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Review Article

18F-FDG-PET and other imaging modalities in the diagnosis and management of inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD), which encompasses ulcerative colitis (UC) and Crohn's disease (CD), is a chronic inflammatory condition of the gastrointestinal (GI) tract that presents complex diagnostic and management challenges. Early detection and treatment of IBD is paramount, as IBD can present with serious complications, including bowel perforation, arthritis, and colorectal cancer. Most forms of diagnosis and therapeutic management, like ileocolonoscopy and upper endoscopy are highly invasive and require extensive preparation at great discomfort to patients. 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) imaging can be a potential solution to the current limitations in imaging for IBD. This review explores the utility and limitations of various imaging modalities used to detect and manage IBD including ileocolonoscopy, magnetic resonance enterography (MRE), gastrointestinal ultrasound (IUS), and 18F-FDG-PET/computed tomography (18F-FDG-PET/CT) and magnetic resonance imaging (18F-FDG-PET/MR). This review has an emphasis on PET imaging and highlights its benefits in detection, management, and monitoring therapeutic response of UC and CD.

Keywords: 18F-FDG-PET, IBD, non-invasive imaging, ulcerative colitis, Crohn's disease

Introduction

Inflammatory bowel disease (IBD) manifests as inflammation of the digestive tract and consists of two main types: Crohn's disease (CD) which affects the gastrointestinal tract from the mouth to the anus and ulcerative colitis (UC) which is primarily restricted to the large intestine and rectum [1]. These disorders are characterized by abdominal pain, vomiting, weight loss, fever, and inflammatory bowel syndrome, among other symptoms [2-4]. Although CD and UC are somewhat similar, there are distinguishing factors in presentation. CD associated inflammation affects the full thickness of the bowel, while UC commonly affects the innermost layers, the mucosa and submucosa; inflammation in CD can occur in non-contiguous patches or "skip lesions", while inflammation in UC tends to be contiguous [5]. Due to these patterns of inflammation and areas of the gastrointestinal tract that are involved, the two disorders can be distinguished symptomatically. CD patients more commonly suffer from malnutrition, and in severe cases may suffer from intestinal abscesses and fistulas, while UC patients usually suffer from bloody diarrhea [6, 7]. The pathogenesis of IBD has not been clearly attributed to any single cause but rather associations have been found between incidence of disease and the presence of various gut microbiota, mutations associated with immune system dysregulation, as well as environmental factors [8-10]. The lack of a cure for CD and UC ensues from the incomplete understanding of the pathogenesis of IBD, yet there are common treatments that have varying degrees of success in achieving remissions such as enteric-coated budesonide for CD and aminosalicylates for UC; immunomodulators and anti-TNFα inhibitors are implemented in the treatment plan when remission is not sustained [11, 12].

Despite incomplete knowledge of IBD manifestations in various patient populations, diagnostic modalities have seen promising improvements and innovations in recent years. The purpose of these techniques is primarily to properly diagnose patients in cases of suspected IBD and record disease progression, including extraintestinal manifestations [13]. Ileocolonoscopy and upper endoscopy with biopsy have been considered the golden standard of differentially diagnosing CD versus UC because they allow for direct visualization of various parts of the gastrointestinal tract, leading to proper diagnosis in over 75% of cases because different patterns of inflammation can be differentiated histopathologically, and because of what traditionally have been considered endoscopic-specific features [14-18]. In UC, these features are mucosal erythema, mucosal edema, and mucosal friability, while in CD they are aphthous ulcers, discontinuous longitudinal ulcers, and cobblestone appearance in the mucosa [19, 20]. Beyond diagnosis, ileocolonoscopy and upper endoscopy have been identified as particularly apt for detecting mucosal healing [21-23]. Capsule endoscopy (CE) has emerged as an effective and less invasive substitute to ileocolonoscopy [24, 25].

