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EDITORIAL

Endoscopic ultrasound guided gallbladder drainage - is it ready for prime time?

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Abstract

Management of acute cholecystitis includes initial stabilization and antibiotics. However, the most definitive treatment is cholecystectomy. A small percentage of patients who are not suitable for surgery due to the severity of cholecystitis or comorbidities will require a temporary measure as a bridge to surgery or permanent nonoperative management to decrease the mortality and morbidity. Most of these patients who require conservative management were managed with percutaneous transhepatic cholecystostomy or trans-papillary drainage of gallbladder drainage with cystic duct stenting through endoscopic retrograde cholangiopancreaticography (ERCP). Although, these conservative measures are effective, they can cause significant discomfort to the patients especially if used as a long-term measure. In view of this, there is a need for further minimally invasive procedures, which is safe, effective and comfortable to patients. Endoscopic ultrasound (EUS) guided gallbladder drainage is a novel method of gallbladder drainage first described in 2007[1]. Over the last decade, EUS guided gallbladder drainage has evolved as an effective alternative to percutaneous

cholecystostomy and trans-papillary gallbladder drainage. Our goal is to review available literature regarding the scope of EUS guided gallbladder drainage as a viable alternative to percutaneous cholecystostomy or cystic duct stenting through ERCP among patients who are not suitable for cholecystectomy.

Key words: Acute cholecystitis; Acute acalculous cholecystitis; Endoscopic ultrasound guided gallbladder drainage; Percutaneous cholecystostomy; Trans-papillary gallbladder drainage

Core tip: Acute cholecystitis can be a medical emergency if not treated. The definitive treatment for it is cholecystectomy. However, some patients are not surgically fit and will need to be managed conservatively. Endoscopic ultrasound guided gall bladder drainage is a novel technique and is a means to manage these patients conservatively either as a bridge to surgery until they become surgically fit or a long term management. We discuss the advantages and disadvantages of this technique as an alternative to other known conservative measures.

Boregowda U, Umapathy C, Nanjappa A, Wong H, Desai M, Roytman M, Theethira T, Saligram S. Endoscopic ultrasound guided gallbladder drainage - is it ready for prime time? *World J Gastrointest Pharmacol Ther* 2018; 9(6): 47-54 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i6/47.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i6.47

INTRODUCTION

Acute cholecystitis is a life-threatening inflammatory condition of the gallbladder usually presents with nausea, vomiting, fever and right upper quadrant abdominal pain[2]. Acute cholecystitis is classified into two broad categories based on etiological factors. That is calculous cholecystitis and acalculous cholecystitis.

Gallstones cause more than 90% of the acute cholecystitis, and acalculous cholecystitis accounts for the remaining 5%-10% of the acute cholecystitis. Nearly 10% of the western population is estimated to have gallstones, and 1%-3% of these patients develop symptomatic gallstones. Only 20% of the symptomatic patients eventually develop acute gallstone cholecystitis[3]. Mortality due to acute cholecystitis is approximately 1%-10%[4]. The rate of mortality goes much higher (30% to 90%) depending on the timing of diagnosis[5]. Gallstones cholecystitis is three times more common among women compared to men under age fifty[6].

Acalculous cholecystitis occurs commonly among patients who are on prolonged parenteral nutrition and intensive care stay, trauma, and burns. Other risk factors include uncontrolled diabetes, congestive heart failure, vascular disease, acquired immune deficiency syndrome, drugs (oral contraceptive pills, thiazides) and elderly male patients[7].

SURGICAL MANAGEMENT

Definitive treatment for acute cholecystitis is cholecystectomy. Risk of systemic infection is high if untreated. Complications of acute cholecystitis include gangrenous cholecystitis, gallbladder perforation, biliary peritonitis, cholecystoenteric fistula, pericholecystic abscess, and biliary ileus. The timing of cholecystectomy is usually dependent on the clinical condition of the patient and comorbidities. Approximately 20% of the patients require emergent cholecystectomy. Early laparoscopic cholecystectomy less than 48 h from the time of presentation reduces morbidity, mortality, hospital stay, and costs[8].

Patients with multiple medical comorbidities not suitable for surgery are managed conservatively with gallbladder drainage through cholecystostomy or cystic duct stenting. Early cholecystostomy within 24 h from the time of presentation has shown to reduce hospital stay and procedure related bleeding[9]. Endoscopic ultrasound (EUS) guided gallbladder drainage has created a new paradigm in treating patients with acute cholecystitis who have a contraindication for surgery.

PERCUTANEOUS CHOLECYSTOSTOMY

Percutaneous cholecystostomy is a minimally invasive and safe procedure performed to provide immediate decompression of the distended gallbladder using ultrasound or computed tomography guidance. It can be used as a bridge to elective cholecystectomy or as a definitive treatment in severely ill patients who are not candidates for elective cholecystectomy[10-12]. It allows further evaluation of etiology of acute cholecystitis through cholangiogram. Cystic duct or common bile duct stones could be managed through a percutaneous approach.

Common adverse events due to percutaneous cholecystostomy include bleeding, tube dislodgement, bile leak and peritonitis in approximately 12% of the patients[13]. Percutaneous cholecystostomy is contraindicated in patients with massive ascites, intervening bowel loop, uncorrected coagulopathy or those who require anticoagulation. Intrahepatic gallbladder, shrunken/thick-walled gallbladder or concern for patient's non-adherence is considered as relative contraindications.

ENDOSCOPIC TRANS-PAPILLARY GALLBLADDER DRAINAGE

Gallbladder decompression through trans-papillary cystic duct stenting with the help of endoscopic retrograde

Table 1 Endoscopic ultrasound guided gallbladder drainage using plastic stent

Author	Study design	Year of publication	Number of patients	Technical success	Clinical success	Adverse event rate
Baron *et al*	Case report	2007	1	1 (100%)	1 (100%)	0 (0%)
Kwan *et al*	Case series	2007	3	3 (100%)	3 (100%)	1 (33.3%)
Kamala *et al*	Case report	2009	1	1 (100%)	1 (100%)	0 (0%)
Takasawa *et al*	Case report	2009	1	1 (100%)	1 (100%)	0 (0%)
Subtil *et al*	Case series	2010	4	4 (100%)	4 (100%)	0 (0%)
Song *et al*	Prospective	2010	8	8 (100%)	8 (100%)	2 (25%)
Itoi *et al*	Case series	2011	2	2 (100%)	2 (100%)	0 (0%)

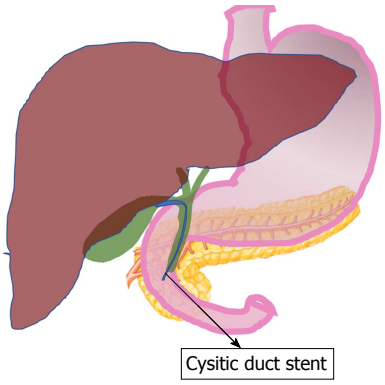


Figure 1 Schematic diagram of trans-papillary cystic duct stenting.

pancreatography and cholangiography (ERCP) can be used to manage acalculous cholecystitis. After cannulating the common bile duct, a guidewire is passed, and the cystic duct is then selectively cannulated. Cystic duct stent is placed to drain the gallbladder content (Figure 1).

