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Small Bowel Imaging in Celiac Disease

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Key Words

Celiac disease · Radiology · Enteroclysis · Magnetic resonance imaging · Small intestine

Abstract

Background: Modern small bowel imaging techniques allow detailed depiction of small-intestinal abnormalities. The role of these techniques in the investigation of celiac disease is increasing, especially in patients with suspected complicated celiac disease. ***Key Messages:*** In general, there is no need for radiological small bowel imaging in uncomplicated celiac disease. It is however important that clinicians and radiologists are aware of certain specific radiological findings that may suggest celiac disease, especially since celiac disease is often not considered in adult patients, and small bowel radiology may be performed before specific tests for celiac disease. Radiological abnormalities can be observed with both conventional small bowel radiology studies, like small bowel follow-through or double-contrast small bowel enteroclysis, and newer modalities, like computed tomography or magnetic resonance enterography or enteroclysis. These signs include a decreased number of jejunal folds, an increased number of ileal folds, small bowel dilatation, wall thickening and intussusception. Extraintestinal abnormalities include mesenteric lymphadenopathy, vascular changes and splenic atrophy. Abnormalities congruent with refractory celiac disease type II include a severe decrease in jejunal folds, infiltration of the mesenteric fat and thickening of the small bowel wall. Additionally, a severely decreased splenic volume may indicate complicated celiac disease. Malignant complications of celiac disease, such as enteropathy-associated T-cell lymphoma and small-intestinal adenocarcinoma, can be reliably investigated with cross-sectional enteroclysis techniques. ***Conclusions:*** Small bowel imaging and especially cross-sectional enteroclysis techniques are important extensions to the diagnostic workup of clinicians involved in the care of patients with celiac disease, especially those with suspected complicated disease.

Introduction

With the current possibilities of serology and histology, radiology plays no important role in the diagnosis of celiac disease (CD). However, it is important that radiological features associated with CD are recognized, especially since in patients with nonspecific symptoms abdominal imaging may be performed before the diagnosis

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Table 1. Diagnostic modalities in small bowel radiology

Modality	Invasiveness	Enteral contrast	Radiation exposure	Luminal detail	Wall detail	Extraintestinal detail	Availability	Costs
Plain abdominal X-ray	–	None	+	+	–	–	++++	+
SBFT	+	Oral	+++	++	+	–	+++	++
Conventional enteroclysis	+++	Nasojejunal tube	+++	+++	+	–	++	++
Double-contrast enteroclysis	+++	Nasojejunal tube	+++	++++	++	–	+	++
Abdominal ultrasound	–	None	–	+	+	++	++++	+
CT enterography	++	Oral	+++	+++	+++	+++	+++	++
CT enteroclysis	+++	Nasojejunal tube	+++	++++	++++	+++	++	++
MR enterography	++	Oral	–	+++	+++	+++	++	+++
MR enteroclysis	+++	Nasojejunal tube	+ (tube placement)	++++	++++	+++	+	+++

of CD is considered and specific testing has been performed. In patients with nonresponsive CD, the possibility of refractory CD (RCD), small bowel adenocarcinoma or lymphoma has to be considered. In these circumstances, small bowel imaging may provide important information.

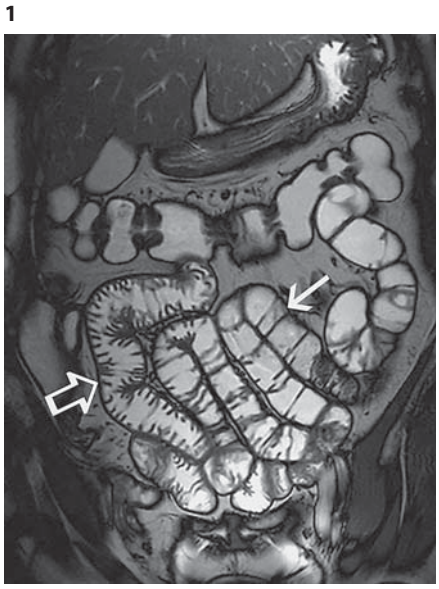
This review aims to provide clinicians involved with the care for patients with CD with some basic knowledge on the strengths and limitations of modern small bowel radiology. Additionally, it aims to inform on the diagnostic accuracy of radiological findings associated with CD, as well as its complications, including RCD and small bowel malignancies.

