

Gut-liver axis: pathogenesis and clinical manifestations of liver damage in coeliac disease

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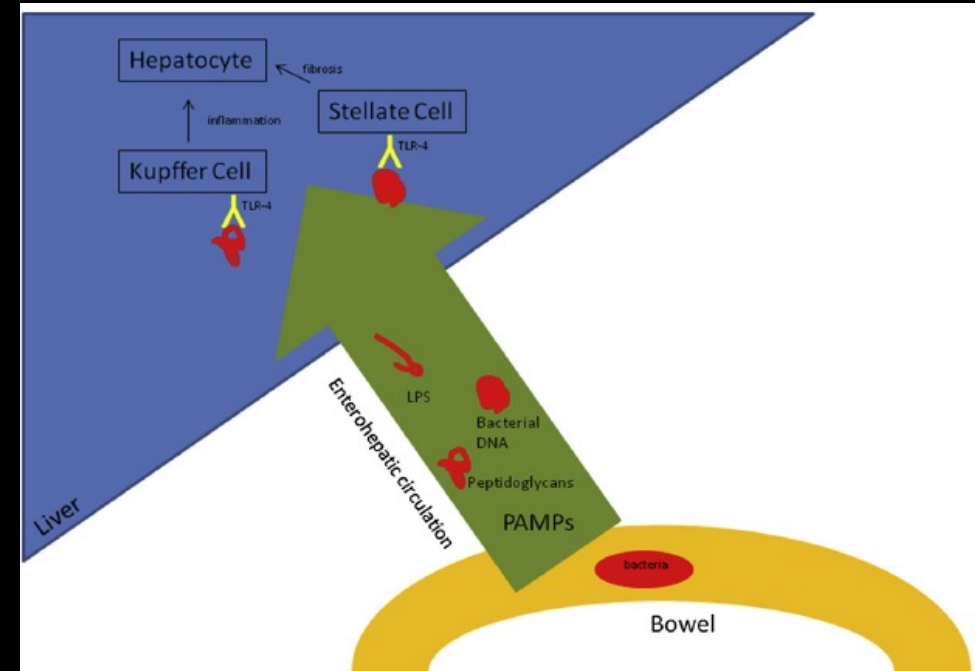
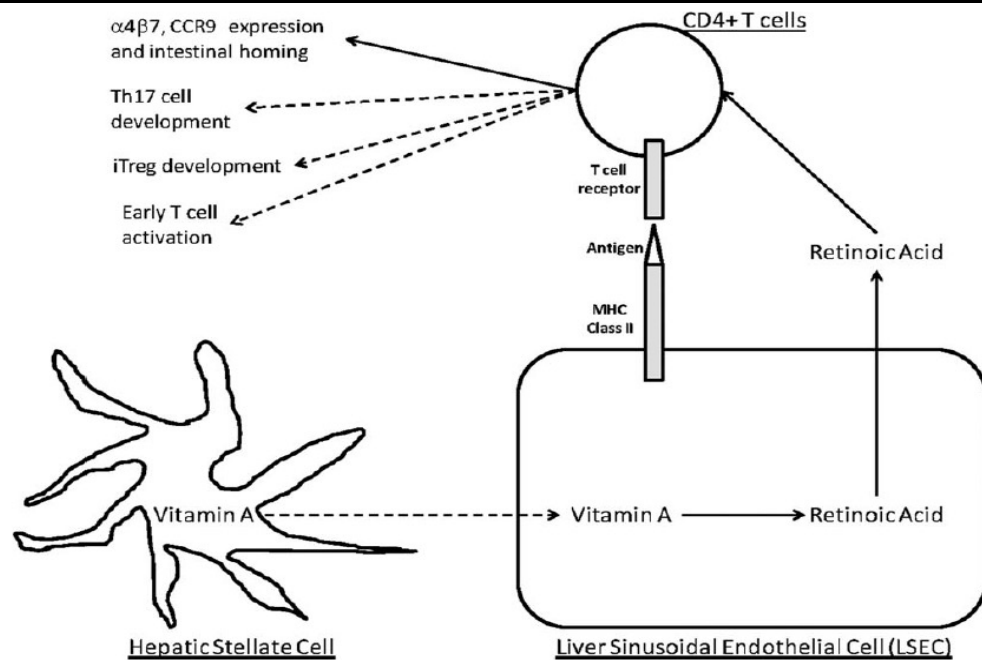
University of Bologna, Italy

Board Italian Association of Celiac Disease (AIC)