MRI has the advantage of not exposing patients to radiation, which allows for motion-free, high resolution images of the body [26, 27]. While MRI has high accuracy with respect to grading frank disease, it has been found to

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overstage disease activity in 38% of patients in remission [28]. MR enterography (MRE) has the disadvantages of high cost, reduced availability, and considerable duration compared to other radiographic techniques [29]. Dynamic contrast enhanced- and diffusion weighted MRI have been found to correlate with histopathological scores of surgical specimens in CD patients in addition to providing additional information beyond that of regular MRI [30]. Similar to MRI, ultrasound (US) has the advantage of not exposing patients to radiation, and also requires minimal bowel preparation [31, 32]. US has some additional unique advantages that help with monitoring of IBD complications. First, US can be used as a staging test to monitor patient's active disease status [33]. Additionally, it provides faster assessment of systemic complications such as fistulas seen in CD, and it is more comfortable for patients who have serial assessment. US has demonstrated greater utility in CD rather than UC [34]. Currently, the usage of US in assessment and management of IBD is dwarfed by more favored structural imaging methodologies, but there is a strong motivation for clinicians to increasingly use US for monitoring IBD [35].

Considering the approximately 600,000 patients each with CD and UC along with the peak incidence years of CD and UC overlapping with the pediatric patient age range, diagnostic measures must take into account the tendencies of younger patients [36-40]. Another important consideration is a diagnostic technique that is apt for frequent application in terms of low cost, time effectiveness, and minimal radiation exposure because of the cumulative 67%-83% relapse rate 10 years after initial diagnosis and high documented remission and relapse rates in patients during and after various treatments [41-43]. Although IBD diagnosis tends to focus on the gastrointestinal tract, detection of extraintestinal manifestations (EIMs) can lead to earlier diagnosis of IBD because EIMs appear before the time of IBD diagnosis in 25% of IBD patients [44, 45]. Earlier detection of IBD and the ensuing earlier treatment of IBD can decrease EIMs because the presence of a symptom outside the bowel increases the risk of inflammation and immune dysregulation complications in other organs; among the most common EIMs is peripheral arthritis [46-48].

To this end, 18F-FDG-PET/CT is noninvasive, has shown promising results in terms of sensitivity and specificity in diagnosing CD and UC, and has utility as a whole-body scanning modality, all contributing to the standing of 18F-FDG-PET/CT as the superior imaging modality for IBD [49, 50]. In this review, we will discuss the utility of various imaging modalities in detecting and managing IBD, especially demonstrating the benefits of 18F-FDG-PET over other non-invasive techniques.

Endoscopy/Ileocolonoscopy

Since about 75% of CD patients have disease in the gastrointestinal tract beyond the ileum, a normal ileocolonoscopy does not indicate that a patient is free of CD [26, 51]. Normal ileocolonoscopy results even within the ileum may not exclude a CD diagnosis because of distal terminal ileum skipping, the phenomenon where the terminal ileum may not be affected by CD but the proximal small bowel may be affected. The proximal small bowel can be beyond the reach of an endoscope, which is cause for concern because Samuel et al. (2012) found that 54% of their cohort had small-bowel CD despite normal ileocolonoscopy results [52].

Capsule endoscopy is not able to distinguish between erosions and ulcers caused by CD and those caused by enteropathy from nonsteroidal anti-inflammatory drugs (NSAIDs) [53], which can lead to false positives for a CD diagnosis because 14% of the cohort took NSAIDs but most did not declare using the medication. Further compounding the possible improper attribution of gastrointestinal lesions to CD is that the correlation between clinical activity of CD and the severity of endoscopic lesions is weak, and many patients with clinically active CD may have no significant endoscopic lesions [54].

Based on a study of 68 patients, it was found that CE had a sensitivity of 77% and specificity of 60% in patients who had fecal calprotectin concentration of 95 mg/kg and sensitivity of 73% and specificity of 65% in patients who had fecal lactoferrin of 1.05 mg/kg [55]. He et al. (2017) found that in the pediatric cohort of CD patients, there was moderate correlation between Lewis Score (LS) and C-Reactive Protein (CRP) and in the adult cohort of CD patients, there was weak correlation between LS and Harvey-Bradshaw Index (HBI) and small bowel transit time (SBTT) [56]. Furthermore, patients who were in clinical remission after four months of treatment did not have a significantly lower LS [56].

One of the risks of capsule endoscopy (CE) is capsule retention, which happened in 3% of the small bowel disease patient cohort despite CT being used to identify the gastrointestinal tract for blockages [57].

The clinical presentation of UC as continuous lesions that start at the rectum and develop backwards into earlier sections of the colon promotes the utility of colonoscopy as the primary diagnostic medium. As previously mentioned, UC does not demonstrate systemic ulceration, aside from a few rare cases, making its diagnosis unique from CD [58].