Modalities in Small Bowel Radiology

In order to be able to appreciate the findings of small bowel radiology, or to efficiently order small bowel radiology, some knowledge on the possibilities and limitations of the different modalities and ways of contrast delivery is important (table 1). The ideal small bowel imaging method is noninvasive, does not require potentially toxic (intravenous) contrast agents, does not use ionizing radiation, and is able to depict the complete small-intestinal lumen, bowel wall, as well as extraluminal structures. In addition, the ideal modality needs to be widely available, result in easy to interpret images and be cost-effective [1]. Small bowel radiological modalities can be classified by the way the image is acquired: fluoroscopy, ultrasound (US), computed tomography (CT) or magnetic resonance (MR) imaging. Except for the modality used, another important factor is whether or not luminal contrast agents are being used, and if so, how these are administered: orally (enterography) or by means of a nasojejunal catheter (enteroclysis). The latter is considered to be more invasive, but allows periprocedural increasing of luminal contrast dose when suboptimal bowel distention is seen, which seems to be particularly important when information on the jejunum is needed [2].

Up to 10 years ago, most small bowel radiology was performed using fluoroscopic techniques. The most prevalent technique was small bowel follow-through (SBFT), which requires the ingestion of at least 0.5 liters of barium suspension. Fluoroscopy is performed when the barium progresses through the intestine. Manual palpation is usually needed to separate individual small bowel loops. Although easy to perform, the poor distention of the small bowel as well as the poor separation of segments limit its accuracy [1]. These problems can be overcome when the barium is administered directly into the small intestine using a fluoroscopically placed nasojejunal catheter, a technique that is called enteroclysis. Even better distention can be achieved when this is followed by administration of methylcellulose suspension or air to enable optimal distension of individual small bowel loops [3]. Limitations of fluoroscopic techniques include the limited information they provide on mural and extraintestinal abnormalities as well as the need for ionizing radiation.

CT is a widely available cross-sectional imaging method, often used in the evaluation of abdominal symptoms. In routine settings, too little luminal contrast agent is administered to prevent collapse of the small-intestinal lumen, and therefore information on the small intestine in limited. Bowel distention can be achieved either by increasing the dose of orally ingested contrast medium (enterography) or by administering methylcellulose (neutral enteral contrast) or barium (positive enteral contrast) directly into the small bowel by means of a nasojejunal catheter (enteroclysis) [1].



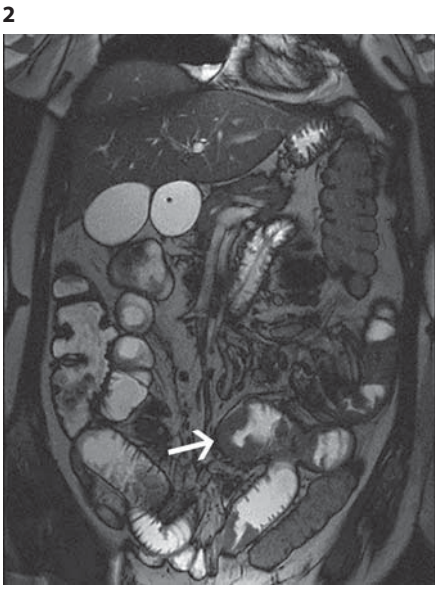


Fig. 1. Coronal MR enteroclysis image shows JFPR in a 45-year-old female with RCD type I. The number of jejunal folds per 5 cm is 2 (arrow), whereas the number of ileal folds per 5 cm is 7 (open arrow).

Fig. 2. Coronal MR enteroclysis image shows EATL (arrow) in a patient with RCD type II.

With the development of fast imaging sequences, small bowel imaging by MR has become possible as well. Advantages include excellent soft tissue contrast and the lack of ionizing radiation. The latter allows for repeated dynamic imaging, so multiple series can be obtained during the same study. This is especially helpful to follow the progression of bowel distention during MR enteroclysis, and allows discrimination between intermittent spasms and stenosis, which often appear the same on static imaging [4]. As in CT, enteroclysis is considered to be more reliable than enterography, although more invasive.

