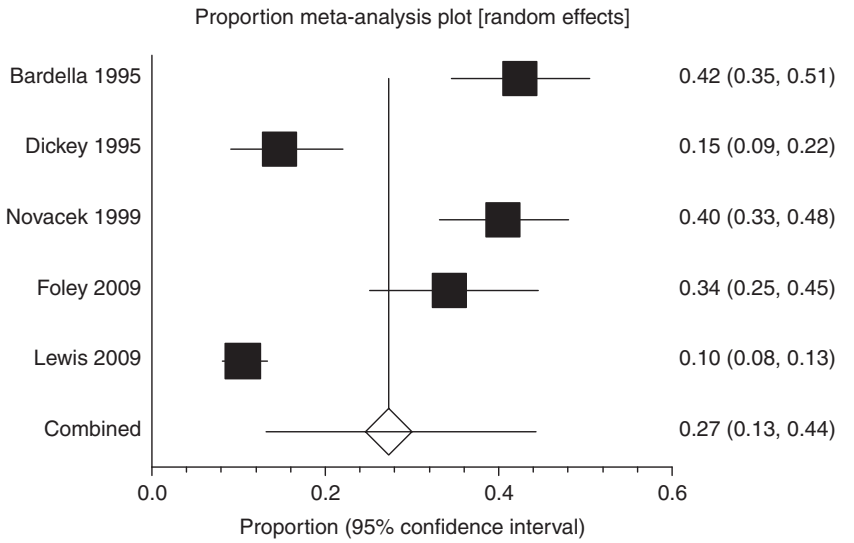

Figure 4 | Forest plot of the pooled prevalence of abnormal serum transaminases in newly diagnosed coeliac disease.

abnormalities found on routine blood testing.[33] Individuals identified with coeliac disease during the investigation of hypertransaminasaemia are presumably detected at an early stage in the course of the condition.[13] It has been suggested that timely diagnosis may be advantageous, in that it may halt or even reverse progression to chronic liver disease.[8] The complications of coeliac disease may also be reduced, including osteoporosis[34] and infertility.[35]

These data also demonstrate that over 20% of individuals with newly diagnosed coeliac disease may have elevated serum transaminases at presentation. All of the included studies reported either improvement in, or normalisation of, serum transaminase levels in the majority of participants following dietary exclusion of gluten. Increased awareness of this phenomenon will enable clinicians to reserve invasive investigations for individuals in whom deranged biochemistry persists despite adherence to a strict gluten-free diet.

The strengths of our study include a rigorous search strategy and extensive literature search, the judging of study eligibility and extraction of data in duplicate, and pooling of data to allow synthesis of all the available published evidence. Limitations of the current study relate to those of the available studies; 8 of 12 studies

were based in tertiary care, which may reduce the applicability of the results to the general population.[36] The Italian population was disproportionately represented, with 7 of the 12 studies conducted in Italy, compared with only two in the UK. The prevalence of coeliac disease in Italy may be somewhat lower than in the UK.[37]

Moreover, robust studies comparing the sensitivity and specificity of coeliac serological tests in different populations are lacking. There was heterogeneity between study results in all of our analyses, which we were unable to uncover reasons for due to the relatively small number of studies available. Finally, in the six studies investigating cryptogenic hypertransaminasaemia, body mass index (BMI) was not included in the panel of liver screening tests. As obesity is a common cause for deranged serum transaminases in the western world, our meta-analysis may have underestimated the true prevalence of coeliac disease in true 'cryptogenic' hypertransaminasaemia.

Consideration should be given to coeliac serology testing in the investigation of deranged liver biochemistry and the term 'cryptogenic hypertransaminasaemia' should be reserved for those in whom a comprehensive non-invasive liver screen has included testing for coeliac disease. However, clinicians should also be aware of the possibility of false positive serological tests for coeliac disease in patients with chronic liver disease,[25] underlining the importance of confirmatory distal duodenal biopsy in these patients. A non-invasive liver screen for abnormal serum transaminases frequently includes tests such as serum caeruloplasmin, although the diagnostic yield is low and Wilson's disease is a rare condition.

Should we as clinicians also consider including coeliac serology as part of the initial non-invasive liver screen? Our data suggest that this may be worthwhile, but the cost-effectiveness of this approach has not been studied to date. Until this issue is examined, these data suggest that routine testing for coeliac disease in patients with cryptogenic hypertransaminasaemia may be a worthwhile strategy.

ACKNOWLEDGEMENTS

Declaration of personal interests: We are grateful to Dr MT Bardella for providing us with supplementary information regarding her study. *Declaration of funding interests:* None.