In both cases of IBD, colonoscopy and histopathology is the current standard for diagnosis according to the guidelines [59]. However, colonoscopy requires a rigorous bowel preparation schedule, much to patient discomfort and dismay [60]. Moreover, patients with a confirmed IBD diagnosis currently require repeat colonoscopy examinations for monitoring disease progression and response to therapy.

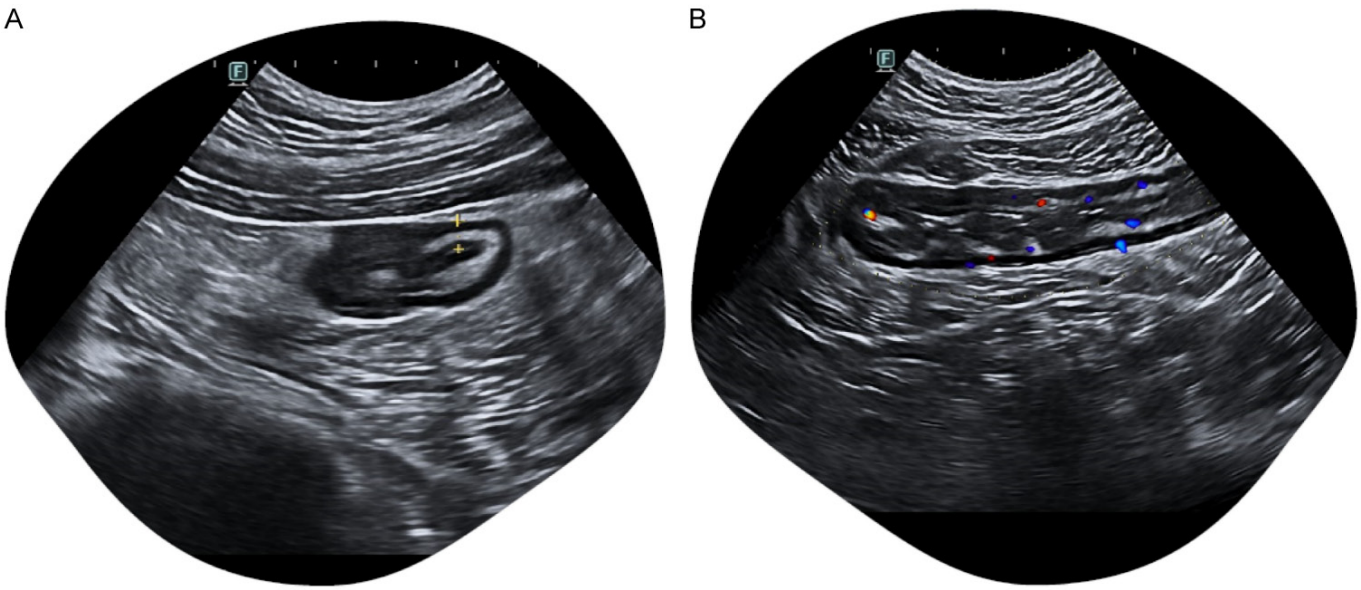

Figure 1. IUS image of active left-sided ulcerative colitis. (A) Increased BWT in the descending colon, depicting mild active ulcerative colitis. (B) Severe acute pancolitis in the sigmoid colon, imaging reveals disruption in bowel wall stratification, deep ulceration, and an increase in BWT. Image reused from [112].

Ultrasound

Intestinal ultrasound (IUS) is an imaging modality that is being adopted to diagnose and monitor IBD, and as it uses no ionizing radiation, it is often well tolerated in patients. IUS is able to measure parameters such as bowel wall thickness (BWT), stenosis, and is able to visualize vascularization and motility [34]. BWT is the preeminent parameter measured by IUS to detect IBD, as it correlates well with endoscopic findings [61] (**Figure 1**). IUS has shown a sensitivity of 95% and a specificity of 96% in detecting UC and a sensitivity of 81% and a sensitivity of 84% in detecting CD [62, 63]. It is notable that BWT may be increased in other conditions such as infective colitis, diverticular disease, and malignancy; BWT also varies based on severity, so IUS is not used alone to diagnose IBD or differentiate between CD and UC [62]. However, IUS can reveal abnormalities in the colon that can prompt early detection with ileocolonoscopy and histopathology [62].