Abdominal US is an easy to perform, noninvasive and readily available imaging modality. However, the lack of bowel preparation often results in intestinal gas or collapse of the bowel wall hindering detailed imaging of the small bowel. However, abdominal US provides better functional evaluation than static small bowel imaging modalities, and especially in case of small bowel obstruction when loops are filled with fluid, the detail with which the intestine can be depicted is impressive [1].

Radiology in Uncomplicated CD

Diagnosis of CD in adults is by serology and duodenal biopsy while the patient is on a gluten-containing diet [5]. The performance of currently available methods for serological diagnosis of CD is very good [6]. For instance, the sensitivity and specificity of IgA anti-endomysial antibodies have been reported to be around 0.84 and 1.00, respectively. For IgA tissue transglutaminase (tTG) antibodies, the sensitivity and specificity have been reported to be around 0.93 and 0.95, respectively [6]. When combined, the diagnostic accuracy of serological tests may approximate 1.0. Despite these performance characteristics, it is generally advised to perform duodenal biopsies, especially in adult patients with gastrointestinal symptoms, before a diagnosis of CD is established [5]. Diagnostic accuracy of duodenal (and bulbar) biopsy specimens for the diagnosis of CD is high, especially when over 4 specimens are obtained [7]. However, one has to be aware that villous atrophy can be caused by more conditions than CD alone, which is why the combination of serology and histology is advocated. In children, the diagnostic accuracy of tTG antibodies is considered that good that in case of tTG raised more than 10× the upper limit of normal, confirmatory duodenal biopsies are no longer required in order to avoid invasive endoscopy [8].

From the above, it can be concluded that modern diagnostic tests for CD are that good that there is no need for radiological methods to investigate the suspected presence of CD in children or adults. However, serological tests for CD, and to a lesser extent duodenal biopsies, are disease-specific tests. In other words, these tests are usually only ordered when a distinct suspicion of CD has arisen. However, the heterogeneous clinical picture of CD remains a challenge to many physicians, and often results in a diagnostic delay of up to 12 years, as well as excessive use of health services [9]. Although there is increasing awareness of CD, this may not be the case for CD present-

Table 2. Radiological findings in CD and its complications

Condition	Intestinal findings	Extraintestinal findings
Untreated CD	Decreased number of jejunal folds Increased number of ileal folds JFPR Jejunal dilatation Wall thickening Intussusception	Presence of nonenlarged mesenteric lymph nodes Presence of enlarged mesenteric lymph nodes Decreased splenic volume Vascular engorgement
RCD type I	As in untreated CD	As in untreated CD
RCD type II	Ulcers Strictures Decreased number of jejunal folds Diffuse bowel wall thickening	Mesenteric fat infiltration Cavitated lymph nodes Severely decreased splenic volume
EATL	Long, smooth small bowel mass Focal small bowel wall thickening	Presence of enlarged mesenteric lymph nodes
Small bowel adenocarcinoma	Circular apple core-like lesion Focal wall thickening Prestenotic dilatation	Presence of enlarged mesenteric lymph nodes

ing with nonspecific, or nongastrointestinal symptoms, which is especially cumbersome now that the classical presenting symptom of CD is less prevalent [10]. For instance, a recent survey among practicing hematologists in the United States revealed that only 8.6% believed that patients with iron deficiency anemia should be screened for CD [11]. In patients with anemia, unintentional weight loss, liver test abnormalities or abdominal pain, it is not unlikely that radiological imaging is performed before CD is considered an option. Radiological imaging has quite often been performed in the diagnostic process of symptoms that were not recognized as being part of the spectrum of CD. This may especially be true in older individuals, where radiological imaging is often used to exclude malignancy. Therefore, it is important that clinicians are aware of the spectrum of radiological findings that may indicate the presence of CD (table 2).