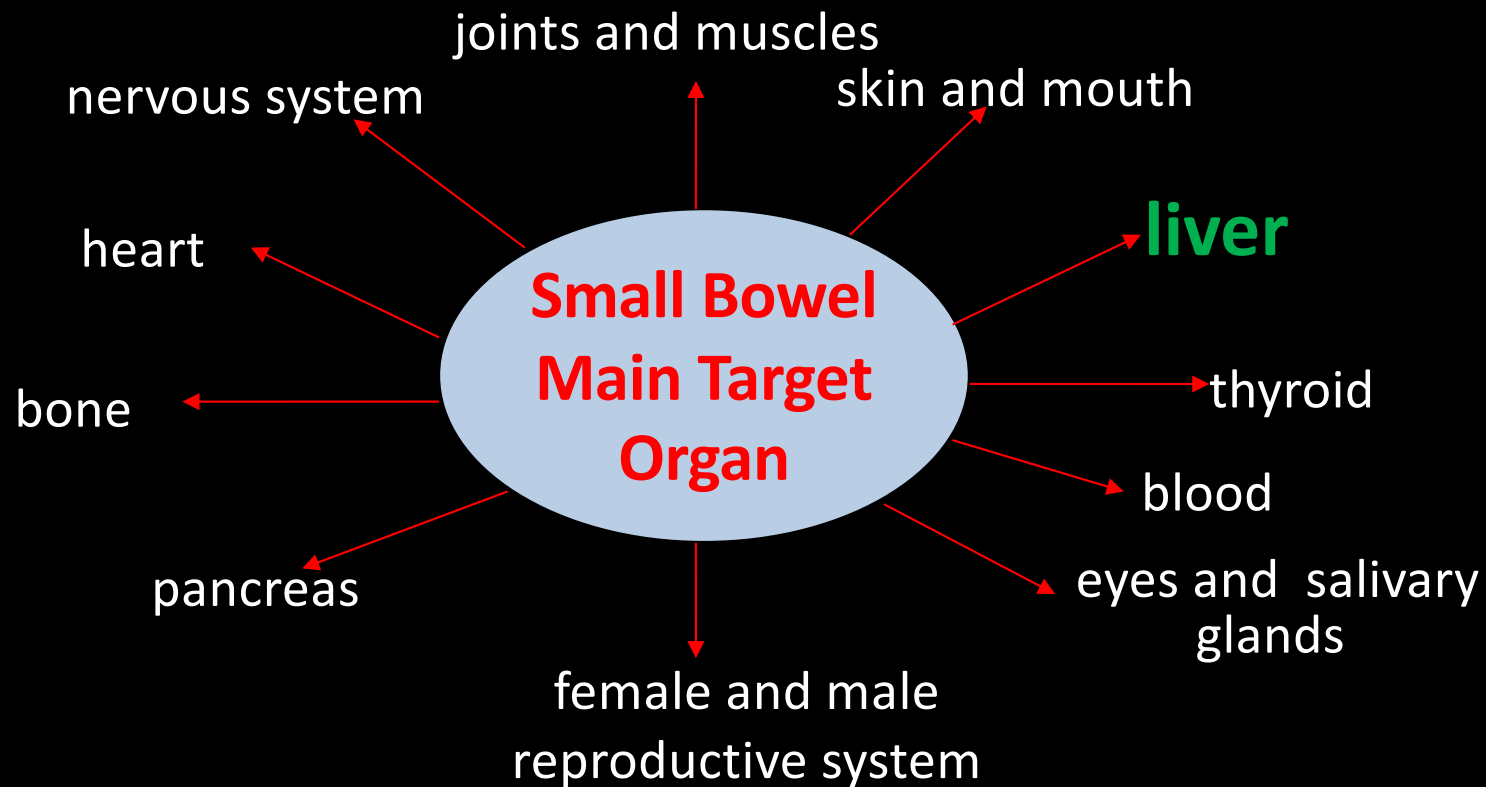


EDITORIALS

The Gut-Liver Axis: A Busy Two-Way Street



Coeliac disease in and outside the gut





Spectrum of liver disorders in coeliac disease (CD)

- Coeliac hepatitis

- Mild liver dysfunction (hypertransaminasaemia with mild histological changes)
- Chronic liver disease (chronic hepatitis, severe fibrosis, cirrhosis, liver failure)

- Autoimmune liver disorders (primary biliary cholangitis, primary sclerosing cholangitis, type 1 and 2 autoimmune hepatitis, autoimmune cholangitis)

Volta U. Clin Rev Allergy Immunol 2009; 36:62-70; Yoosuf S et al. Am J Gastroenterol 2023; 118:820-832



Pathogenesis and Clinical Significance of Liver Injury in Celiac Disease

Umberto Volta

Table 1 Prevalence of raised levels of transaminases and their normalization after a strict gluten-free diet (GFD) in celiac disease (CD)

	Number of patients, female/ male	Mean age (range)	Elevated transaminases at CD diagnosis, %	Transaminase normalization after 6–12 months of GFD, %
Hagander et al. [24]	74, 43/31	42 years (14–73)	39 (29/74)	100
Bardella et al. [31]	158, 127/31	32 years (18–68)	42 (67/158)	95
Molinaro et al. [32]	70, 45/25	42 years (14–79)	47 (33/70)	85
Novacek et al. [33]	178, 130/48	36 years (17–84)	40 (72/178)	95.4
Farre et al. [34]	114, 63/51	5 years (9 months– 17 years)	32 (37/114)	100
Bonamico et al. [35]	65, 43/22	4 years (6 months– 18 years)	57 (37/65)	95
Arslan et al. [36]	27, 17/10	6 years (1–11)	26 (7/27)	100



Hypertransaminasaemia in coeliac disease (CD)