There can be a variability in sensitivity and specificity of detecting IBD and its complications depending on the anatomical location; in CD, for example, there was a variability in the detection of inflammation and other complications in the terminal ileum, left colon, lower rectum, and upper small bowel [64]. In CD, the rectum is usually spared, but rectal involvement is common in UC [58]. IUS has a 15% sensitivity investigating disease processes and complications in the rectum due to its location deep in the pelvis, which may limit its use in the management of active UC [62]. When compared to MRE, IUS may be less likely to detect certain morphological changes due to their anatomical location; it was found that MRE was more diagnostically accurate in defining CD extensions and was able to identify enteroenteric fistulas with a greater accuracy than IUS [64]. The quality of IUS images can also vary greatly depending on the experience level of the user [65].

Currently, IUS is not commonly used in the diagnosis and management of IBD due to the availability of superior imaging modalities. In cases where other imaging is contraindicated or not preferred by the patient, IUS can behave as a proxy for assessing IBD.

MRI/MRE

MRI is particularly applicable to detecting bowel wall thickening, bowel wall enhancement, fibrofatty proliferation, increased vascularity, bowel dilation, associated lymphadenopathy, abdominal extraluminal complications, and perineal complications [66] (**Figure 2**). While the diagnostic yield for detection of active CD was not significantly different for CE and magnetic resonance enterography (MRE), CE had a significantly higher diagnostic yield for proximal small bowel CD cases [67].

Among the pediatric population with suspected or known IBD, MRE has a sensitivity of 83% and specificity of 93% [68]. However, the utility of MRE in the pediatric population is limited by the requirement for patient compliance during breath-hold sequences and the risk of motion artifacts [29]. In order to reduce the artifacts caused by suboptimal patient compliance, it was found that MRI can best detect intestinal lesions when intravenous and oral contrasts are administered [69].