The most striking radiological abnormalities encountered in CD are abnormalities of the intestinal fold pattern (fig. 1). The normal jejunum has over 10 folds per 5 cm, whereas the ileum usually has less than 4 folds per 5 cm [12]. In CD, the number of jejunal folds is often decreased. In severe cases, complete loss of jejunal folds can result in an appearance not unlike that of the colon ('moulage sign') [13]. In contrast, the number of ileal folds is often increased in CD. This probably is the result of ileal adaptation in order to compensate for the loss of absorptive capacity of the jejunum. When the number of ileal folds per 5 cm exceeds the number of jejunal folds per 5 cm, this is called jejunoileal fold pattern reversal (JFPR). This finding, which was first described by Bova in 1985, is considered to be the most specific radiological finding in CD [14]. Lomoschitz et al. [15] identified JFPR on conventional enteroclysis studies in 16/27 patients with CD, compared to 0/123 control patients. Using CT enteroclysis, Soyer et al. [12] found the median number of jejunal and ileal folds in patients with CD was 7 and 8 per 5 cm, respectively, compared to 10 and 4 per 5 cm in controls. The sensitivity and specificity of JFPR in the diagnosis of CD was 0.64 and 1.00, respectively, with an overall accuracy of 0.82. Adequate distention of the small intestine is however mandatory. In a study on abdominal CT after oral administration of 800–1,000 ml Gastrografin, it was not possible to count the number of jejunal folds in 7/52 (13.5%) study subjects [16]. Again, JFPR was only found in patients with CD. Despite the lack of special bowel preparation, Bartusek et al. [17] were able to diagnose a decreased number of jejunal folds in 90%, and an increase in ileal folds in 75% of patients with CD using abdominal US. Abnormalities in fold pattern usually resolve after the introduction of a gluten-free diet [18].

Measurements of small bowel wall thickness usually require cross-sectional imaging and optimal distention of the small intestine in order to prevent false-positive findings caused by collapsed loops. In optimally distended loops, the small bowel wall is usually <3–4 mm thick.

With CT enterography, Tomei et al. [19] found this feature in 21% of patients with CD, the mean thickness being 9 mm (range 5–18). In a study on CT enteroclysis that included 44 patients with CD and 44 control subjects, the sensitivity and specificity of diffuse jejunal wall thickening were 0.66 and 0.98 [12]. Establishing bowel wall thickness with fluoroscopy is less reliable.

Small bowel hypotonia associated with CD may result in jejunal dilatation. In normal subjects, the diameter of the jejunum is usually <4 cm, although this depends on the way it is studied. Using SBFT, McCrae and Sweet [20] showed that in children with CD, the diameter of the jejunum was increased when compared to controls. It could be that the process of enteroclysis diminishes the value of jejunal diameter as a relevant feature. Lomoschitz et al. [15] identified jejunal dilatation in 5/27 patients with CD, and in 9/123 control subjects using conventional enteroclysis. Soyer et al. [12] in a study on CT enteroclysis found the sensitivity and specificity of jejunal dilatation to be 0.16 and 0.95, respectively. In older days, the dilatation of the jejunum as well as the excess fluid in the jejunum resulted in the uneven distribution of barium throughout the jejunum. This finding, called flocculation, has been reported in up to 66% of patients with CD undergoing SBFT, but was much less prevalent with enteroclysis techniques [15, 21]. With modern barium solutions, flocculation is now very rare.

Intussusception is a finding in which one part of the intestine slides into the adjacent part. It is important to realize that intussusceptions in CD are usually transient and may be completely asymptomatic. Intussusception is the most common cause of small bowel obstruction in children aged 3 months to 5 years [22]. Usually, no lead point can be identified. A study from the United States showed that 1.2% of children with CD had experienced a symptomatic intussusception <9 months before the diagnosis of CD. In a large control population, this had occurred in 0.07% of children, within the same time frame [23]. On SBFT, intussusception results in a spring coil-like configuration. On US and cross-sectional imaging, a target sign, reflecting the bowel-in-bowel, is pathognomonic [13]. In adults with CD, intussusception has been reported in up to 20% of patients examined with SBFT [24]. Using abdominal US, Bartusek et al. [17] found transient intussusception in 30% of patients with CD, which reflects the dynamic nature of US.

Extraintestinal findings in CD include changes in blood vessels, lymph nodes and splenic atrophy. All these findings can only be reliably depicted in cross-sectional imaging and to a lesser extent with abdominal US.