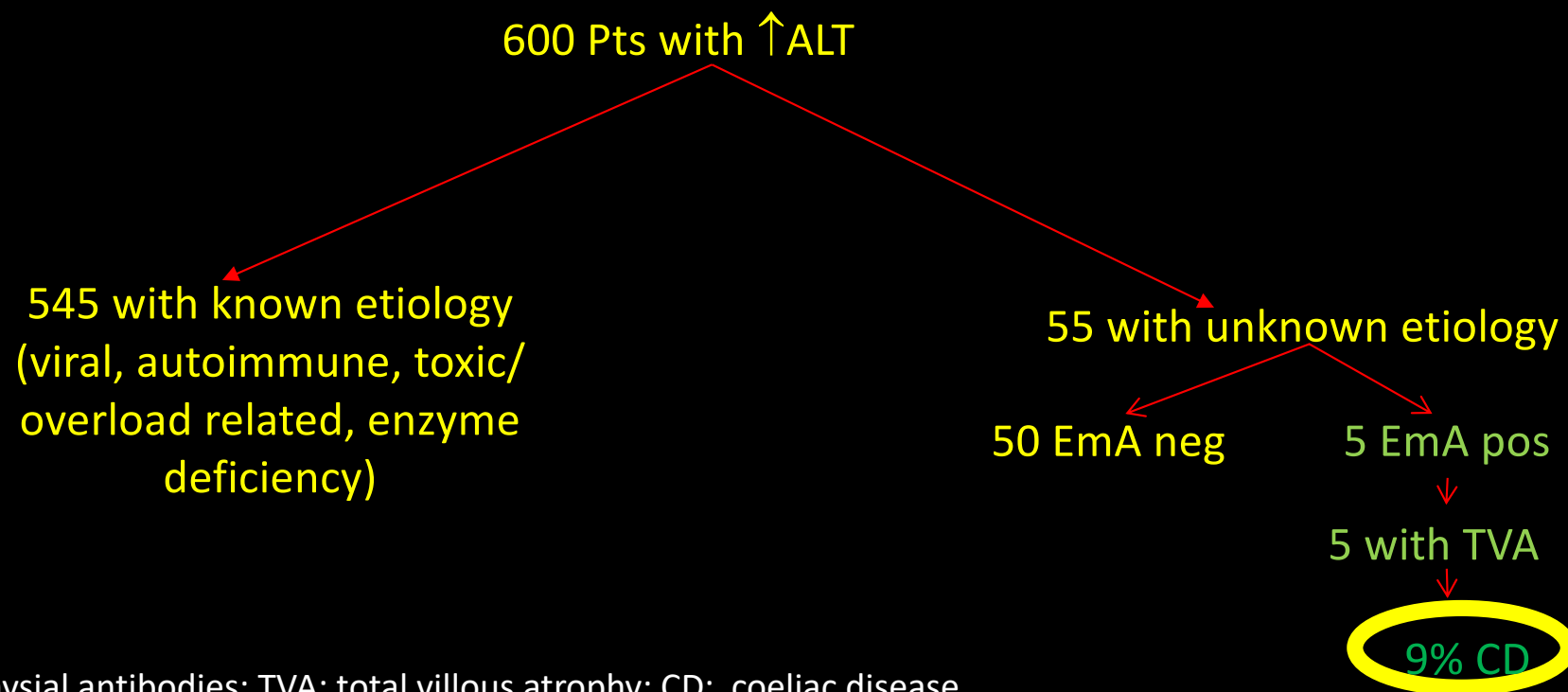
- More frequent elevation of alanine than aspartate transaminases, usually with normal levels of γ -GT, alkaline phosphatase and bilirubin
- Increase in transaminase levels usually mild ($<2x$), but in some cases up to ten times the normal limit
- Transaminases revert to normal within 6-12 months of gluten-free diet
- Hypertransaminasaemia can be the only sign of CD without any gastrointestinal or other gluten-induced symptoms



Coeliac disease hidden by cryptogenic hypertransaminasaemia

The Lancet 1998;352:26-9

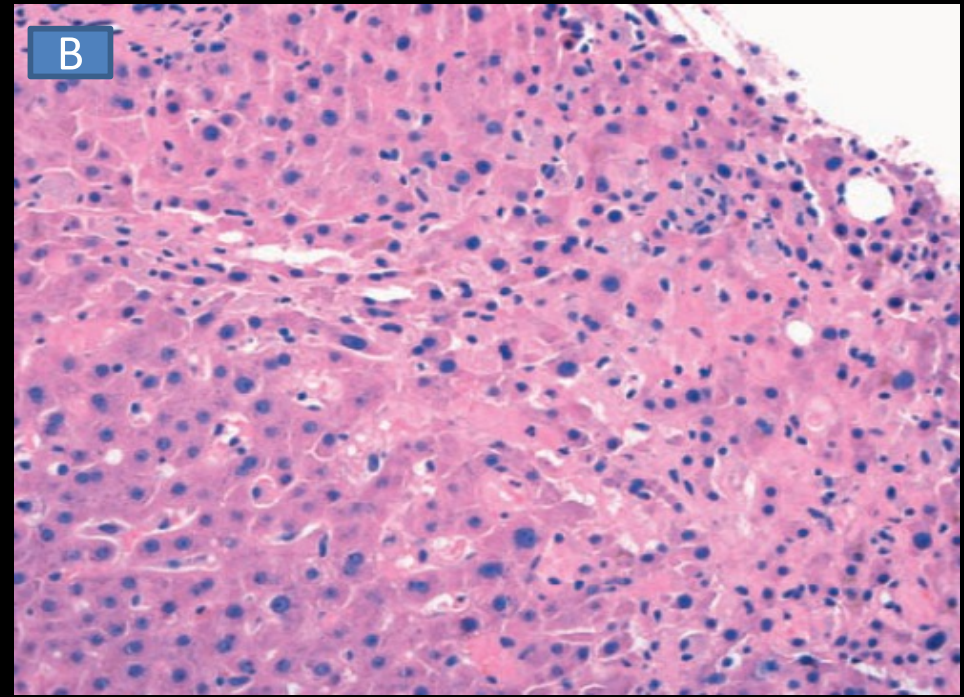
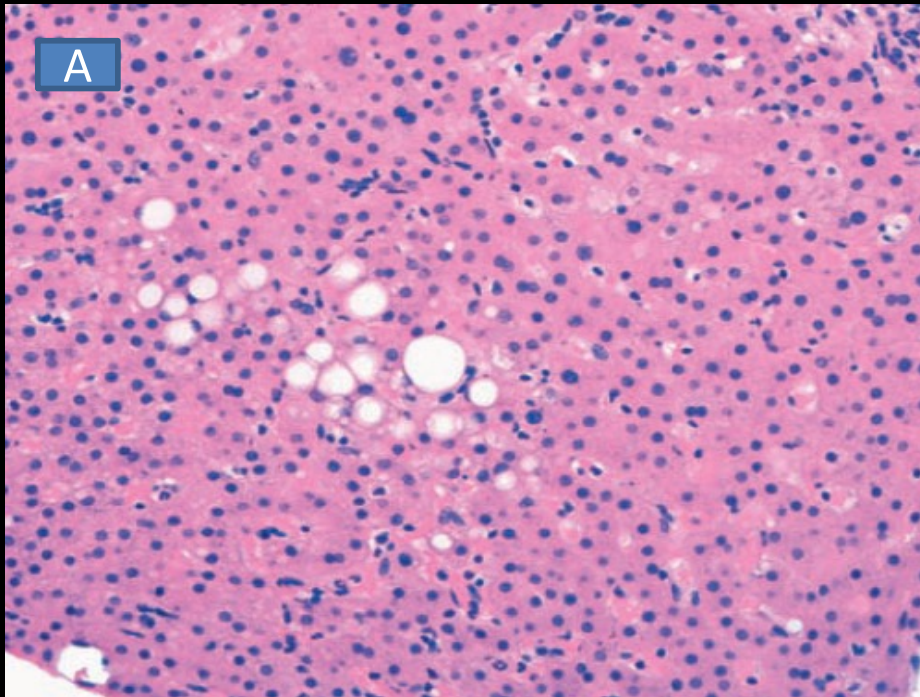
Umberto Volta, Lucia De Franceschi, Federico Lari, Nicolino Molinaro, Marco Zoli, Francesco B Bianchi