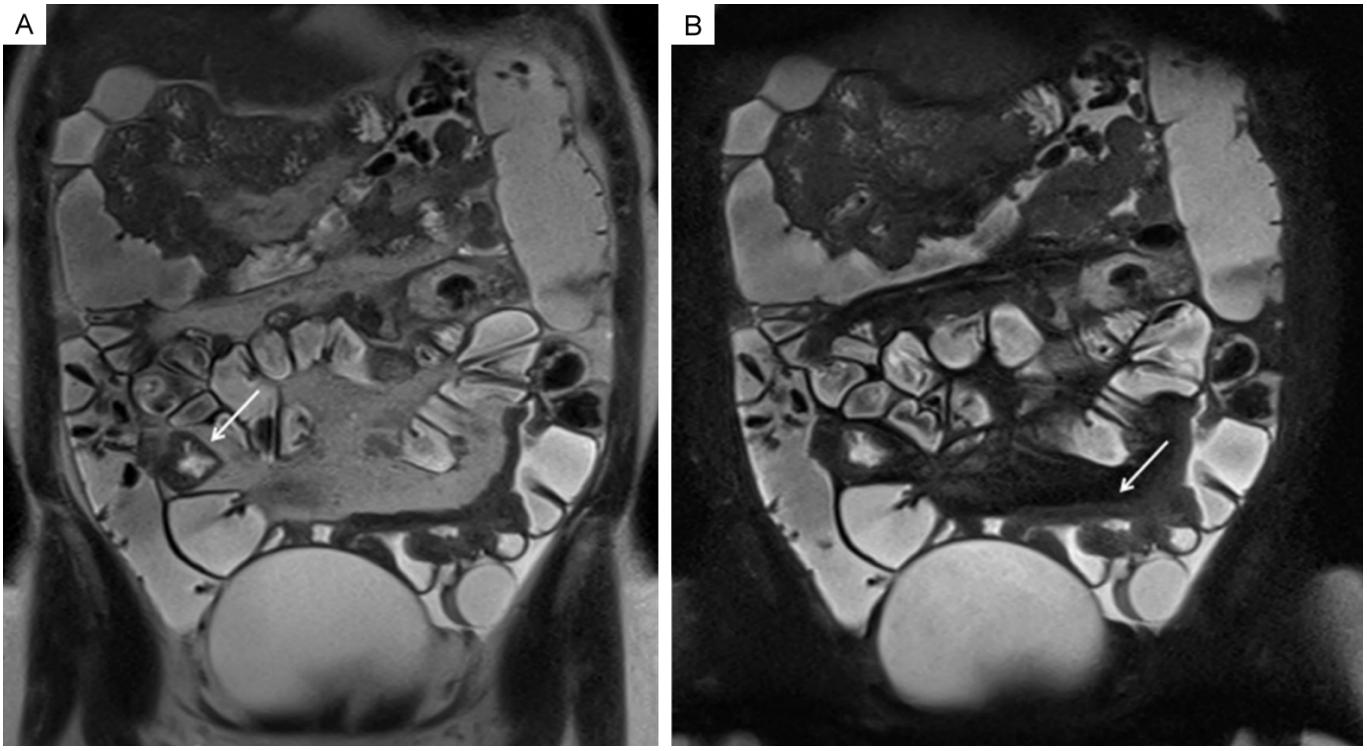

Figure 2. The coronal T2 FSE images, with (B) and without (A) FS, show moderate thickening of the small bowel wall (9 mm) in the right flank and pelvic cavity, as highlighted by white arrows. Additionally, there is free fluid present in the left iliac fossa. Image reused from [113].

Diffusion weight imaging (DWI) generates an image based on the movement of water and small molecules within tissue. Since inflammation is associated with lymphocyte infiltration, increased restriction of movement of water in DWI can be an indicator of disease activity. For active disease in CD, indicated by calprotectin levels greater than 120 μg/l, sensitivity was 83% and specificity was 52% by the use of DWI, lending to the susceptibility of false positives [70]. In blind analysis of pediatric patients with suspected or known IBD, sensitivity and specificity with DWI for the detection of at least one lesion were 88.1% and 83.3% respectively, while segment-level analysis of intestinal lesions showed a sensitivity and specificity of 62.5% and 97.1% respectively [71]. The low sensitivity in segment-level analysis of intestinal lesions leads DWI to be susceptible to false negative results.

Overall, MRI is quite helpful in assessing structural changes associated with both UC and CD, but is not informative in the continuous assessment of inflammation associated with IBD. Indeed, MRI/MRE is increasingly being used in all gastrointestinal diseases due to its high anatomical specificity; by combining it with PET imaging, clinicians can be better informed as to the degree of disease progression and repression.

18F-FDG and 18F-FDG quantification

18F-FDG-PET/CT has been shown to be highly sensitive and specific in detecting malignant lesions due to the hypermetabolic nature of malignant cells. Malignant cells demonstrate increased expression of GLUT transporters and hexokinase, which leads to an increased uptake of 18F-fluoro-deoxyglucose (18F-FDG); 18F-FDG cannot be metabolized in the Krebs cycle due to the bonded fluorine. Additionally, malignant cells have a decreased expression of glucose-6-phosphatase, which prevents 18F-FDG from exiting the cell and leads to metabolic trapping [72-74]. This is reflected by the efficacy of 18F-FDG in detecting and managing various malignancies [75-77]. Similarly, the hypermetabolic nature of inflammation has allowed 18F-FDG-PET/CT to have broad applications in the imaging of inflammatory diseases. The process of inflammation involves mononuclear cells that have increased expression of GLUT transporters, hexokinase and glucose-6-phosphatase, which leads to increased uptake and increased clearance of 18F-FDG. This allows visualization of inflammation, and the increased clearance rate of 18F-FDG in the inflammatory process compared to malignant lesions allows for differentiation between malignant and inflammatory processes. This makes 18F-FDG-PET/CT an ideal modality for detecting infectious and inflammatory diseases [78-81].

Furthermore, the corroboration of 18F-FDG-PET with CT allows clinicians to ascertain the anatomical correlations of areas with increased 18F-FDG uptake. This is especially important in detecting anatomical abnormalities that occur in IBD. 18F-FDG-PET/CT is also advantageous due to it being an imaging modality that allows for sensitive