In a retrospective case study on 43 patients who underwent ERCP and cystic duct stent for cholecystitis, 83.7% patients had technical success, and 97% had a clinical success of whom 91.7% improved within 72 h[14]. There were no significant adverse events, and 9% of the patients had an elevated amylase level without abdominal pain.

A retrospective study compared percutaneous cholecystostomy (n = 38) and trans-papillary gallbladder drainage (n = 57) using plastic cystic duct stent with ERCP. Technical success of trans-papillary drainage (89% *vs* 93%) was lower compared to percutaneous cholecystostomy. However, recurrent cholecystitis in trans-papillary drainage (2%) group was lower compared to percutaneous cholecystostomy (11%) with similar adverse events (8% *vs* 4%). Patients who underwent cystic duct stenting had the stent in place much longer compared to percutaneous cholecystostomy (three months *vs* one month)[15].

The role of trans-papillary drainage is limited since it is restricted to patients with acalculous cholecystitis.

EUS-GUIDED GALLBLADDER DRAINAGE

The procedure is usually performed using therapeutic linear array echoendoscope. A trans-gastric or trans-duodenal gallbladder puncture is performed under the EUS guidance using a 19-gauge needle. After removing the stylet biliary aspiration and cholecystography are performed in sequence. A 0.035 or 0.025-inch guidewire is introduced through the cannula and coiled in the gallbladder. The gallbladder puncture site is dilated with a Cystotome or needle, and a stent is introduced into the gallbladder. Various types of stents have been used in the past including plastic stent, a self-expandable metal stent and recently lumen apposing metal stents (LAMS). The technical and clinical success of EUS guided drainage by plastic stents is 100%, and pooled analysis showed the adverse events occurred in 5.4% of the patients (Table 1). The technical and clinical success of EUS guided drainage by Naso-biliary drainage is 95.2% and 73.7% respectively, and pooled analysis showed the adverse events occurred in 27.2% of the patients (Table 2). The technical and clinical success of EUS guided drainage by the self-expandable metal stent is 97.5% and 98.5% respectively, and pooled analysis showed the adverse events occurred in 10.4% of the patients (Table 3).

EUS guided gall bladder drainage with LAMS

The recent success of LAMS in the drainage of pancreatic pseudocyst and walled off pancreatic necrosis lead to the development of similar LAMS for gallbladder drainage. An electrocautery-enhanced LAMS (EC-LAMS) has made the procedure simpler and reduced the number of instrument exchanges (Figure 2 and Figure 3). The stent can be delivered in a single step[16].

A meta-analysis included 13 studies (7 retrospective studies, five prospective studies, and 1 case-control study) using LAMS involving 233 patients showed EUS guided gallbladder drainage to be an effective, safe and viable alternative to percutaneous cholecystostomy. Technical success and clinical success were 93.86%, and 92.48% respectively. Overall procedure related adverse events were 18.31% and stent-related adverse events were 8.16%[16]. In most cases the stent was left in situ permanently since patients were not suitable for surgery. Outcomes of prior studies on EUS guided gallbladder drainage by LAMS is shown in Table 4.

Advantages of LAMS

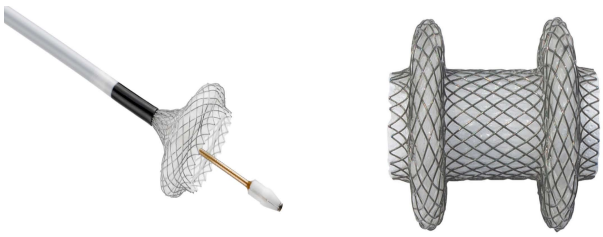
Electrocautery enhanced LAMS can be placed in a single step using EUS scope alone without the need for fluoroscopy, guidewire placement, and tract dilation. LAMS provides better tissue apposition at both the ends

Table 2 Endoscopic ultrasound guided gall bladder drainage using naso-biliary drainage

Author	Study design	Year of publication	Number of patients	Technical success	Clinical success	Adverse event rate
Lee *et al*	Prospective	2007	9	9 (100%)	9 (100%)	0 (0%)
Hikichi *et al*	Retrospective	2007	1	1 (100%)		1 (100%)
Jang *et al*	Prospective	2012	30	29 (97%)	29 (100%)	0 (0%)
Itoi *et al*	Retrospective	2008	43	36 (84%)	35 (95%)	4 (9%)

Table 3 Endoscopic ultrasound guided gall bladder drainage using self-expanding metal stents

Author	Type of study	Year of publication	Number of patients included in the study	Technical success (%)	Clinical success (%)	Adverse events (%)
Widmer *et al*	Retrospective	2015	11	100	100	8
Choi *et al*	Retrospective	2017	14	85.7	91.7	28.5
Jang *et al*	Prospective	2011	15	100	100	13
Moon *et al*	Prospective	2014	7	100	100	0
Takagi *et al*	Retrospective	2016	16	100	100	6
Ahmed *et al*	Retrospective	2017	13	100	92.3	7.7
Oh *et al*	Retrospective	2018	76	99.3	99.3	7.1



Lumen-apposing metal stent (LAMS)

Figure 2 Lumen apposing metal stent.

and reduces the risk of stent migration. Presence of silicon lining reduces the risk of leakage and prevents tissue ingrowth, which can aid in the removal of the stent once the fistula matures. The large diameter of the LAMS reduces the risk of stent stenosis or obstruction and allows extraction of gallstones or cholecystography.

Patients with EUS gallbladder drainage procedure have a lower rate of post-procedure pain and the stent can remain patent for a prolonged period. It also adds to the patient's comfort since there is no need for external drainage to be carried around and mimics natural drainage of biliary secretions into the duodenum. LAMS can be potentially left in situ indefinitely, according to the published literature the longest period of follow up of 3 years, stent patency of 86% was noted[17].