EmA: endomysial antibodies; TVA: total villous atrophy; CD: coeliac disease

Coeliac hepatitis: minimal liver changes

Volta U et al, The Lancet 1998; 352:26-9



Minimal liver changes observed in coeliac hepatitis:

A – minimal macrovesicular steatosis, B - Kupffer cell hyperplasia (H & E 100 X)

Chronic Unexplained Hypertransaminasemia May Be Caused by Occult Celiac Disease

HEPATOLOGY 1999;29:654-657.

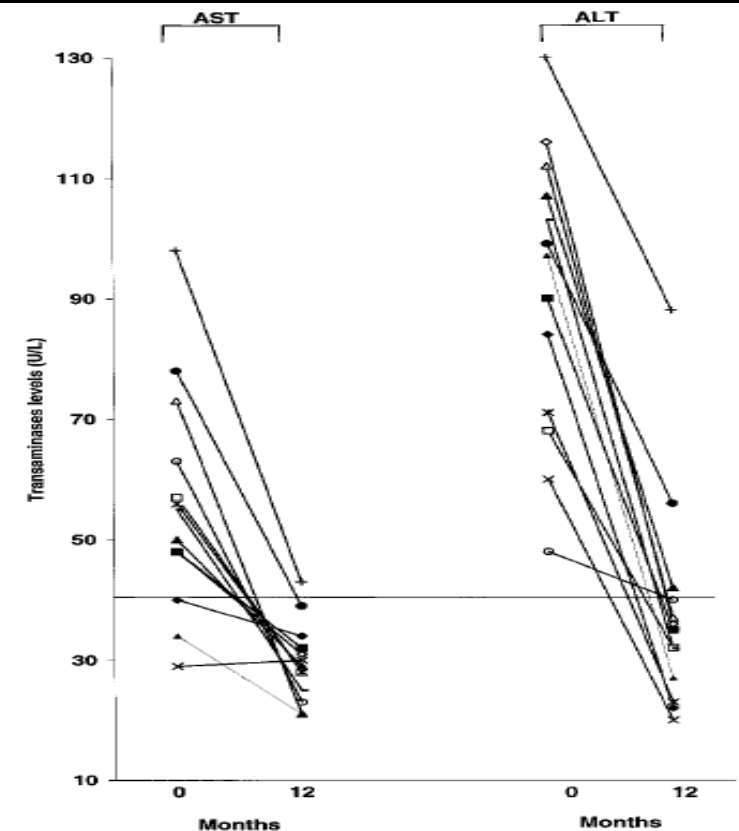
MARIA TERESA BARDELLA,¹ MAURIZIO VECCHI, DARIO CONTE,¹ ERSILIO DEL NINNO, MIRELLA FRAQUELLI,¹ STEFANIA PACCHETTI,² ELISEO MINOLA,¹ MARINA LANDONI, BRUNO MARIO CESANA,¹ AND ROBERTO DE FRANCHIS



TABLE 1. Demographic Characteristics, Main Serological Findings, Antigliadin (AGA) and Antiendomysium (EmA) Antibodies, Hepatic Ultrasound and Histological Findings, and Duodenal Histology in 13 Patients With Chronic Hypertransaminasemia of Unknown Cause and Celiac Disease

Patient	Sex	Age (yrs)	BMI (kg/m ²)	AST/ALT (U/L)	Hb (g/dL)	Ferritin (μg/L)	AGA	EmA	Hepatic Findings		Duodenal Histology
									US	Histology	
1	M	44	23	48/116	12.5	104	+	+	MS	Microvesicular steatosis	SVA
2	F	32	19	57/68	10.8	11	+	+	N	Minimal changes	SVA
3	F	50	22	48/90	12.0	6.5	+	+	MS	ND	IIEs/MA
4	F	38	21	37/48	11.6	21	+	+	N	Minimal changes	TVA
5	F	23	18	56/71	11.2	10	+	+	N	Macrovesicular steatosis	TVA
										Periportal piecemeal necrosis	
6	F	24	22	78/99	11.0	6	+	+	MS	Minimal changes	TVA
7	M	23	23	80/130	13.3	210	+	+	MS	Minimal changes	SVA
8	F	30	30	55/103	16.0	7	+	+	MS	ND	ND
9	F	28	23	34/97	13.0	14	+	+	MS	Minimal changes	SVA
10	F	40	20	40/84	11.1	4	+	+	N	ND	SVA
11	M	25	25	73/112	12.7	173	+	+	MS	Microvesicular steatosis	IIEs/MA
12	M	30	24	50/107	13.2	68	+	+	N	Minimal changes	IIEs/MA
13	M	62	23	29/60	14.0	485	+	+	N	ND	SVA