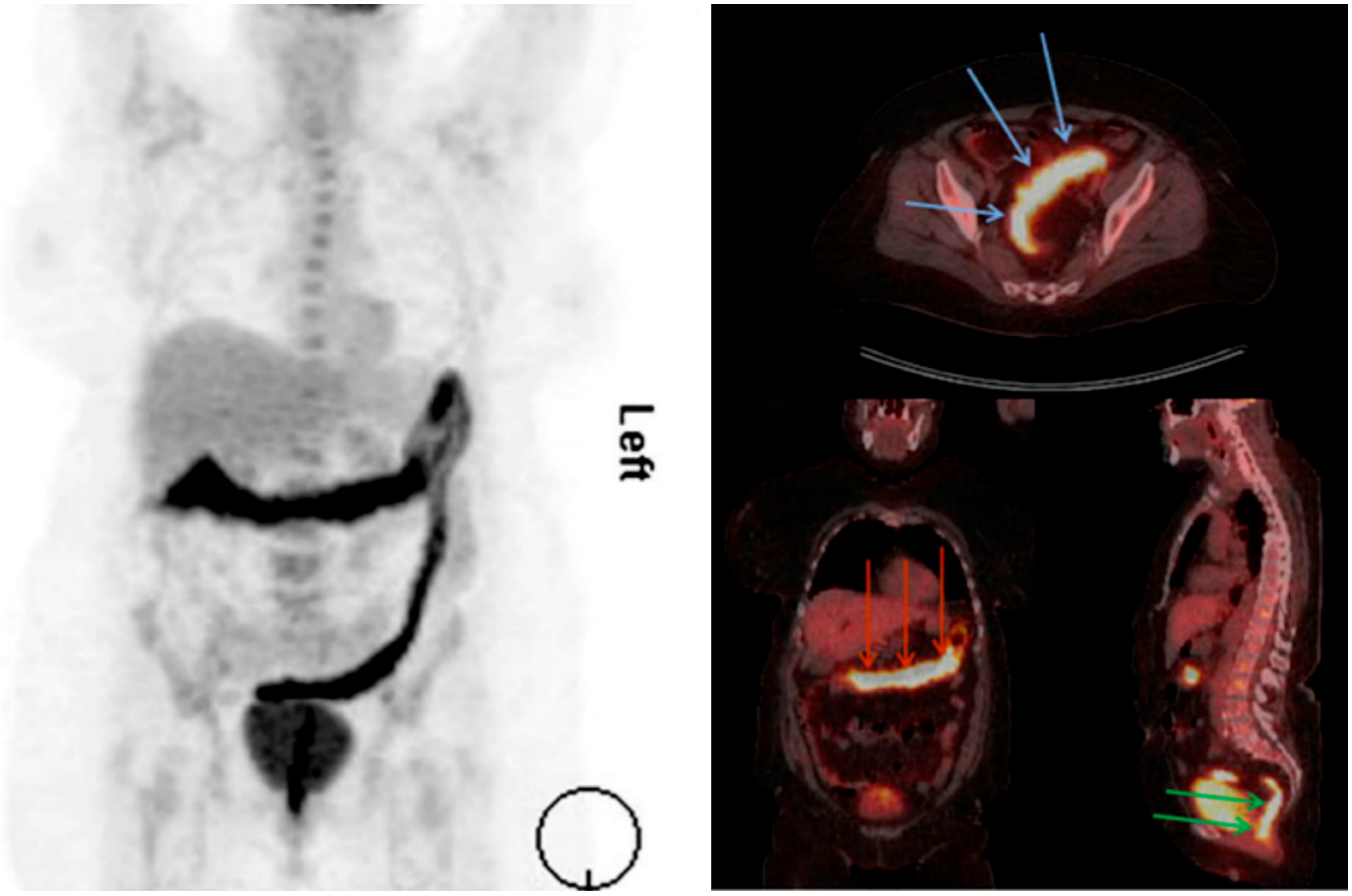

Figure 3. 18F-FDG PET/CT scan of UC patient. Axial view on the left depicts the extent of disease and inflammation. Right panel shows additional coronal, axial, and sagittal views of the extent of disease. Image reused from [114].

and specific quantification of inflammation. The key metric of 18F-FDG uptake in a region of interest is the standard uptake value (SUV), which is measured a certain time after the 18F-FDG injection and is normalized to the dose injected and the whole-body distribution based on the patient's body weight. SUV is a convenient metric as it can be collected without blood samples or dynamic imaging; most PET centers report SUV, so it is also a readily accessible measurement [72-74].

