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Clinical Utility of Intestinal Ultrasound in Ulcerative Colitis Patients

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1. Introduction

Advances in the field of therapeutics in inflammatory bowel disease (IBD) have raised the expectation of what could be achieved through medical treatment. In the era of 'treat to target' approach, objective criteria of disease activity are researched and implemented to guide clinical decision to achieve the target. Mucosal healing (MH) is the current target of medical management of IBD and was proven to decrease clinical relapse rate, hospitalization and surgery (Peyrin-Biroulet et al., 2015; Stenczel et al., 2021).

The benefit of endoscopic evaluation of the mucosa is that it can be performed by the treating physician, who can then use the endoscopic evaluation to make prompt changes to medical treatment. However, Endoscopic examination of the mucosa is invasive, expensive, and carries some risk. Moreover, due to issues regarding cost and accessibility colonoscopy is not performed with the same frequency recommended by STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) (Peyrin-Biroulet et al., 2015). These issues, together with the rising global and regional burden of IBD, have increased the importance of imaging and noninvasive markers as a diagnostic and monitoring tool for intestinal inflammation (Mosli et al., 2021; GIBD, 2020).

Intestinal ultrasound (IUS), usually performed by gastroenterologists as a point-of-care examination, is a radiation-free, non-invasive, well tolerated, cost-effective, easily accessible, accurate and reproducible imaging technique, and allows transmural assessment of the bowel wall (Alloca et al., 2021). However, IUS until recently has only been practiced by gastroenterologists in few countries

around the world and several recommendations have been published on its use (Christian et al., 2022). It is often seen as an operator dependent technique with limited clinical utility (Maaser et al., 2020). However, operator dependency in not limited to ultrasound and every diagnostic modality is prone to a degree of subjectivity and operator-dependency, and this criticism is likely to reflect previous lack of performance guidelines and standardized training in IUS (Atkinson et al., 2016). Data on the accuracy and the advantages and disadvantages of IUS in IBD compared with other imaging techniques and endoscopy have been extensively reviewed, however guidelines for incorporation of IUS into clinical practice are not widely available. Moreover, IUS can be used in a variety of clinical settings and the level of evidence for its use needs to be demonstrated compared to other imaging modalities and endoscope (Bryant et al., 2018).

The use of IUS in ulcerative colitis (UC) is often questioned. This is because UC is essentially a mucosal disease, with its involvement starting distally in the rectum, easily reachable by sigmoidoscope. However, several recent studies showed significant IUS findings in UC with bowel wall thickness (BWT) to be the most relevant measure (Christian et al., 2022).

Role of intestinal ultrasound in detection and diagnosis of UC
The findings on conventional IUS in patients with UC can be equivalent to those described in cases of Crohn's disease, acute infective colitis, ischemic colitis, radiation colitis, diverticular disease, and malignancy, according to the findings of various studies investigating mixed cohorts (Smith et al., 2020).

Although several of the HCS investigations suggested that bowel wall thickening was less pronounced in UC than in Crohn's disease, it is crucial to understand that BWT changes according to the severity of the disease. There are no particular criteria on IUS to warrant its use alone to distinguish UC from other bowel disorders, even if it may be able to show pathological abnormalities within the colon, which may prompt an early study with a colonoscopy. Additionally, ultrasound alterations in mild disease may be modest, and UC may still be present despite a negative IUS test. The two main diagnostic procedures continue to be colonoscopy and histopathology. In addition, when compared to other inflammatory bowel diseases, the use of extended procedures during regular examinations, such as HCS and the hemodynamic assessment of the abdominal vessels, would not yield a definitive diagnosis of UC. Additionally, these tests either necessitate additional preparation or are susceptible to physiological change without providing any discernible benefits, as shown, in particular, by the equivalent sensitivity and specificity of HCS to the usual IUS test (Smith et al., 2020).