REFERENCES

1. Marsh MN. Clinical and pathological spectrum of coeliac disease. *Gut* 1993; **34**: 1740.
2. Sanders DS, Patel D, Stephenson TJ, *et al.* A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* 2003; **15**: 407–13.
3. Mustalahti K, Catassi C, Reunanen A, *et al.* The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010; **42**: 587–95.
4. Bahari A, Karimi M, Sanei-Moghaddam I, Firouzi F, Hashemi M. Prevalence of celiac disease among blood donors in Sistan and Balouchestan Province, Southeastern Iran. *Arch Iran Med* 2010; **13**: 301–5.
5. Katz KD, Rashtak S, Lahr BD, *et al.* Screening for celiac disease in a North American population: sequential serology and gastrointestinal symptoms. *Am J Gastroenterol* 2011 [Epub ahead of print].
6. Sanders DS, Hurlstone DP, Stokes RO, *et al.* Changing face of adult coeliac disease: experience of a single university hospital in south Yorkshire. *Postgrad Med J* 2002; **78**: 31–3.
7. Sjöberg K, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but not gliadin antibodies predict coeliac disease in patients with chronic liver disease. *Scand J Gastroenterol* 1997; **32**: 1162–7.
8. Hagander B, Berg NO, Brandt L, Nordén A, Sjölund K, Stenstam M. Hepatic injury in adult coeliac disease. *Lancet* 1977; **2**: 270–2.
9. Lindberg T, Berg NO, Borulf S, Jakobsson I. Liver damage in coeliac disease or other food intolerance in childhood. *Lancet* 1978; **1**: 390–1.
10. Volta U. Liver dysfunction in celiac disease. *Minerva Med* 2008; **99**: 619–29.
11. Naschitz JE, Yeshurun D, Zuckerman E, Arad E, Boss JH. Massive hepatic steatosis complicating adult celiac disease: report of a case and review of the literature. *Am J Gastroenterol* 1987; **82**: 1186–9.
12. Clemente MG, De Virgiliis S, Kang JS, *et al.* Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function. *Gut* 2003; **52**: 218–23.
13. Volta U, De Franceschi L, Lari F, Molinaro N, Zoli M, Bianchi FB. Coeliac disease hidden by cryptogenic hypertransaminasaemia. *Lancet* 1998; **352**: 26–9.
14. Bardella MT, Fraquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasaemia in adult celiac patients and effect of gluten-free diet. *Hepatology* 1995; **22**: 833–6.
15. Floch MH, Thomassen RW, Guerra R, Cox RS, Sheehy TW, Plough IC. The structural and functional status of the liver in tropical sprue. *Am J Dig Dis* 1963; **8**: 344–52.
16. Peláez-Luna M, Schmulson M, Robles-Díaz G. Intestinal involvement is not sufficient to explain hypertransaminasemia in celiac disease? *Med Hypotheses* 2005; **65**: 937–41.
17. Korponay-Szabó IR, Halttunen T, Szalai Z, *et al.* In vivo targeting of intestinal and extraintestinal transglutaminase 2 by coeliac autoantibodies. *Gut* 2004; **53**: 641–8.
18. Cobbold JF, Anstee QM, Thomas HC. Investigating mildly abnormal serum aminotransferase values. *Br Med J* 2010; **341**: c4039.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
20. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003; **327**: 557–60.
21. Bardella MT, Vecchi M, Conte D, *et al.* Chronic unexplained hypertransaminas-

emia may be caused by occult celiac disease. *Hepatology* 1999; **29**: 654–7.
22. Mugica F, Castiella A, Otazua P, *et al.* Prevalence of coeliac disease in unexplained chronic hypertransaminasemia. *Rev Esp Enferm Dig* 2001; **93**: 707–14.
23. Soresi M, Amplo M, Agliastro R, *et al.* Screening for autoantibodies to tissue transglutaminase reveals a low prevalence of celiac disease in blood donors with cryptogenic hypertransaminasemia. *Digestion* 2001; **64**: 87–91.
24. Volta U, Granito A, De Franceschi L, Petrolini N, Bianchi FB. Coeliac disease in patients with hypertransaminasaemia of unknown origin. *Dig Liver Dis* 2001; **33**: 420–5.
25. Carroccio A, Soresi M, Di Prima L, Montalto G. Screening for celiac disease in patients with chronic liver disease. *Gastroenterology* 2003; **125**: 1289–90.
26. Lo Iacono O, Petta S, Venezia G, *et al.* Anti-tissue transglutaminase antibodies in patients with abnormal liver tests: is it always coeliac disease? *Am J Gastroenterol* 2005; **100**: 2472–7.
27. Dickey W, McMillan SA, Collins JSA, Watson RGP, McLoughlin JC, Love AHG. Liver abnormalities associated with celiac sprue: How common are they, what is their significance, and what do we do about them? *J Clin Gastroenterol* 1995; **20**: 290–2.
28. Novacek G, Miehsler W, Wrba F, Ferenci P, Penner E, Vogelsang H. Prevalence and clinical importance of hypertransaminasaemia in coeliac disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 283–8.
29. Foley A, Shepherd SJ, Gibson PR. Frequency of elevated ALT in untreated coeliac disease and the impact of compliance with gluten free diet on ALT normalisation. *J Gastroenterol Hepatol* 2009; **24**: A337.
30. Lewis NR, Sanders DS, Teahon K, Logan RFA, Fleming KM, West J. Prevalence and consequence of hypertransaminasaemia in incident coeliac disease: How common is it and does it matter? *Gut* 2009; **58**: A6.
31. Bardella MT, Fredrella C, Saladino V, *et al.* Gluten intolerance: gender- and age-related differences in symptoms. *Scand J Gastroenterol* 2005; **40**: 15–9.
32. Dubé C, Rostom A, Sy R, *et al.* The prevalence of celiac disease in average-risk and at-risk Western European populations: a systematic review. *Gastroenterology* 2005; **128**(Suppl. 1): S57–67.
33. Lo W, Sano K, Lebwohl B, Diamond B, Green PH. Changing presentation of adult celiac disease. *Dig Dis Sci* 2003; **48**: 395–8.
34. McFarlane XA, Bhalla AK, Reeves DE, Morgan LM, Robertson DA. Osteoporosis in treated adult coeliac disease. *Gut* 1995; **36**: 710–4.
35. Collin P, Vilska S, Heinonen PK, Hällström O, Pikkarainen P. Infertility in coeliac disease. *Gut* 1996; **39**: 382–4.
36. Layde PM, Broste SK, Desbiens N, *et al.* Generalizability of clinical studies conducted at tertiary care medical centers: a population-based analysis. *J Clin Epidemiol* 1996; **49**: 835–41.
37. Catassi C, Ratsch IM, Fabiani E, *et al.* High prevalence of undiagnosed coeliac disease in 5280 Italian students screened by antigliadin antibodies. *Acta Paediatr* 1995; **84**: 672–6.