One recent retrospective analysis of long-term outcomes in 21 patients who had documented follow up for more than 12 mo, there were no significant adverse events. Only two patients required repeat endoscopy and found to have tissue overgrowth in one and patent fistula in the other[18].

Complications

Most common complications of EUS guided gallbladder drainage are transient abdominal pain, pneumoperitoneum, biliary peritonitis, and stent migration requiring repeat intervention[19]. Bleeding occurs in up to 13% and stent migration in up to 8% of the patients[20]. Other complications include fever, duodenal perforation, stent occlusion, and hematochezia without anemia. Late complications due to EUS guided gallbladder drainage include recurrent cholecystitis in up to 3.2% of the patients and abscess formation[21,22].

Technical approach

Gallbladder drainage with LAMS can be performed though trans-duodenal or trans-gastric approach. Though there is no clear evidence to show that one is better than the other, most endoscopists prefer trans-duodenal approach since the duodenum is retroperitoneal and has minimal peristaltic movements compared to the stomach, which has stronger peristaltic movements. It reduces the chance of stent migration[23]. Due to the presence of larger food particles, stent occlusion is likely to be more in common in the stomach compared the duodenum.

Large multicenter studies are required to define the advantages and disadvantages of each approach. The invention of electrocautery-enhanced LAMS has reduced the need for instrumentation, the time needed for the procedure, and the stent can be delivered in one step.

EUS guided gallbladder drainage and future surgery

EUS guided gallbladder drainage can complicate future cholecystectomy and may not be used as bridge therapy. Previous studies have reported up to 79% of the patients who underwent EUS guided gallbladder drainage had successful cholecystectomy[24]. Remaining patients who did not have surgery were either nonsurgical or refused the procedure. However, the real concern is a permanent fistula could have been created due to EUS guided gallbladder drainage, which could have prevented definitive surgery. While most fistulas can close on their own, it is unclear from prior literature the exact number

Table 4 Endoscopic ultrasound guided gallbladder drainage using lumen apposing metal stents

Author	Type of study	Year of publication	Number of patients	Technical success (%)	Clinical success (%)	Adverse events (%)
de la Serna-Higuera *et al*	Retrospective	2013	13	86.4	100	18
Irani *et al*	Retrospective	2015	15	93	100	13
Walter *et al*	Prospective	2016	30	90	96	Not available
Law *et al*	Retrospective	2016	7	100	100	0
Kahaleh *et al*	Retrospective	2016	35	91.4	89	11
Irani *et al*	Retrospective	2017	45	98	96	11
Dollhopf *et al*	Retrospective	2017	75	98.7	95.9	10.7
Teoh *et al*	Prospective	2017	59	100	100	23.7

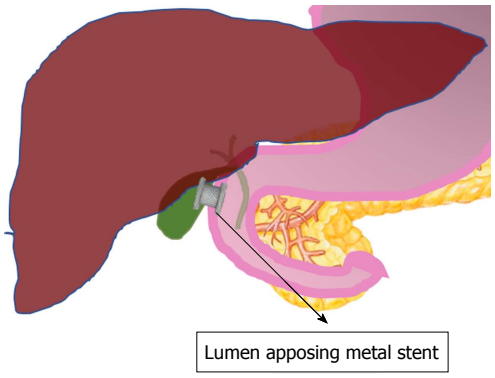


Figure 3 Endoscopic ultrasound guided gallbladder drainage.

of the fistulas that can close spontaneously.

A recent multicenter study on 34 patients showed that 21 patients with percutaneous cholecystostomy tube and 13 patients who had undergone EUS guided gallbladder drainage by LAMS as a bridge therapy all successfully underwent cholecystectomy[25]. There was no difference in the comorbidity index or post-surgical adverse events. However, data on large multicenter studies are still lacking. The areas that need further research are the technique (trans-gastric *vs* trans-duodenal) that creates fewer fistulas and the exact rate of spontaneous closure of the fistula so that it can be used a bridge therapy prior to surgery.

Percutaneous cholecystostomy vs EUS guided gallbladder drainage

In a prospective study, Jang *et al*[24] compared percutaneous cholecystostomy and EUS guided gallbladder drainage as an alternative for acute cholecystitis in patients who are not candidates for cholecystectomy. A total of 59 patients were randomized into either percutaneous cholecystostomy (n = 29) or EUS guided gallbladder drainage (n = 30) after the failure of medical treatment. Both EUS guided gallbladder drainage and percutaneous cholecystostomy had comparable technical success (97% *vs* 97%, P = 0.001 for non-inferiority margin of 15%), clinical success (96% *vs* 100%, P = 0.0001 for non-inferiority margin of 15%), and complications (7% *vs* 3%, P = 0.999 in the Fisher exact test) rates. The rate of conversion to open cholecystectomy was 9% and 12% respectively. Post-procedure pain score was significantly low among patients who underwent EUS guided drainage compared to percutaneous cholecystostomy (P = 0.001)[24].

In another retrospective comparative study, technical and clinical successes in EUS guided gallbladder drainage (n = 45) and percutaneous cholecystostomy (n = 45) were similar. Technical success was achieved in 98% and 100% respectively (P = 0.88), whereas clinical success was 96% and 91% respectively (P = 0.20). Post-procedure pain score (2.5 *vs* 6.5; P < 0.05), hospital stay (three days *vs* nine days, P = 0.05) and repeat interventions (11 *vs* 12) were significantly low in EUS guided gallbladder drainage compared to percutaneous cholecystostomy. This study also demonstrated a non-significant trend towards lower adverse events (11% *vs* 32%; P = 0.27) in EUS guided gallbladder drainage compared to percutaneous cholecystostomy[26].

In a prospective cohort study of 118 patients technical success and clinical success for EUS guided gallbladder drainage (n = 59) and percutaneous cholecystostomy (n = 59) were comparable. The rate of overall adverse events (32.2% *vs* 74.6%; P < 0.001), serious adverse events (23.7% *vs* 74.6%; P < 0.001) and procedure related readmission rates (6.8% *vs* 71.2%; P < 0.001), were significantly lower in EUS guided gallbladder drainage compared to percutaneous cholecystostomy. Recurrent acute cholecystitis was also lower in the EUS group (0% *vs* 6.8%) compared to percutaneous cholecystostomy[27].

In a multicenter retrospective study, technical success of EUS guided drainage (n = 42) and percutaneous cholecystostomy (n = 113) drainage (95% *vs* 99%; P = 0.179) as well as clinical success (95% *vs* 86%; P = 0.157). EUS guided drainage required a lower number of repeat procedures compared to percutaneous drainage (10% *vs* 24%; P = 0.037). There was no significant difference in readmission rate or adverse events between the two[28].