Defining disease extent:
Numerous studies have compared the accuracy of traditional IUS to other methods and modalities for determining the extent of disease. The majority employed histopathological or endoscopic evaluation as the standard for assessing the severity of disease in both active and inactive UC (10). The studies' methods for identifying disease varied; some employed a BWT >4 mm. (Antonelli et al., 2011) and others BWT >3 mm, (Pradel et al., 1997, Pascu et al., 2004, Allocca et al., 2018). BWT and evaluation of the intestinal wall layers were two sonographic findings that Kinoshita et al. used to grade the severity of the disease (Kinoshita et al., 2019).

IUS was observed to have an accuracy range of 88.5 to 95% when compared to endoscopy, with a sensitivity and specificity of 95% and 96%, respectively. One study showed perfect agreement between IUS and endoscopic results, and another showed a strong correlation (r = 0.660) between the two (Smith et al., 2020).

Correlation with endoscopic severity and other disease markers
Studies comparing conventional IUS to endoscopic severity and/or degree of biochemical or clinical activity of UC patients are significantly heterogenous. This includes varying spectra of disease severity in the various study cohorts and various measures of BWT to detect abnormality. The majority of studies, but not all, also included other sonographic measurements, such as color Doppler signal, wall stratification, haustration patterns, compressibility, and extraluminal characteristics. To rate the grade of IUS findings, some authors suggested various ranking systems (Smith et al., 2020).

The scoring system developed using BWT, color Doppler signal, compressibility, and wall stratification had the strongest correlation with the Endoscopic Activity Index [EAI], a modified score based on the Baron score, in the study by Pascu et al. (2004) [r = 0.974, p .001]

Different IUS measurements and inflammatory indicators, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were positively correlated in several studies (Antonelly et al., 2011). In one study, FC and ultrasonography results were used to determine disease activity in using endoscopy as a reference standard. A BWT >3 mm or faecal calprotectin >101 µg/g showed a 100% sensitivity and 53% specificity for endoscopic activity, while the two tests together gave an 84% sensitivity and 93% specificity (Smith et al., 2020).

Intestinal ultrasound scores for disease activity
In order to assess the disease activity in UC patients, a number of sonographic scoring systems have been proposed, some of which include variables in addition to BWT. Tissue elastography was utilized in one investigation to create a sonographic score for UC. The more accurate UC rating scores have shown variable but adequate sensitivity, specificity, and association with endoscopic severity, clinical, and biochemical evaluation (Smith et al., 2020).

Fifty-three UC patients were included in a prospective observational study by Allocca et al., who found a correlation between endoscopic disease activity and BWT > 3 mm, hypoechogenicity, a signal on power Doppler, and lymphadenopathy. Based on them, a score was developed consisting of BWT > 3 mm + colonic wall vascularity or flow, or BWT > 4.43 mm alone without vascular signal. This score exhibited a high inter-observer agreement (k = 0.86) and had a sensitivity of 0.71 and a specificity of 1.00 in determining disease activity (Allocca et al., 2018).

In a group of 98 UC patients, it was recently validated as the "Milan ultrasound criteria (MUC)". The Mayo Endoscopic Score (MES) and MUC had a significant correlation at baseline (p = 0.653; p 0.001), Additionally, patients with a baseline MUC 6.2 had a significantly decreased cumulative likelihood of therapy escalation, needing corticosteroids, hospitalization, and colectomy than those with a baseline MUC > 6.2 (HR: 3.87, 95% CI: 2.25-6.64, p 0.001) (Alloca et al., 2018).

Similar to this, Bots et al. created and internally validated a novel score for assessing disease activity using endoscopy and MES in 60 patients with UC. According to this index, a BWT > 2.1 mm separated between mild endoscopic activity (Mayo 1) and remission (Mayo 0), a cut-off of 3.2 mm distinguished between mild and moderate endoscopic activity (Mayo 0-1 vs. Mayo 2-3), and, ultimately, a BWT > 3.9 mm was associated with severe endoscopic activity. Additional factors that predicted disease activity were an increased color Doppler signal and a lack of haustrations. Additionally, fat wrapping was a sign of severe activity (Bots et al., 2021).