18F-FDG-PET/CT

In specific application to IBD, 18F-FDG PET is correlated with many diagnostic indexes that are utilized to assess UC and CD. 18F-FDG-PET/CT has been shown to have a significant correlation with Mayo score, which combines endoscopic findings and clinical assessment of UC patients, fecal calprotectin, and histological score [82]. PET activity was found to correlate well with active inflammation in both UC and CD in addition to CRP and Harvey-Bradshaw index [83-86]. These findings are in accordance with a study conducted on subjects who had undergone both 18F-FDG-PET/CT and ileocolonoscopy. The global CD activity score (GCDAS) was calculated based on the partial volume-corrected SUV and total lesion glycolysis; GCDAS was correlated with CD activity index (CDAI) and fecal calprotectin [87]. In addition, based on a meta-analysis of seven studies with a total of 219 IBD patients, the sensitivity of 18F-FDG-PET/CT in diagnosing IBD was determined to be 85% and the specificity was 87% [88]. 18F-FDG-PET/CT has demonstrated itself to be a modality that can accurately assess IBD and differentiate it from other pathology.

18F-FDG-PET/CT is especially distinguished from other modalities in its ability to predict remission due to its ability to detect active inflammation [89] (**Figure 3**). 18F-FDG-PET/CT may play a role in staging and response to treatment; a decrease in active inflammation after treatment may mark the start of remission [90]. Palatka et al. (2017) calculated a global PET score based on 18F-FDG uptake in the small intestine and each of four segments of the colon; in patients with active inflammation, global PET scores correlated better with CDAI than did simple endoscopic score for CD (SES-CD) [91]. Further contributing to the predictive ability of inflammation response to biological treatments of 18F-FDG-PET/CT are the findings of Epelboym et al. (2017) that patients who had a decrease in SUV two weeks after initiation of anti-TNF therapy correlated with clinical improvement, steroid-free remission, and reductions in CRP over the next 52 weeks [92].

Mucosal healing is one of the treatment goals for IBD patients, so a strong positive correlation between increa-