Changes in blood flow in CD result in several findings. Abdominal US studies have shown that basal mesenteric blood flow is increased in patients with CD, and that the caliber of the superior mesenteric artery is increased [25]. On cross-sectional imaging, increased blood flow results in a specific image often referred to as vascular engorgement, which is defined as an increase in size and number of proximal and mesenteric vessels, as well as an increase in the number of distal mesenteric vessels adjacent to the small bowel loops [12]. This finding has a reported sensitivity and specificity of 0.64 and 0.91, respectively [12]. This increased blood flow can also be observed in the bowel wall itself. Masselli et al. [26] found that in CD dynamic contrast-enhanced MR imaging showed increased enhancement of the duodenal wall after administration of intravenous contrast. Additionally, this enhancement was very fast, as was the washout of contrast, which probably indicates increased capillary permeability associated with chronic inflammation. As is clear, such measurements require repeated imaging, which is one of the main benefits of MR imaging, compared to CT.

The presence of nonenlarged lymph nodes frequently occurs in the general population, although it is more frequently encountered in patients with CD. Using abdominal US, Bartusek et al. [17] found mesenteric lymph nodes in 95% of patients with CD. Enlarged mesenteric lymph nodes, defined as measuring >1 cm in their short-axis length, were found in 18% of patients with CD [12]. Care is needed in evaluating the aspect of enlarged lymph nodes: enlarged lymph nodes with central hypoattenuation (CD) or a hypoechoic core (abdominal US) are highly suggestive of cavitating lymph node syndrome, especially when associated with splenic atrophy. This very rare syndrome may indicate the presence of lymphoma. Although mortality rates of up to 50% have been reported, spontaneous recovery has been reported as well [13]. Hyposplenism is associated with CD, although the exact mechanism is unclear. On imaging studies, splenic atrophy is often encountered. With CT, Soyer et al. [12] found the median splenic volume of controls was 254 cm^3 compared to 157 cm^3 in patients with untreated CD. Using receiver operating characteristics curve analysis, splenic atrophy was defined as the presence of a splenic volume <145 cm^3. Sensitivity and specificity of this finding were 0.47 and 0.98, respectively.

One has to be aware that many signs associated with CD can also be observed in other conditions resulting in malabsorption. The reported sensitivities and specificities of signs may be inflated by the much larger prevalence of CD than other conditions, like auto-immune enter-

opathy and Whipple's disease. In many more rare or emerging small-intestinal conditions, no studies on radiological findings have been performed. Therefore, radiological findings that may indicate CD need serological and histological confirmation before a diagnosis of CD can be established.

Radiology in Complicated CD

The role of radiology in patients with complicated CD is much more important than it is in patients with uncomplicated CD. In patients with nonresponsive CD, symptoms may be caused by RCD, or small-intestinal malignancies like small bowel adenocarcinoma or enteropathy-associated T-cell lymphoma (EATL). In these patients, abnormalities are often not within reach of conventional gastroscopes, and especially in the presence of symptoms that may indicate small bowel obstruction, video capsule endoscopy is contraindicated [27, 28]. Therefore, small bowel radiology can be a helpful tool to investigate these patients (fig. 2). However, little is known on radiological findings in patients with complicated CD, and unfortunately, most recent studies were all performed in one expert center, limiting their generalizability.

Ulcerative jejunitis may appear on double-contrast enteroclysis studies as thickened segments with ulcerative lesions and stenosis [13]. On cross-sectional imaging, the bowel wall thickening is the most striking abnormality. Discrimination from lymphoma is often not possible. However, there are no studies that have investigated the diagnostic accuracy of these findings.

Mallant et al. [29] reported on CT enterography performed in patients with CD because of persisting abdominal symptoms and/or suspicion of EATL. The final diagnosis was uncomplicated CD in 14, RCD type I in 10, RCD type II in 15 and EATL in 7. For analysis, patients with uncomplicated CD or RCD type II were put in group A, and patients with RCD II and EATL in group B. There were no statistical differences regarding fold patterns. However, because of lack of intraluminal contrast or lack of distention of small bowel loops, the number of jejunal folds could not be counted in 43% of all patients. Jejunal dilation or increased wall thickness did not differ significantly between both groups. Intussusception was found in 1 patient in group A, and in 5 patients in group B, although this difference failed to reach statistical significance. The presence of mesenteric lymph nodes was similar in both groups, but the presence of enlarged lymph nodes was only found in 5 patients in group B. Splenic volume <122 cm^3 was observed in 27% of patients in group A, and 73% of patients in group B, a difference that was statistically significant.