13/140 (9.3%) pts with unexplained raised transaminases had coeliac disease. Transaminases reverted to normal within 12 months of gluten-free diet





Coeliac Disease (CD) and NASH/NAFLD

- About 4-10% of patients with NASH and NAFLD are positive for tissue transglutaminase antibodies, but duodenal biopsy confirms CD diagnosis only in a proportion of them

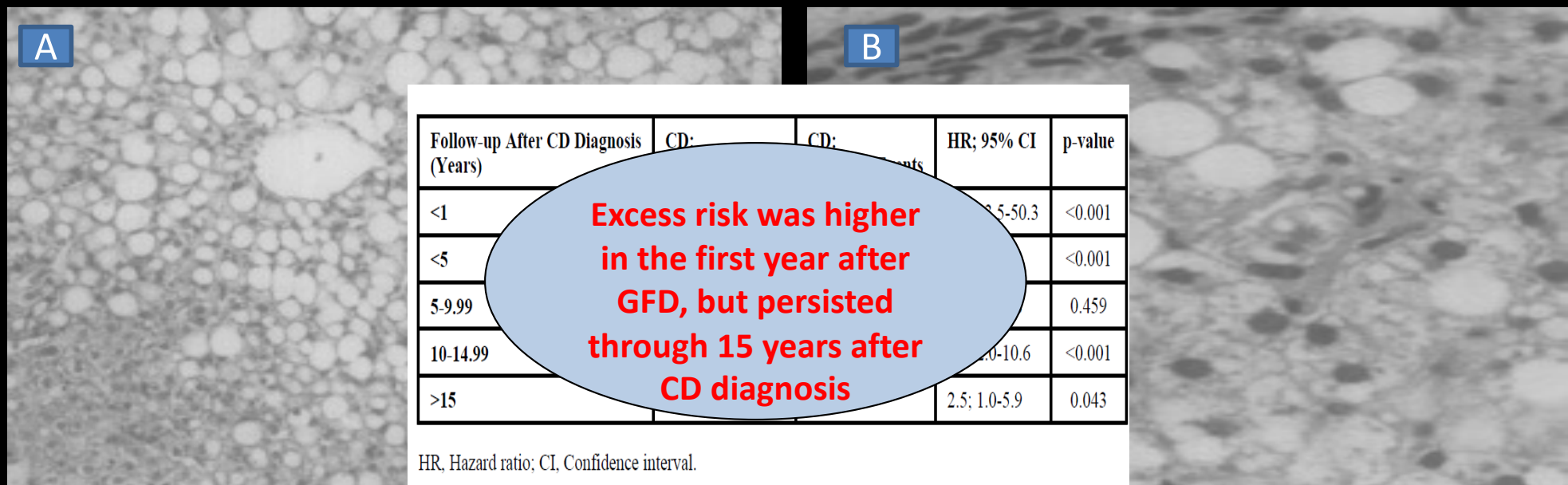
Nehra V et al. , Dig Dis Sci 2001; 46:2347-52; Bardella MT et al. , Dig Liver Dis 2004; 34:333-6

Abenavoli L et al, Endocrine 2013; 43:65-67; Hoffmanova I et al, Nutrients 2018; 10:892

- The coexistence of NASH/NAFLD and untreated CD is likely to be coincidental rather than a true association due the high prevalence of both conditions in the general population

Rubio-Tapia A et al. , Hepatology 2007; 46:1650-8; Volta U, Clin Rev Allergy Immunol 2009; 36: 62-70 ; Roderburg C et al., Eur J Gastroenterol Hepatol 2022; 34:328-31; Narciso-Schiavon JL et a., World J Hepatol 2023;

Increased risk of NAFLD in coeliac disease (CD) after gluten-free diet



A-Conventional haematoxylin-eosin staining: NAFLD high grade pericentral steatosis (magnification 40x)

B-Conventional haematoxylin-eosin staining: NAFLD presence of ballooning degeneration (magnification 120x)



Increased risk of nonalcoholic fatty liver disease in patients with coeliac disease on a gluten-free diet: beyond traditional metabolic factors

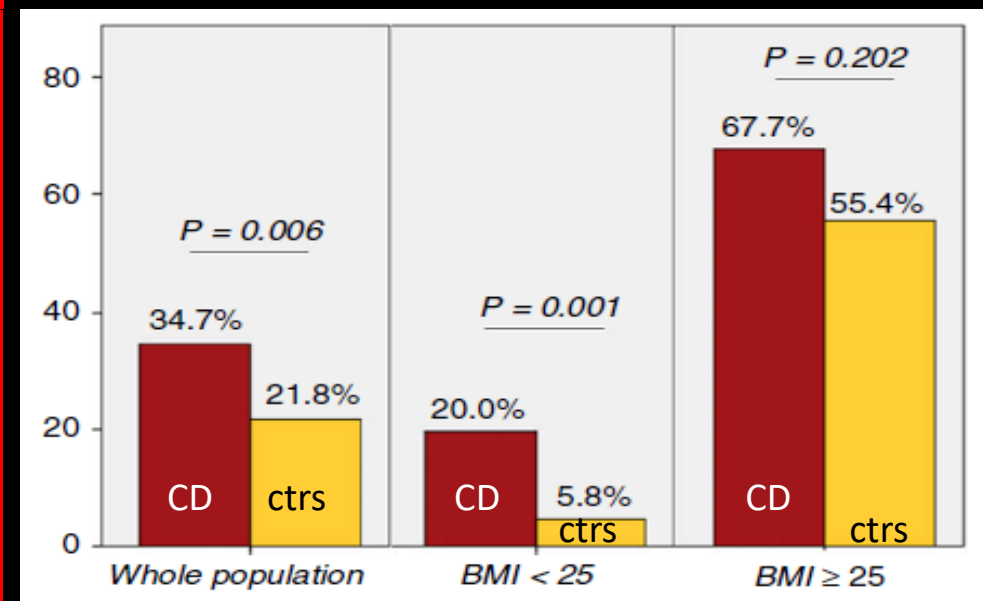
F. Tovoli  | G. Negrini | R. Farì | E. Guidetti | C. Faggiano | L. Napoli  |
L. Bolondi  | A. Granito 