Response to therapy and prognosis:
IUS is a potentially valuable tool for patient monitoring because of its non-invasive nature. several studies assessed various IUS grading systems and measures to determine how well patients responded to various treatments. The sole study that came to negative conclusions was a 1984 case series involving five patients. Following a follow-up period of 2-4 months, there was no evidence of a change in BWT. The most recent studies, however, support the use of IUS in determining treatment response (Smith et al., 2020).

Clinical response and normalization of BWT displayed a strong correlation in the multicenter TRUST and UC trial, which involved 42 German IBD centers and prospectively assessed IUS response in 224 UC patients with a clinical flare needing medicinal therapy. The percentage of individuals with an elevated BWT at baseline in the sigmoid and descending colon reduced dramatically at week 2 after initiating an anti-inflammatory medication and remained low at weeks 6 and 12 (Maaser et al., 2020).

Recently, de voogd et al., found that IUS was responsive to improvement in endoscopic activity following 8 weeks of tofacitinib treatment in patient with to moderate to severe endoscopic activity. BWT correlated with endoscopic mayo sub score ($\rho = 0.68$, P < .0001), UC endoscopic index for severity ($\rho = 0.73$, P < .0001) and Robarts Histopathologic Index ($\rho = 0.49$, P = .002) at both baseline and follow up (de Voogd et al., 2022).

In another recent study, using MUC in UC patients starting biological treatment, alloca et al., showed that improvement in IUS performed 12 weeks after staring treatment is predictive of achievement of mucosal healing at 1 year (Mayo ≤ 1, OR 5.80, p=0.010 (Alloca et al., 2023).

4. Conclusion

To summarize, IUS can be seen as a more beneficial investigational technique than other imaging modalities and endoscopy due to its non-invasive nature, convenience of use, and lack of radiation exposure, A growing body of research supports IUS examinations conducted by gastroenterologists as an addition to normal clinical examinations in IBD patients. IUS has been shown to have advantages in UC diagnosis, disease severity assessment, disease extent delineation, and therapy response prediction. Extensions of the regular examination appear to offer minimal advantage over the traditional IUS examination, according to this systematic evaluation of the evidence. The extended techniques discussed call for additional preparation or may be vulnerable to physiological change without a documented benefit for diagnosis. HCS and the evaluation of the hemodynamic vessels don't seem to be very viable at this point or to offer any distinct advantages above standard evaluation. In contrast to standard color Doppler examination, contrast-enhanced ultrasonographic assessment seeks to provide a measurable assessment of vascularity. However, the limited patient populations evaluated and the absence of agreed measurements or key measures that correlate with the activity of the UC disease and response to medication suggest that this technique is still experimental and does not yet appear to offer any distinct clinical advantages (Smith et al., 2020).

References:

Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. (2015). Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. *Am J Gastroenterol*, 110(9), 1324-1338. https://doi.org/10.1038/ajg.2015.233

Stenczel ND, Purcarea MR, Tribus LC, Oniga GH. (2021). The role of the intestinal ultrasound in Crohn's disease diagnosis and monitoring. *J Med Life*, 14(3), 310-315.

Mosli M, Alawadhi S, Hasan F, Abou Rached A, Sanai F, Danese S. (2021). Incidence, Prevalence, and Clinical Epidemiology of Inflammatory Bowel Disease in the Arab World: A Systematic Review and Meta-Analysis. *Inflammatory Intestinal Diseases*, 6(3), 123-131.

Collaborators GIBD. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*, 5(1), 17-30.