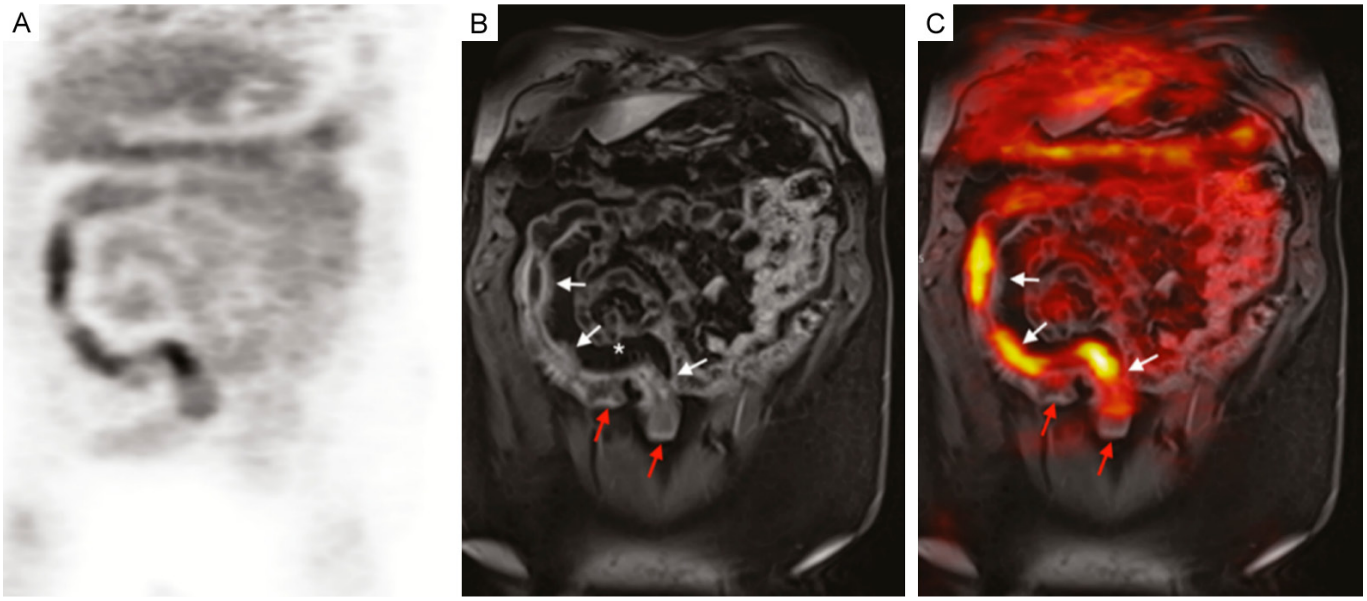

Figure 4. (A) 18F-FDG PET image of a patient with Crohn's disease. (B) T1-weighted MRI of the same patient. (C) Combined PET/MRI image. White arrows indicate areas of acute inflammation, while red arrows point to damage from previous disease activity. The asterisk (*) marks a site with fibrofatty tissue proliferation in the mesentery. The SUVmax for 18F-FDG ranges from 5.6 to 9.2, compared to a background bowel SUVmax of 1.5 to 2.8. Image reused from [115].

se in intestinal lesions and higher 18F-FDG uptake would be highly clinically valuable [93-95]. As such, the findings of Bettenworth et al. (2013) that 18F-FDG uptake increased after dextran sodium sulfate (DSS) colitis induction in a murine model, as well as increased 18F-FDG uptake being found in 87% of deep mucosal ulcerations in IBD patients reflects the application of 18F-FDG-PET/CT to monitor mucosal healing [96].

18F-FDG-PET/CT can also be an effective and accurate means of determining drug efficacy because increased 18F-FDG-PET/CT uptake in the intestine correlates with greater presence of inflammatory cytokines. Thus a reduction in 18F-FDG-PET/CT uptake after drug treatment can be an indicator of positive response to drug treatment [97]. In IBD patients, inflammation can be detected with 18F-FDG-PET/CT before anatomical manifestations of that inflammation can be detected by means like capsule endoscopy and ileocolonoscopy [98].

18F-FDG-PET/MR has also shown promise in detecting the complications of IBD and has shown similar promise in the management of IBD (**Figure 4**). 18F-FDG-PET/MR has a high diagnostic accuracy of 91%, which is significantly higher than MR alone at 83% [99]. An important aspect of evaluating CD complications is differentiating between inflammatory and non-inflammatory strictures, as these pathological changes have different courses of treatment; fibrotic strictures require surgical intervention, while inflammatory strictures can be resolved with non-surgical therapy. 18F-FDG-PET/MR has the potential to differentiate these two with a hybrid biomarker [100]. In terms of UC, 18F-FDG-PET/MR can be useful in determining subclinical inflammation that cannot be accessed in endoscopy [101]. Aside from being a tool to assess inflammation activity in UC patients, PET/MR can also be used to assess mucosal healing in UC patients, which is important to measure for treatment response monitoring [102].

Although radiation exposure is among one of the most commonly cited concerns for 18F-FDG-PET/CT, the procedure can be optimized by the implementation of 3D PET acquisition mode, adaptive statistical iterative reconstruction (ASIR) to reduce radiation dosage [103-106]. Another optimization technique to take into account is the use of the delayed phase rather than early phase in dual-time-point 18F-FDG-PET/CT because physiological uptake of 18F-FDG is significantly greater in the delayed phase [107]. Oral negative contrast agents like mannitol and scopolamine butylbromide increase distension of the gastrointestinal tract and decrease physiological intake of 18F-FDG, thereby improving image quality in 18F-FDG-PET/CT [108]. Other concerns with 18F-FDG-PET/CT exist regarding required ketogenic diet prior to imaging to suppress baseline inflammation throughout the body [109-111]. However, this can only currently be improved through patient compliance though current studies are exploring ways to alleviate dietary prep. Currently, serial 18F-FDG-PET/CT is not recommended for IBD due to its cost and radiation exposure compared to other imaging modalities. However, improvement of scanner technology may allow for untapped potential in monitoring small changes in disease progression.

Conclusion

IBD is a chronic inflammatory disease that leverages non-invasive imaging techniques for early diagnosis and

repeat assessments of disease activity. The current diagnostic standard remains colonoscopy and histopathology, but non-invasive imaging techniques may be favorable in long-term management and monitoring response to treatment. Though MRI and US are traditionally used in this manner, 18F-FDG-PET/CT demonstrates great utility in monitoring disease progression, remission, and response to immunotherapy due to its superiority in quantification and visualization. Cost and radiation exposure may be limitations to this modality, but further study and scanner improvements may alleviate said limitations and offer a convenient alternative for physicians and patients alike.

Disclosure of conflict of interest

None.

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