Alimentary Pharmacology and Therapeutics 2018; 48:538-546

More than one predisposing factor

- Persistence of microbiota changes after GFD
- Altered intestinal permeability still present after GFD
- Increased intestinal absorption due to intestinal villi regrowth
- High content of lipids and carbohydrates in commercially available gluten-free food favoring metabolic syndrome

NAFLD in CD and controls after GFD related with BMI





Celiac Disease in Patients With Severe Liver Disease: Gluten-Free Diet May Reverse Hepatic Failure

Gastroenterology 2002; 122:881-8

KATRI KAUKINEN,* LEENA HALME,† PEKKA COLLIN,* MARTTI FÄRKKILÄ,† MARKKU MÄKI,*
PAULA VEHMANEN,§ JUKKA PARTANEN,§ and KRISTER HÖCKERSTEDT†

- Celiac disease (CD) was detected in four patients with cryptogenic liver cirrhosis, already enrolled for OLT
- Hepatic dysfunction significantly improved in all these 4 pts when gluten-free diet (GFD) was adopted and 3 of them were removed from OLT programme
- In another series of 185 pts with severe liver failure, investigated in the same study, 8 (4,3%) were found to have CD after OLT
- CD should be rigorously investigated in all patients with autoimmune and cryptogenic liver cirrhosis in study for OLT, since CD diagnosis and the consequent GFD may prevent progression to end-stage liver failure

Gut–liver axis: an immune link between celiac disease and primary biliary cirrhosis

Volta U, Caio G, Tovoli F, De Giorgio R.
Expert Rev. Gastroenterol. Hepatol. 7(3), 253–261 (2013)



Table 1. Prevalence of celiac disease in patients with primary biliary cirrhosis and vice versa.

Study (year)	Patients with PBC (n)	CD in patients with PBC (n)	Patients with CD (n)	PBC in patients with CD (n)	Ref.
Dickey <i>et al.</i> (1997)	57	4 (7%)			[48]
Bardella <i>et al.</i> (1997)	65	0	336	1 (0.29%)	[49]
Kingham <i>et al.</i> (1998)	67	4 (6%)	143	4 (2.8%)	[50]
Niveloni <i>et al.</i> (1998)	10	2 (20%)			[51]
Sorensen <i>et al.</i> (1999)			8631	24 (0.27%)	[52]
Gillett <i>et al.</i> (2000)	378	10 (2.6%)			[53]
Floreani <i>et al.</i> (2002)	87	3 (3.4%)	108	4 (3.7%)	[54]
Volta <i>et al.</i> (2002)	173	7 (4%)			[9]
Chatzicostas <i>et al.</i> (2002)	62	0			[55]
Habior <i>et al.</i> (2003)	115	1 (0.9%)			[56]
Sum of the ten studies considered	1014	31 (3.1%)	9218	33 (0.36%)	

CD: Celiac disease; PBC: Primary biliary cirrhosis.

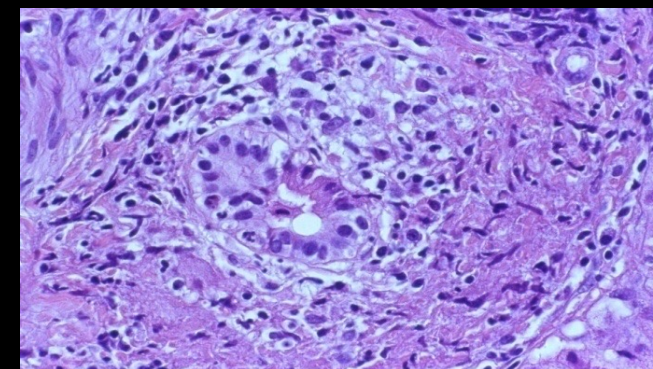


Prevalence of Coeliac Disease (CD) in Autoimmune Cholestatic Liver Disorders

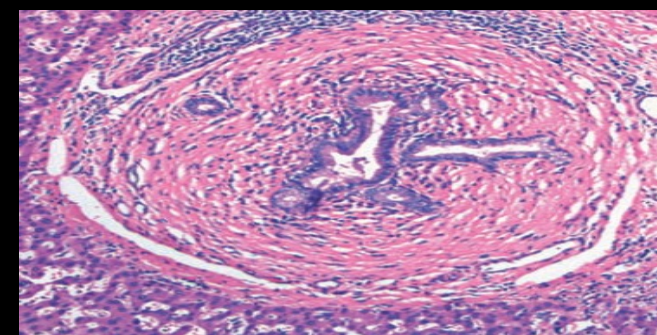
	PBC n° 173	PSC n° 61	AIC n° 21	PBC+PSC+AIC n ° 255
Coeliac Disease	7 (4%)	1 (1.6%)	1 (4.8%)	9 (3.5%)

PBC: primary biliary cirrhosis; PSC: primary sclerosing
cholangitis; AIC: autoimmune cholangitis

Volta U et al, AJG 2002; 97:2609-13



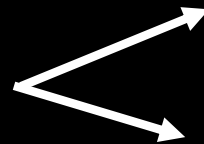
PBC: florid duct lesion



PSC: classic concentric periductal fibrosis

Effect of gluten withdrawal on autoimmune cholestatic liver disorders

- Severe liver disease



resolution of malabsorption with clinical improvement

liver enzymes and pruritus unchanged after GFD

- Mild liver disease



a 4-year-follow-up with GFD and ursodeoxycholic acid treatment slowed down the progression of liver disease