Allocca M, Filippi E, Costantino A, Bonovas S, Fiorino G, Furfaro F, et al. (2021). Milan ultrasound criteria are accurate in assessing disease activity in ulcerative colitis: external validation. *United European Gastroenterol J*, 9(4), 438-442. https://doi.org/10.1177/2050640620963823

Christian M, Giovanni M, Torsten K, Mariangela A. (2022). Ultrasonography in inflammatory bowel disease - So far we are? *United European Gastroenterol J*, 10(2), 225-232. https://doi.org/10.1002/ueg2.12202

Maaser C, Petersen F, Helwig U, Fischer I, Roessler A, Rath S, et al. (2020). Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. *Gut*, 69(9), 1629-1636. https://doi.org/10.1136/gutjnl-2019-320153

Atkinson NS, Bryant RV, Dong Y, Maaser C, Kucharzik T, Maconi G, et al. (2016). WFUMB Position Paper. Learning Gastrointestinal Ultrasound: Theory and Practice. *Ultrasound Med Biol*, 42(12), 2732-2742.

Bryant RV, Friedman AB, Wright EK, Taylor KM, Begun J, Maconi G, et al. (2018). Gastrointestinal ultrasound in inflammatory bowel disease: an underused resource with potential paradigm-changing application. *Gut*, 67(5), 973-985. https://doi.org/10.1136/gutjnl-2017-314868

Smith RL, Taylor KM, Friedman AB, Gibson RN, Gibson PR. (2020). Systematic Review: Clinical Utility of Gastrointestinal Ultrasound in the Diagnosis, Assessment and Management of Patients With Ulcerative Colitis. *J Crohns Colitis*, 14(4), 465-479. https://doi.org/10.1093/ecco-jcc/jjz146

Kinoshita K, Katsurada T, Nishida M, Omotehara S, Onishi R, Mabe K, et al. (2019). Usefulness of transabdominal ultrasonography for assessing ulcerative colitis: a prospective, multicenter study. *J Gastroenterol*, 54(6), 521-529. https://doi.org/10.1007/s00535-018-1511-1

Pascu M, Roznowski AB, Müller HP, Adler A, Wiedenmann B, Dignass AU. (2004). Clinical relevance of transabdominal ultrasonography and magnetic resonance imaging in patients with inflammatory bowel disease of the terminal ileum and large bowel. *Inflamm Bowel Dis*, 10(4), 373-382.

Antonelli E, Giuliano V, Casella G, Villanacci V, Baldini V, Baldoni M, et al. (2011). Ultrasonographic assessment of colonic wall in moderate-severe ulcerative colitis: comparison with endoscopic findings. *Dig Liver Dis*, 43(9), 703-706. https://doi.org/10.1016/j.dld.2011.03.005

Bots S, Nylund K, Lowenberg M, Gecse K, D'Haens G. (2021). Intestinal Ultrasound to Assess Disease Activity in Ulcerative Colitis: Development of a novel UC-Ultrasound Index. *J Crohns Colitis*, 15(8), 1264-1271. https://doi.org/10.1093/ecco-jcc/jjab002

Maaser C, Petersen F, Helwig U, Fischer I, Roessler A, Rath S, et al. (2020). Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. *Gut*, 69(9), 1629-1636. https://doi.org/10.1136/gutjnl-2019-320153

de Voogd F, van Wassenaer EA, Mookhoek A, Bots S, van Gennep S, Löwenberg M, et al. (2022). Intestinal Ultrasound Is Accurate to Determine Endoscopic Response and Remission in Patients With Moderate to Severe Ulcerative Colitis: A Longitudinal Prospective Cohort Study. *Gastroenterology*, 163(6), 1569-1581. https://doi.org/10.1053/j.gastro.2022.07.018

Allocca M, Dell'Avalle C, Furfaro F, Zilli A, D'Amico F, Peyrin-Biroulet L, et al. (2023). Early Intestinal Ultrasound Predicts Long-Term Endoscopic Response to Biologics in Ulcerative Colitis. *Journal of Crohn's and Colitis*.