A retrospective study evaluated the role of EUS guided gallbladder drainage (n = 14) and percutaneous cholecystostomy (n = 19) in patients with malignant cystic duct obstruction. The technical success (85.7% *vs* 100%) and clinical successes (91.7% *vs* 86.4%) were comparable. Adverse events were similar in both the groups (28.5% *vs* 21.1%). In this study, none of the patients who had clinically successful EUS guided gallbladder drainage required stent removal until endo of life. The mean duration of stent patency was 130.3+/-

35.3 d. However, only in 35.5% of the patients, the cholecystostomy tube was kept until the end of life[29].

The above studies have clearly shown that in appropriately selected patients EUS guided gallbladder drainage is an efficient and safe alternative to percutaneous cholecystostomy for acute cholecystitis among non-surgical patients. EUS guided gallbladder drainage is associated with a reduced hospital stay, adverse events and requires fewer repeat interventions, and is associated with less severe procedure-related pain. The rate of adverse events is either similar or trend lower than percutaneous cholecystostomy. In a retrospective study, the rate of recurrent cholecystitis (17.2% *vs* 0%; $P = 0.043$) was also noted to be significantly low in patients who had EUS guided gallbladder drainage when compared to percutaneous cholecystostomy[30].

EUS guided gallbladder drainage unlike percutaneous cholecystostomy obviates the need for external drainage tube, discomfort, and pain caused by percutaneous cholecystostomy. EUS procedures may require general anesthesia and can take a longer time to complete the procedure compared to percutaneous cholecystostomy. Since patients who are not suitable for surgery also tend to be high-risk for general anesthesia[31]. LAMS allows extraction of gallstones and provides better tissue apposition. They reduce the risk of biliary leak and peritonitis but do not completely mitigate the risk and therefore the caution has to be exercised when using it in patients with coagulopathy and ascites[32-34]. Even though lumen-apposing metal stents can be left in situ, permanently stent migration, occlusion and dislodgement have occurred. The reported adverse events after EUS guided gallbladder drainage by LAMS are recurrent cholecystitis (5.1%), gastrointestinal bleeding (2.6%) and stent migration (1.1%)[35].

Internalization of biliary drainage after placement of a percutaneous cholecystostomy

A percutaneous cholecystostomy tube can be replaced with EUS guided gallbladder drainage through LAMS. It can be considered when percutaneous cholecystostomy tube is used as a bridge therapy for surgery, but the disease course of the patient makes them unsuitable for surgery. This will prevent unwanted discomfort the external drain that comes with percutaneous cholecystostomy.

The gallbladder is usually shrunken after the placement of a percutaneous cholecystostomy. Saline with some contrast can be injected through the tube to enlarge the shrunken gallbladder, and subsequently, it can be punctured under direct visualization by EUS and placement of LAMS. A retrospective study of 7 patients demonstrated 100% technical and clinical success with successful removal of the cholecystostomy tube[36].

In another retrospective study, 21 patients had a replacement of percutaneous cholecystostomy tube with EUS guided LAMS gallbladder drainage with 90.5% technical success. There were no early adverse events. However, two patients required repeat interventions[37]. Larger studies are lacking at this time to accurately predict the risks and benefits of replacing percutaneous cholecystostomy with EUS guided LAMS drainage.

EUS guided gallbladder drainage vs Endoscopic trans-papillary gallbladder drainage

A recent retrospective study compared EUS guided gallbladder drainage to endoscopic trans-papillary drainage. EUS guided gallbladder drainage had significantly better technical success (100% *vs* 77.3%; $P = 0.028$). Clinical success (88.9% *vs* 72.4%; $P = 0.076$) and adverse events (19.1% *vs* 16.3%; $P = 0.76$) were comparable[38].

In a multicenter comparative study, 372 patients were included in the study, 102 patients underwent EUS guided gallbladder drainage, 124 by endoscopic trans-papillary drainage and 146 by percutaneous cholecystostomy. The mean follow up period was 5.2 mo (range 1-34). The technical success for EUS guided gallbladder (94%) and percutaneous cholecystostomy (98%) were significantly higher than trans-papillary drainage (88%) ($P = 0.004$). The clinical success rate for EUS guided drainage (90%) and percutaneous cholecystostomy was also significantly higher ($P = 0.001$) compared to trans-papillary drainage (80%). Mean number of procedures required for clinical success was significantly lower for EUS guided drainage compared to trans-papillary and percutaneous cholecystostomy drainage (1 *vs* 1.7 *vs* 2.2; $P < 0.001$). EUS guided drainage and trans-papillary drainage had significantly lower adverse events (13% *vs* 7% *vs* 20%; $P = 0.01$) and unplanned hospital admissions (4% *vs* 3.2% *vs* 19.8%; $P < 0.001$) compared to percutaneous cholecystostomy. Mean hospital stay for EUS drainage was significantly lower compared to both trans-papillary drainage and percutaneous cholecystostomy (16 *vs* 18 *vs* 19 d; $P = 0.01$)[39].

A retrospective study compared EUS guided gallbladder drainage ($n = 76$) to trans-papillary gallbladder drainage ($n = 96$). Technical success (98.8%, 82/83 *vs* 83.3%, 80/96, $P < 0.01$) and clinical success (98.8%, 82/83 *vs* ETC: 82.3%, 79/96, $P < 0.01$) of EUS guided gallbladder drainage was significantly better compared to trans-papillary drainage. Post-procedure adverse events were significantly lower in EUS guided gallbladder drainage compared to trans-papillary gallbladder drainage[22].

Above studies and previously published data has shown a clear advantage of EUS guided gallbladder drainage to be a safe and efficient procedure compared to trans-papillary drainage with significantly better technical and clinical success with lower adverse events and lesser hospital stay and fewer repeat procedures.

CONCLUSION

Cholecystectomy is the gold standard for treatment of acute cholecystitis, and early cholecystectomy is

preferred over delayed or interval cholecystectomy. Elderly patients with significant comorbidities and not candidates for surgery are usually managed with non-surgical interventions like percutaneous cholecystostomy or ERCP. Recent advances in endoscopic methods and utilization of EUS guided LAMS has led to the development of EUS guided gallbladder drainage. Over last decade EUS guided gallbladder drainage has gained significant popularity with high technical and clinical success comparable to that of percutaneous cholecystostomy or trans-papillary drainage. It has lower adverse events, hospital stay and requires fewer repeat procedures[24,26-28,32].