Researchers from the same group also studied MR enteroclysis in patients with nonresponsive CD [30]. Patients with de-novo EATL were not included in this study. Radiological parameters were evaluated in a test group consisting of 28 patients (uncomplicated CD, n = 10; RCD type I, n = 8; RCD type II, n = 10). No differences between patients with uncomplicated CD or RCD type I could be observed. Multivariate analysis identified three parameters associated with the presence of RCD type II: the presence of <10 jejunal folds per 5 cm, diffuse thickening of the small bowel wall, and infiltration of the mesenteric fat. The median splenic volume in patients with RCD type II was 117 cm^3 compared to 212 cm^3 in patients without RCD II. Using the optimal cutoff value of <160 cm^3, splenic atrophy was present in 33% of patients without RCD type II, and 70% of patients with RCD type II, although this difference was not statistically significant in multivariate analysis. The three identified features associated with RCD II were tested in a validation group consisting of 40 patients, 15 of whom had RCD type II. For the presence of <10 jejunal folds per 5 cm, sensitivity and specificity were 0.93 and 0.88, respectively. For mesenteric fat infiltration, this was 0.87 and 0.80, and for diffuse bowel wall thickening, this was 0.47 and 0.84. A positive MR score was defined as 2 or more of these three features present, and showed sensitivity and specificity of 0.87 and 0.96, respectively, for the diagnosis of RCD type II. This MR score was also associated with mortality: 5-year survival was 95% in patients with a negative MR score, and 56% in patients with a positive MR score. In 8 patients, a small bowel malignancy was present, which was detected by MR enteroclysis in 7, resulting in a specificity and sensitivity of 0.88 and 0.97, respectively, for the diagnosis of small bowel malignancy in patients with CD.

The Amsterdam group also compared findings of CT enterography and ^{18}F-FDG-PET performed in 8 patients with EATL and 30 patients with RCD type II [31]. ^{18}F-FDG-PET could reveal sites histologically proven to be EATL in all 8 patients, whereas CT showed normal findings in 1 patient with EATL. ^{18}F-FDG-PET detected unsuspected extraintestinal sites affected by EATL in 2 patients. CT showed abnormalities such as a thickened small bowel wall or lymphadenopathy in 14 patients with RCD lacking evidence of EATL at follow-up. ^{18}F-FDG-PET findings were positive in 3 and equivocal in another 3 patients with RCD. ^{18}F-FDG-PET was more sensitive

and specific than CT (100 vs. 87% and 90 vs. 53%, respectively).

Lohan et al. [32] found that lymphomas in patients with CD were more often solitary, over 10 cm in length and appearing smoother than lymphomas in patients who did not have CD.

Small bowel adenocarcinomas in CD are often, but not solely, located in the proximal jejunum. On SBFT and in conventional enteroclysis studies, they appear as apple core lesions. On cross-sectional imaging, they usually show as solitary, mass-forming lesions, with a predominant intraluminal growth pattern [33, 34].

Besides the studies mentioned, there is limited additional information on the reliability of small bowel imaging for detecting cancer in patients with CD. However, there is emerging evidence that in the detection of small bowel neoplasms in other patient groups, cross-sectional enteroclysis studies are the preferred method, and may even perform better than video capsule endoscopy [2, 33, 35]. Enterography studies often do not result in adequate distention of the jejunum, which is essential in the diagnosis of intraluminal abnormalities.

Conclusions

Small bowel radiology may reveal striking abnormalities in patients with uncomplicated CD. However, in light of the excellent performance characteristics of CD serology and small bowel histology, its role in the diagnosis is limited. However, radiological findings may be the first clues that point physicians to the diagnosis of CD.

The role of radiology in complicated CD seems to be more important, especially when patients present with symptoms that may indicate RCD type II or small bowel malignancy. However, more studies from more centers are needed, which should include a comparison with capsule endoscopy and flexible enteroscopy. Future research should also investigate combined modalities such as PET-CT and PET-MR imaging.

Disclosure Statement

All authors declare that they have no competing interests.

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