Prevalence of coeliac disease (CD) in patients with autoimmune hepatitis (AIH)

*only serology 8/181= 4.4%

5 CD/181 AIH*

2.8%

*Volta U et al.,
Dig Dis Sci 1998*



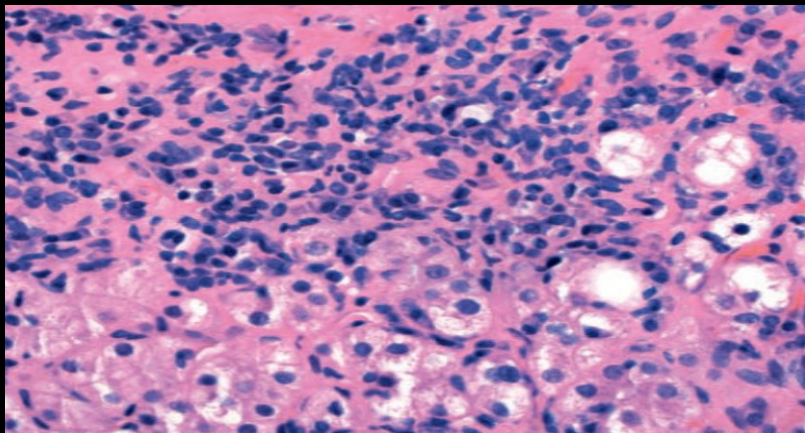
3.5%

(range 2.8-6.4%)

3 CD/47 AIH

6.4%

*Villalta D et al.,
J Clin Lab Anal 2005*



Classic AIH features with a portal space
infiltrated by lymphocytes and plasmacells

Clinical features of autoimmune hepatitis (AIH) with and without coeliac disease (CD)

	AIH with CD 8 cases	AIH without CD 173 cases	P
Age (yr)			NS
Gender (F/M)			NS
AST (nl. 37u/l)			NS
γ -globulins (0.7-1.7 g/l)			NS
HLA-DQ2		61%	NS
Treatment outcome			
- Remission	62%	75%	NS
- Failure	38%	25%	NS
P: Fisher exact test, unpaired Student's t test			

- Gluten-free diet (GFD) did not change the outcome of AIH
- Positive effect of GFD on preventing osteoporosis and intestinal absorption (including drugs)