EUS guided gallbladder drainage is a safe, effective and viable non-surgical method of gallbladder drainage for acute cholecystitis, in patients who are deemed to never undergo cholecystostomy as they are not fit for surgery. Although the limited available evidence is promising, prospective large multicenter studies are needed before EUS guided gallbladder drainage can be used as a first-line treatment instead of percutaneous cholecystostomy as a bridge therapy for all patients who are non-surgical candidates initially and require definitive surgical intervention later for acute cholecystitis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet

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Abstract

AIM

To analyze the relationships between pre-diagnosis coeliac serology, duodenal histopathology, primary presenting symptoms, coeliac-related comorbidity and response to treatment in a modern cohort with new diagnosis of coeliac disease (CD).

METHODS

A retrospective cohort study including 99 participants diagnosed with CD between 1999 and 2013. All patients had the following data recorded: baseline characteristics, coeliac serology, small bowel histopathology. A subset of this cohort underwent a repeat small bowel biopsy. Independent associations were assessed with logistic regression.

RESULTS

The mean age at diagnosis was 43 years (Interquartile range 30-53 years) and 68% of the cohort was female. At diagnosis 49 (49%) patients had total villous blunting (MS 3c), 12 (12%) had subtotal villous blunting (MS 3b), and 29 (29%) had partial villous blunting (MS 3a). The prevalence of symptoms pre diagnosis was not related to the severity of villous blunting (P = 0.490). 87 (88%) of the cohort underwent repeat small bowel biopsy after a median of 7 mo (IQR 6-11 mo). 34 (39%) patients had biopsy results $\geqslant$ MS 3a which

compared to 90 (90%) at the initial biopsy. 24 (71%) of this group reported adherence to a gluten free diet (GFD). Persistent MS ⩾ 3a at repeat biopsy was not associated with symptoms (P = 0.358) or persistent positive coeliac serology (P = 0.485).

CONCLUSION

Neither symptoms nor serology predict the severity of the small bowel mucosal lesion at CD diagnosis. Whilst a GFD was associated with histological improvement many patients with newly diagnosed CD had persistent mucosal damage despite many months of gluten restriction. Negative CD serology did not exclude ongoing mucosal injury.

Key words: Coeliac disease; Gluten-free diet

Core tip: Coeliac disease (CD) is a common, under-recognized gastrointestinal disorder. The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD. Thyroid related autoimmune co-morbidities were common (n = 17, 17%). Symptoms at presentation were not associated with the degree of villous blunting on biopsy. Similarly, persistent villous blunting at repeat biopsy was not associated with symptoms or positive coeliac serology. Negative coeliac serology did not exclude ongoing mucosal injury.

Cronin O, Flanagan E, Dowling D. Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet. *World J Gastrointest Pharmacol Ther* 2018; 9(6): 55-62 Available from: URL: http://www.wjgnet.com/2150-5349/full/v9/i6/55.htm DOI: http://dx.doi.org/10.4292/wjgpt.v9.i6.55

INTRODUCTION

Coeliac disease (CD) is estimated to affect 1.2% of Australians[1]. It is a gastrointestinal disorder that involves an immune response to dietary gluten, resulting in small bowel mucosal damage[2]. Most common presentation of CD in adults is diarrhea although this presentation occurs in less than 50% of cases. Silent or atypical presentations of CD are becoming more common[3,4]. The diagnosis of CD is dependent on correlation between history, serological markers and characteristic histological features on duodenal biopsy[1]. It is currently unclear whether the presenting symptoms of CD have any relationship to the severity of small bowel injury at diagnosis. It also remains unclear whether the severity of small bowel mucosal injury is related to complications of CD such as osteoporosis.

The only known treatment for CD is adherence to a gluten free diet (GFD) which may reduce the risk of long-term complications such as osteoporosis and malignancy[5]. Whilst small bowel mucosal injury is known to improve on a GFD, the rate and completeness of such improvement has been a subject of limited study.

In the current study we analysed the relationship between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a GFD.

MATERIALS AND METHODS

This retrospective cohort study included 99 participants who presented to a single Gastroenterology practice in Victoria (Australia) from 1999-2013. Patients were referred to this practice either by General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data collected at baseline included: Gender, age at diagnosis, primary presenting symptom as assessed by a Gastroenterologist, duration of symptoms prior to diagnosis, family history of CD, complications of CD, associated autoimmune condition. Serological and histology data included the presence of anti- tissue transglutaminase (tTG) antibodies or endomysial (EM) antibodies; small bowel histopathology at the time of diagnosis and at least six months after commencing a GFD, quantified by Marsh-Oberhuber Score (MS). Data were recorded in a Microsoft Excel (2011) spreadsheet and then transferred to SPSS Version 25.0 (IBM SPSS Inc., Chicago, IL, United States) for statistical analysis. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

RESULTS

Presentation

Among the cohort of 99 patients the mean age at diagnosis was 43 years (IQR 30-53 years) and 68% of the cohort was female (Table 1). Over half of the patients (n = 51, 52%) were asymptomatic at presentation, some of whom for example had been referred by their General Practitioner after having positive CD serology as part of a work-up to investigate iron deficiency. The most common presenting symptom was diarrhoea (n = 31, 31%). Of symptomatic patients, the majority (n = 34, 71%) described symptoms for over 1 year prior to diagnosis (Table 2).

At diagnosis, 17 (17%) patients had an associated autoimmune condition including thyroid pathology (n = 10), Type 1 Diabetes (n = 8), Rheumatoid Arthritis (n = 1) and Pernicious anaemia (n = 1) (Table 3).

Diagnosis

88 (89%) patients had positive CD serology at the time of diagnosis. Small bowel histopathology at diagnosis revealed total villous blunting (MS 3c) in 49 (49%), subtotal villous blunting (MS 3b) in 12 (12%) and partial

Table 1 Comparison of 99 patients with coeliac disease n (%)

	n (%)
Age, yr	43 (30-53)
Male gender	32 (32)
Family history	24 (24)
Main symptom at presentation	
Abdominal pain	5 (5)
Bloating	6 (6)
Bone disease	6 (6)
Diarrhoea	31 (31)
Fatigue	6 (6)
Iron deficiency	21 (21)
Incidental[1]	6 (6)
Screening	14 (14)
Other[2]	4 (4)

[1]Gastroscopy performed to investigate dyspepsia; [2]Vitamin B12 deficiency (n = 3), hypoalbuminaemia (n = 1). Continuous variables are presented as median (inter-quartile range).

Table 2 Comparison of duration of 48 patients with symptoms at diagnosis

Duration of symptoms prior to diagnosis	*n* (%)
< 1 yr	14 (29)
1-3 h	12 (25)
> 3 yr	22 (46)

villous blunting (MS 3a) in 29 (29%) patients, while 9 (9%) patients had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis (Table 4). Of the patients with MS 3b or 3c, 10 (83%) and 44 (90%) had positive serology respectively (Table 4). The majority of patients with MS ⩾ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c (P = 0.490) (Table 5). Of the 9 patients who had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis, 2 (22%) patients had presented with fatigue, 4 (44%) patients had been detected on screening by a General Practiotioner, 2 (22%) had been investigated for iron deficiency and 1 (11%) patient had been investigated for dyspepsia. Concomitant autoimmune conditions were present in 4 (10%) patients with MS 3a/b and 9 (18%) patients with MS 3c (P = 0.298). 2 (5%) of patients with Marsh 3a/b had osteoporosis or osteopenia at diagnosis compared to 4 (8%) of patients with Marsh 3c (P = 0.534).

Follow-up

87 (88%) of the cohort underwent repeat small bowel biopsy after a minimum of six months (Table 6). Of this group 76 (87%) reported adherence to a GFD at the time of repeat biopsy.

Of the 76 patients reporting adherence to a GFD at the time of the second biopsy 48 (63%) had negative serology, 14 (18%) had positive serology and 14 (18%) did not have serology results available. 37 (49%) were asymptomatic, 7 (9%) reported symptoms and 32 (42%) did not have data recorded. All 7 patients with a concomitant autoimmune disorder who reported compliance with a GFD and had negative serology had persistent MS ⩾ 3a.

Table 3 Comparison of 17 patients with an associated autoimmune condition at diagnosis

Thyroid pathology	
Graves' disease	4
Autoimmune thyroiditis	1
Hypothyroidism[1]	5
Type 1 diabetes	5
Rheumatoid arthritis	1
Pernicious anaemia	1

[1]Includes 1 patient with Hashimoto's thyroiditis.

30 (34%) patients had biopsy results revealing a normalization of histology (MS0), 18 (60%) of whom had negative repeat serology, 6 (20%) had positive serology and 6 (20%) did not have serology results available. All 30 patients with MS0 reported adherence to a GFD.

34 (39%) patients had biopsy results ⩾ MS 3a which compared to 90 (90%) at the initial biopsy. Of the 34 patients with persistent ⩾ MS 3a, 18 (53%) had negative repeat serology, 8 (24%) had positive serology and 8 (24%) did not have serology results available. 24 (71%) of this group reported adherence to a GFD.

47 patients reported compliance with a GFD and had negative serology consistent with absent dietary gluten exposure. Among this cohort the repeat biopsy was undertaken at a median of 7 mo (IQR 6-11 mo) and the incidence of persistent villous blunting was 62%. Among the 29 patients with persistent villous blunting, in 16 (55%) the change was ⩾ MS 3a.

Multivariate analysis did not reveal an association between MS ⩾ 3a at diagnosis of CD and positive serology or symptoms at diagnosis (Table 7). Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy (Tables 8 and 9).

DISCUSSION

The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD rather than the traditional presentation of diarrhea[4,6-8]. The "coeliac iceberg" is often used to describe the large proportion of undiagnosed asymptomatic or subclinical coeliac disease[9,10]. Nenna *et al*[10] reported that the traditional presentation of CD accounted for 28% of cases, whereas the majority of cases presented as silent forms or non-classical presentations of CD. A third group termed latent CD is also described comprising individuals who are considered at risk due to having a coeliac related HLA type and positive coeliac serology in the absence of current villous blunting. Genetic composition plays a pivotal role in determining the predisposition to CD, with

Table 4 Symptoms, serology and histology results for 99 patients divided by severity of duodenal histology at initial biopsy

Biopsy score[1]	*n* (%)	Positive serology[2]	Symptoms at diagnosis (%)
0	0 (0)	-	-
1	7 (7)	Positive = 7 (100) Negative = 0 (0) Unknown = 0 (0)	0 (0)
2	2 (2)	Positive = 2 (100) Negative = 0 (0) Unknown = 0 (0)	2 (100)
3a	29 (29)	Positive = 25 (86) Negative = 4 (14) Unknown = 0 (0)	14 (48)
3b	12 (12)	Positive = 10 (83) Negative = 1 (8) Unknown = 1 (8)	7 (58)
3c	49 (49)	Positive = 44 (90) Negative = 2 (4) Unknown = 3 (6)	25 (51)

[1]Marsh-Oberhuber score at diagnosis; [2]tissue Transglutaminase antibodies or endomysial antibodies.

Table 5 Presenting symptom of Marsh-Oberhuber score 3c compared to Marsh-Oberhuber score 3a/b *n* (%)

Presentation	Marsh-Oberhuber score 3a/b[1]	Marsh-Oberhuber score 3c[2]	Odds ratio	95%CI	*P* value
Diarrhoea	13 (32)	18 (37)	1.39	0.33-5.79	0.66
Iron deficiency	8 (20)	11 (22)	1.38	0.30-6.40	0.69
Bone disease	2 (5)	4 (8)	2.00	0.24-16.36	0.52
Bloating	4 (10)	2 (4)	0.50	0.06-4.09	0.52
Fatigue	1 (2)	3 (6)	3.00	0.23-39.60	0.40
Abdominal pain	3 (7)	2 (4)	0.67	0.76-5.88	0.72
Incidental	2 (5)	3 (6)	1.50	0.17-13.23	0.72
Screening	5 (12)	5 (10)	0.33	0.25-4.40	0.40
Other	3 (7)	1 (2)	1.38		0.89

[1]n = 41; [2]n = 49. CI: Confidence interval.

HLA-DQ2 and DQ8 haplotypes expressed in 90% and 5% of affected patients respectively[11]. Gluten is required to trigger the disease but the transition from tolerance to a gluten related immune response is poorly understood[11]. Possible triggers for this immune transition include intestinal infections, the amount and quality of gluten and the composition of the intestinal microbiota[11]. A gluten related immune response may develop early in life and many silent cases are unrecognized for many years, if ever[12]. It has been suggested that although the majority of CD cases have not been diagnosed, population screening may not be appropriate as evidence is lacking as to whether the majority of silent CD cases actually translate into any significant morbidity. It also remains unclear whether these clinically silent cases would benefit from a GFD[13,14].