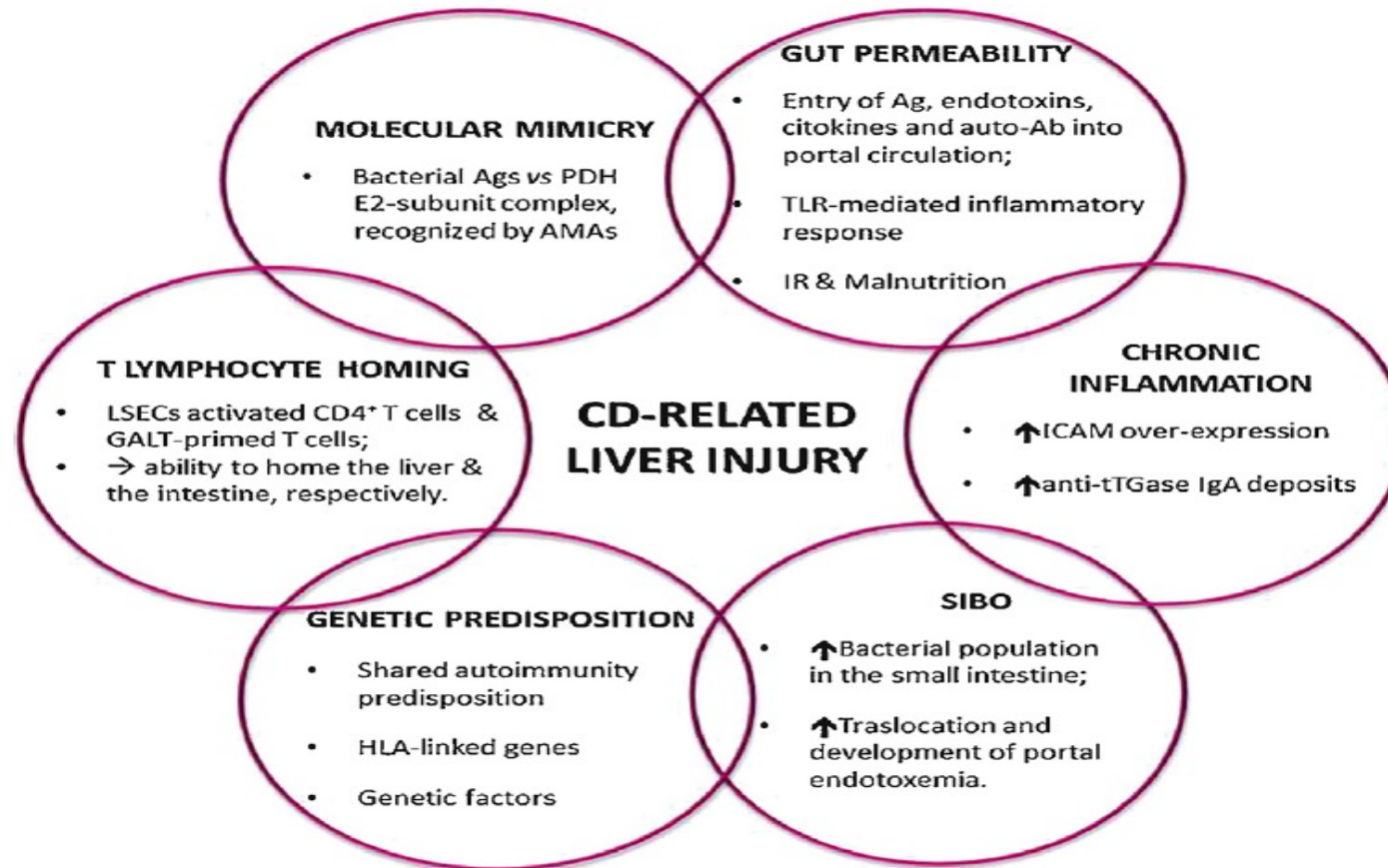


Coeliac disease (CD) in patients with viral hepatitis

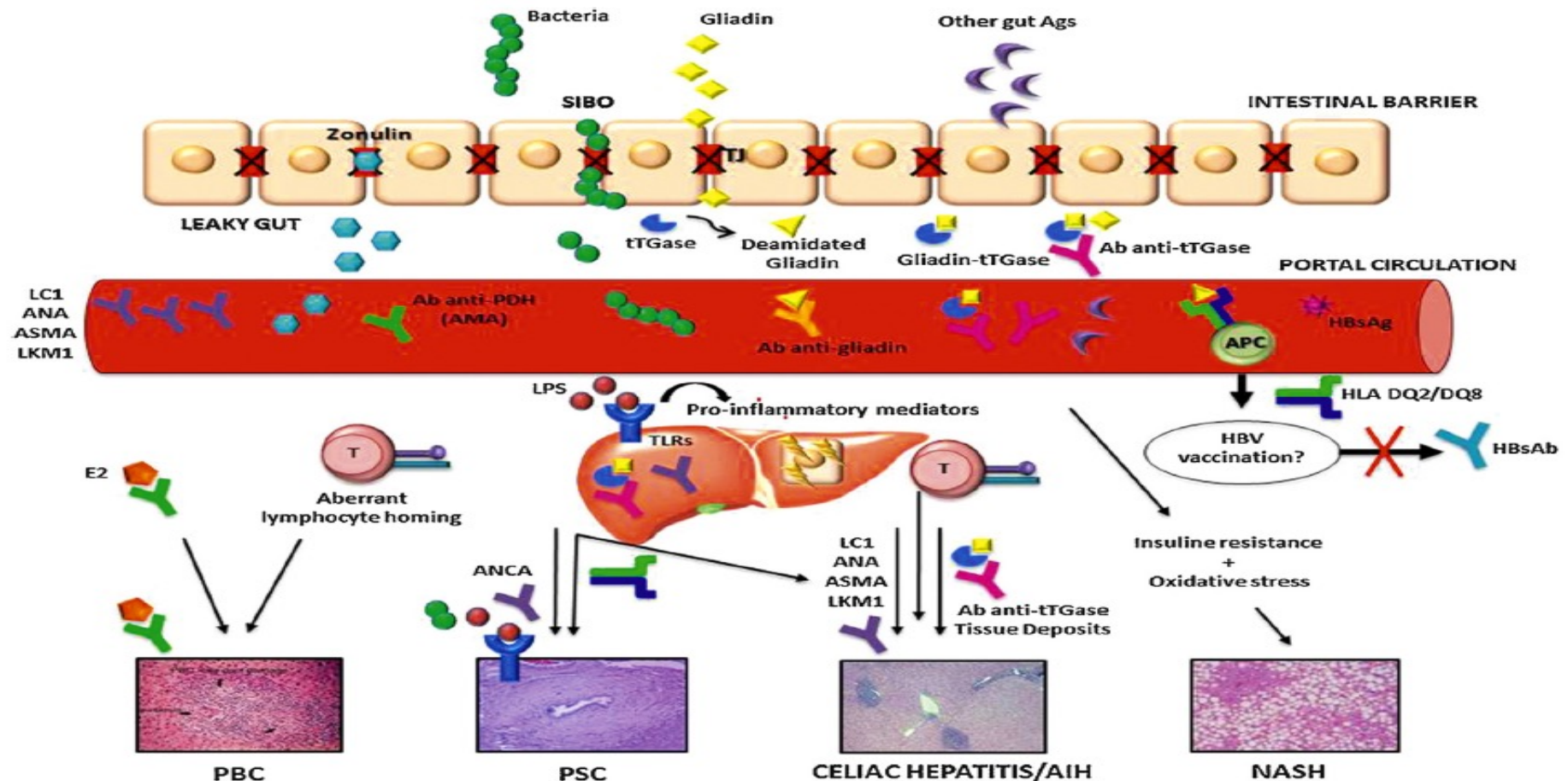
- The prevalence of CD in patients with hepatitis C was found to be 1.2% and it did not differ from CD finding in the general population
- Treatment of hepatitis C by IFN in patients with a coexistent CD is recommended only when CD is in remission with negativity for all CD-related autoantibodies
- An undetected CD can impair the immune response to HBV vaccine which should be administered to CD patients after GFD

Silano M & Volta U, Eur J Microbiol Infect Dis 2009 ; 28:1267-9

Principal pathways involved in coeliac disease(CD)-liver injury



Coeliac disease-related liver damage: cross-talk among several pathophysiologic mechanisms





Take home message

- Coeliac disease (CD) is one of the best pathological example of the close interaction of the gut-liver axis
- Liver abnormalities are frequent in CD ranging from celiac hepatitis to autoimmune liver disorders
- Gluten-free diet (GFD) heals coeliac hepatitis, improves hepatic function in CD-related advanced liver failure, stabilizes autoimmune liver disease associated with CD, thus confirming that liver damage in CD patients is partially or totally gluten-dependent
- Serological screening for CD should be always performed in pts with hypertransaminasaemia of unknown origin
- Liver function should be explored in CD at diagnosis and its etiology (including autoimmune) should be re-assessed in those patients with persistent liver abnormalities after GFD
- Screening for CD should be performed in all patients with autoimmune liver disorders and with severe liver damage of unknown origin