Microscopic enteritis is a histopathological inflammatory condition (Marsh 0-Ⅱ) which clinically may present as malabsorption or more subtle micronutrient deficiencies but with a relatively intact villous structure[15]. 9 (9%) patients in this cohort could be classified at initial biopsy with microscopic enteritis secondary to CD. Microscopic enteritis is an important, novel diagnostic category of patients whom were previously diagnosed with a functional enteropathy[15].

The contrary view has also been argued, that population screening may be beneficial given there is a high prevalence of associated autoimmune conditions and nutritional deficiencies could contribute greatly to population morbidity[16]. Owing to the absence of identifiable features predicting risk, targeted screening of at risk populations would be difficult. Whilst most seropositive patients will have villous blunting[17], among those seropositive patients with normal small bowel mucosa there is no reliable means of identifying which subsets will go on to develop villous blunting and potentially long term complications of CD. Further clarification *via* large population studies is needed to resolve issues around cost-benefits of screening, which populations and age groups to screen as well as laboratory reference range cut-offs for screening tests[9].

This study found the majority of patients to be female, most patients to be asymptomatic and a minority to present with diarrhea. The widely reported trend toward silent CD could possibly be partly explained by the increased access to serology and upper gastrointestinal endoscopy which have enabled for easier diagnosis of CD[18]. However the reported decrease in the proportion of patients presenting with symptoms such as diarrhea started before the advent widespread availability of

Table 6 Symptoms, serology and histology results for 87 patients with repeat biopsy

Biopsy score[1]	Repeat biopsy score	Positive serology[2]	Reported gluten free diet adherence	Symptoms at repeat biopsy
0	31 (36)	Positive = 6	Yes = 31	Yes = 4
		Negative = 19	No = 0	No = 14
		Unknown = 6		Unknown = 13
1	17 (20)	Positive = 4	Yes = 16	Yes = 2
		Negative = 9	No = 1	No = 10
		Unknown = 4		Unknown = 5
2	5 (6)	Positive = 1	Yes = 5	Yes = 1
		Negative = 4	No = 0	No = 2
		Unknown = 0		Unknown = 2
3a	26 (30)	Positive = 4	Yes = 20	Yes = 3
		Negative = 17	No = 6	No = 12
		Unknown = 5		Unknown = 11
3b	1 (1)	Positive = 0	Yes = 1	Yes = 0
		Negative = 0	No = 0	No = 0
		Unknown = 1		Unknown = 1
3c	7 (8)	Positive = 4	Yes = 3	Yes = 1
		Negative = 1	No = 4	No = 4
		Unknown = 2		Unknown = 2

[1]Marsh-Oberhuber score at diagnosis; [2]Anti-transglutaminase antibodies or endomysial antibodies.

Table 7 Independent predictors of a Marsh-Oberhuber score ⩾ 3a at diagnosis of coeliac disease for 99 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	0.38	0.08-1.85	0.231
Female gender	3.20	0.35-29.10	0.301
Positive serology	2.06	0.17-25.52	0.573
Symptoms for over 3 yr	0.70	0.04-11.37	0.804
Symptoms at diagnosis	4.54	0.51-40.60	0.176

CI: Confidence interval.

Table 8 Independent predictors of a Marsh-Oberhuber score ⩾ 3a after repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	0.59	0.23-1.57	0.292
Female gender	1.13	0.40-3.20	0.824
Gluten free diet	0.03	0.00-0.34	0.004
Symptoms at second biopsy[1]	0.45	0.81-2.48	0.358
Positive serology at second biopsy	0.64	0.18-2.27	0.485

[1]*n* = 51 patients. CI: Confidence interval.

serologic testing[4]. The proportion of atypical or silent presentations of CD is increasing, most often manifesting as bone disease, anaemia or an incidental finding at the time of investigation of dyspepsia *via* endoscopy[8,19]. There is also an increased proportion of diagnoses through screening of first degree relatives[20]. Age at diagnosis has slightly increased since the 1960s, which it is suggested is at least partly related to the later administration of dietary gluten to infants[21].

17 (17%) of cases in this study had autoimmune co-morbidities, mainly thyroid-related. Other studies have reported increased rates of autoimmunity, predominantly thyroid-related although at rates are slightly lower than reported in this study[3,16,22,23]. Ventura *et al*[11] reported a higher prevalence of autoimmune disorders in a CD population relative to healthy controls. While the higher prevalence of autoimmune conditions in CD is often explained by shared HLA antigens, Ventura *et al*[24] reported that the prevalence of autoimmune disorders in CD was associated with the duration of exposure to gluten. They found that the age at diagnosis of CD was the single best predictor of the prevalence of autoimmune disease when corrected for gender and actual age of the patients[24]. It is possible that the increased prevalence of autoimmune comorbidity in the current cohort compared with other cohorts reported in the literature[3,16,22,23], reflect the relatively advanced age at diagnosis which correlated with many years of gluten exposure prior to diagnosis.

We identified 6 (6%) of patients in this study to have osteoporosis or osteopenia. Low BMD is more common in patients with CD[25]. Compared with the current cohort, Kemppainen *et al*[25] have previously reported higher rates bone disease at the time of CD diagnosis (*n* = 20, 26%) although this could perhaps be explained by the relatively older study population in that study (mean 46 years). Kemppainen *et al*[25] has previously reported that low BMD was associated with a new diagnosis of CD, as well as patients not in disease remission. Kemppainen *et al*[25] did not find that mean BMD differed between patients classified by disease severity. Patients with newly diagnosed osteoporosis have higher rates of CD relative to the general population with one study reporting the prevalence of CD in an osteoporotic population to be 3.4%[26]. Patients with CD have significantly decreased bone mineral density (BMD) in the femoral neck and lumbar spine. The pathogenesis of bone mineral loss associated with CD is not well understood. Chronic inflammation of the damaged intestinal mucosa results in release pro-inflammatory cytokines such as tumour

Table 9 Independent predictors of a Marsh-Oberhuber score < 3 on repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients

Characteristic	Odds ratio	95%CI	*P* value
Age below 40 yr	1.16	0.63-4.31	0.313
Female gender	0.90	0.32-2.52	0.834
Negative serology at time of repeat biopsy	0.72	0.26-1.99	0.524
Asymptomatic at repeat biopsy	1.07	0.41-2.80	0.899
Gluten-free diet	23.57	2.61-212.99	0.005

CI: Confidence interval.

necrosis factor α and Interleukin (IL)-6. Higher levels of these cytokines, which directly trigger osteoclasts, have been found in untreated CD patients[27,28]. At the same time lower levels of IL-18 and IL-12, which play an inhibitory role, have been observed in CD patients[27,28]. Other important contributors of decreased BMD may differ between patients but include: malabsorption of calcium; secondary hyperparathyroidism driven by vitamin D deficiency; inadequate dietary intake; lapses from GFD[29,30]. Treatment of CD with a GFD has been shown to improve axial BMD however loss of peripheral skeletal BMD may persist[29]. While patients with CD have increased bone loss, the overall fracture rate is only slightly increased and therefore it is argued osteoporosis related morbidity does not justify population screening for coeliac disease[31]. It has been suggested that screening for CD should be performed in all patients with osteoporosis[26]. However other studies have not supported screening of this population citing that while the prevalence of CD may be increased in osteoporotic cohorts, it makes up only a small contribution relative to the overall post-menopausal osteoporotic population[32,33].

After diagnosis, the key endpoints for CD management are absence of symptoms and histologic evidence of mucosal healing[34]. As was found in this study, negative serological markers are not reliable surrogates for mucosal healing[17,19,35]. Serum EM antibodies and tTG antibodies are often used as surrogate measures of villous health. However these tests were designed for screening for CD among untreated persons consuming gluten. For monitoring known CD patients on a GFD, both EM and tTG antibodies have a high specificity but a low sensitivity resulting in the majority of patients on a GFD with villous blunting having normal serological levels. This is contrasted with a high specificity and sensitivity in patients with untreated CD. False positive tests for patients on a GFD are less common[36].

39% of patients in the current study had persistent villous blunting at repeat biopsy which is higher than similar studies[37,38]. Hutchinson *et al*[37] reported 80% of cases demonstrated histological improvement while Ciacci *et al*[38] reported severe intestinal damage persisted in only 23.8% of patients. An explanation for the difference could be the longer time to follow-up relative to our study of 1.0 year[37] and 6.9 years[38]. There is no consensus on timing of repeat biopsy; some experts favour repeat biopsy in 1 year and others do not recommend a repeat biopsy in the management of uncomplicated CD cases[39]. Serology often does not reflect the mucosal health in patients on a GFD however there is a paucity of evidence to address whether a repeat biopsy changes clinical outcomes and the cost-benefit analysis is yet to be established. A repeat biopsy may be needed, especially in patients with ongoing symptoms. The optimal timing of any such biopsy is unclear[39]. In a cohort of 39 patients with CD reporting GFD adherence all of whom had responded clinically, 77% had abnormal endoscopic and histopathologic appearances on repeat biopsy performed after a mean of 8.5 years[40]. A strict GFD is associated with improvement of histology which has been supported by previous studies, re-enforcing that diet modification is the only known effective management option for these patients[41,42]. The cause of persistent villous blunting is thought to often be caused by trace amounts of gluten consumed inadvertently by the patient. GFD adherence as assessed by interview has been demonstrated as an effective low-cost, non-invasive surrogate for villous damage[38].

This study has a number of limitations. Firstly, this is a relatively small study from a single specialist centre, thus may not reflect results in the greater community. However, a strength is that all patients were assessed by the same local protocol by a single Gastroenterologist which avoided heterogeneity between observers. Secondly, data were collected retrospectively. A number of patients did not have a repeat biopsy nor had missing data at the time of the repeat biopsy. A strength of this study is that it is the first study to look at the presentation of CD in an Australian population in the modern era. There are no published Australian studies which have recognized the changing nature of CD presentations and a prospective study would further add to this field.

In this study, the majority of patients were asymptomatic at the time of CD diagnosis. Neither symptoms nor serology predicted the severity of the small bowel mucosal lesion. The majority of patients had histological improvement on repeat biopsy. Whilst a GFD was associated with histological improvement many patients had persistent mucosal damage despite a GFD. Early repeat duodenal biopsy may have limited diagnostic and prognostic value due to delayed mucosal healing. Biopsy after at least 1 year may provide more valuable results rather than an earlier biopsy as was done in this cohort. Negative CD serology did not exclude ongoing mucosal

injury.

ARTICLE HIGHLIGHTS

Research background

Coeliac disease (CD) is a common gastrointestinal disorder that involves an immune response to dietary gluten. The condition is under recognised, particularly because silent or atypical presentations are becoming more common. Diagnosis is made with the combination of symptoms, serology and characteristic features seen on duodenal biopsy. It remains unclear whether there is an association between symptoms at diagnosis and the degree of small bowel injury. In addition, it is unclear whether symptoms and serology at the time of repeat duodenal biopsy are associated with the degree of mucosal healing.

Research objectives

The aim of this study was to analyze the association between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a gluten-free diet (GFD). Most patients in this study were asymptomatic at diagnosis. Neither symptoms nor serology were associated with the severity of small bowel injury. Many patients had persistent mucosal damage at the time of repeat duodenal biopsy despite reported adherence to a GFD suggesting that mucosal healing may take longer than previously reported. These findings have revealed the increasing difficulty in recognizing the symptoms of CD. Further research is needed to develop more reliable non-invasive biomarkers to be used as surrogates to assess mucosal healing.

Research methods

This was a retrospective cohort study which included 99 participants who presented to a single Gastroenterology practice in Victoria, Australia from 1999-2013. Patients were referred from General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data recorded included: baseline demographics, co-morbidities, family history, duration of symptoms, complications of CD. Serology and histology results were recorded for each patient. The majority of these patients underwent repeat duodenal biopsy after a period on a GFD to check for mucosal healing. Results were compared to repeat serology and symptoms. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

Research results

The mean age at diagnosis was 43 years (IQR 30-53 years) and the majority was female. Most patients (n = 51, 52%) were asymptomatic at diagnosis. 17 (17%) patients had an associated autoimmune condition, the majority of whom had thyroid pathology (n = 10, 59%). The majority of patients with Marsh-Oberhuber Score (MS) $\geqslant$ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c. There was no difference of concomitant autoimmune conditions between patients with MS 3a/b (n = 4, 10%) and MS 3c (n = 9, 18%). Multivariate analysis did not reveal an association between MS $\geqslant$ 3a at diagnosis of CD and positive serology or symptoms at diagnosis. 87 (88%) patients had repeat biopsy. Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy.

Research conclusions

This study supports larger studies that have reported an increase in asymptomatic presentations of CD. Severity of villous blunting at diagnosis was not associated with symptoms. This study did not find an association between symptoms and serology at the time of repeat duodenal biopsy with persistent villous blunting. Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

Research perspectives

Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

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