

## EDITORIAL

**THE ROLE OF POSITRON EMISSION TOMOGRAPHY  
IN INFLAMMATORY BOWEL DISEASE**

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**Inflammatory bowel diseases (IBD) are a group of pathological conditions characterized by chronic inflammation of the gastrointestinal tract, including Crohn's disease and ulcerative colitis. To date, imaging of IBD is based on several radiological techniques such as barium studies, magnetic resonance imaging, and computed tomography (CT). Endoscopy is the gold standard for the assessment of the large bowel and proximal small intestine in patients with IBD allowing the biopsy of the visualized bowel. Positron emission tomography (PET) and PET/CT with Fluorine-18-fluoro-2-deoxy-D-glucose (FDG) is a functional imaging method used to detect abnormalities in glucose metabolism in a variety of disorders. FDG accumulates mainly in tumours, but increased uptake and retention has been shown also in lesions with a high concentration of inflammatory cells, such as granulocytes and activated macrophages. Recent literature data demonstrate that FDG-PET and PET/CT may be useful noninvasive tools for identifying and localizing active IBD. In patients with an established diagnosis of IBD, FDG-PET and PET/CT may provide information about disease activity, location and extent of the disease within the intestinal tract, allowing early recognition of disease relapse and possible complications. Furthermore, these techniques may play a role in assessing the treatment response to medical therapy in patients with IBD.**

Idiopathic inflammatory bowel diseases (IBD) consist of two types of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). The hallmark of both diseases is a chronic, uncontrolled inflammation of the intestinal mucosa, which can affect any part of the gastro-intestinal tract from the mouth to the anus. In CD the inflammation is often transmural, whereas in UC the inflammation

is typically confined to the mucosa. CD can be associated with intestinal granulomas, strictures, and fistulas, but these are not typical findings in UC (1).

The hallmark of active IBD is a pronounced infiltration of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B cells and T cells) into the lamina propria. Increased production of

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cytokines and chemokines by immune cells results in recruitment of additional leukocytes, producing a cycle of inflammation (1).

IBD may present without clinical manifestations more frequently in an early stage. This suggests that early identification of such occult lesions may have an impact on patient management and outcome. The clinical course is characterized by a succession of periods of clinical relapse and remission (1). The goal of the treatment in these patients is to maintain a normal quality of life by sustaining remission and avoiding complications. In this scenario two different situations may be problematic for the clinicians: patients with symptoms suggesting active disease but with biologic markers within the normal range, and patients with clinically inactive disease but who may silently evolve toward stricturing or fistulising complications. In the first situation, a differential diagnosis must be made between truly active inflammatory disease, associated irritable bowel symptoms, and effects of previous surgery. In the second situation, often after a clinically effective treatment, it may be tempting to simply try to prolong the obtained clinical remission.

The aims of imaging techniques in inflammatory bowel disease are: a) diagnosis of CD or UC; b) assessment of disease extent and severity; c) assessment of possible complications; d) treatment response evaluation. To date, imaging of IBD is based on several radiological techniques such as barium studies, magnetic resonance imaging (MRI), and computed tomography (CT) (2). However, endoscopy is the gold standard for assessment of the large bowel and proximal small intestine in patients with IBD, allowing the biopsy of the visualized bowel (2).

Positron emission tomography (PET) and PET/CT with Fluorine-18-fluoro-2-deoxy-D-glucose (FDG) are functional imaging methods used to detect abnormalities in glucose metabolism in a variety of disorders ranging from neurological diseases to oncology (3).

FDG is a glucose analogue that accumulates in neoplastic cells, but increased uptake and retention of this tracer has been also shown in lesions with a high concentration of inflammatory cells, such as granulocytes and activated macrophages. Several studies have indicated that FDG-PET and PET/

CT can be used for the detection of areas with chronic inflammation (4, 5). In fact, FDG uptake increases in cells with high glycolytic rates such as in inflamed tissue leading to accumulation of FDG-6-phosphate. Such increased glucose consumption allows visualization of inflammatory foci (4, 5). Nevertheless, FDG-PET and PET/CT are not able to discriminate between infection/inflammation and neoplastic disease (4, 5).

Recent literature data demonstrate that FDG-PET and PET/CT may be also useful noninvasive tools for identifying and localizing active IBD.

#### *PET and IBD*

Usually IBD may present a diffuse or segmental pattern of FDG uptake in the bowel; however, this pattern may be focal for IBD complications (6, 7). Physiological FDG uptake by normal bowel is well known: the mechanism of this is not fully understood but factors such as smooth muscle contraction and uptake of FDG by gastrointestinal lymphoid tissue are thought to be involved (6); physiological uptake of FDG by the bowel could lead to false positive results in patients with suspected IBD (7). To reduce this possibility, the morphological information provided by CT scan with integrated PET/CT systems offers an anatomic reference frame to functional information provided by FDG-PET (7-10). The use of water (1,500 mL per os) as a negative contrast agent for CT, allows avoiding the attenuation correction artifacts due to dense contrast agents. This method permits to obtain a distension of the bowel and an optimal evaluation of the wall thickening. There are also some negative oral contrast media commercially available (7-10).

To date, several articles have assessed the role of FDG-PET and PET/CT in patients with IBD (28-46). The PET image analysis has usually been performed by using qualitative and semi-quantitative criteria, the latter based on the calculation of standardized uptake values (SUV) of the bowel segments, usually compared with reference region (as the liver).

#### *FDG-PET and PET/CT in the assessment of IBD in adult patients*

First of all, in 1997, Bicik et al. suggested that FDG-PET may be a useful noninvasive method to identify active inflammation in IBD and for long-

term monitoring of these patients (11).

In 2002, Neurath et al. found that FDG-PET was a reliable noninvasive tool for simultaneous detection of inflamed areas in the small and large bowel of patients with CD with a high per segment-based sensitivity (85%) and specificity (89%). Furthermore, the diagnostic accuracy of FDG-PET in the assessment of IBD was superior compared to hydro-MRI and granulocyte scintigraphy with labeled antibodies (12).

In their pilot study, Meisner et al. demonstrated that FDG-PET bowel activity correlated well with active inflammation in both UC and CD, confirming that this imaging method may be a noninvasive tool in identifying disease activity in patients with IBD (13).

FDG-PET/CT well correlates with the clinical, endoscopic, and biologic activity of CD, as demonstrated in a prospective study of Louis et al.; above all, this technique demonstrated to have a good sensitivity for the detection of intestinal and colonic segments with moderate to severe mucosal lesions (14).

Das et al. described promising results with FDG-PET/CT enteroclysis in assessment of IBD. This technique detected a significantly higher number of lesions both in the small and large bowel in comparison to those detected by conventional barium studies and colonoscopy combined together (15).

In their prospective study, Rubin et al. demonstrated that FDG-PET/CT was useful to detect subclinical inflammation in patients with UC in remission. In particular, FDG-PET demonstrated inflammatory activity in the colon despite negative endoscopic, histologic, and symptom assessment (16).

The accuracy of FDG-PET/CT for differentiating fixed muscle hypertrophy and fibrotic stenoses from acute transmural inflammatory stenoses in patients with CD scheduled to undergo surgical resection for obstructive symptoms was also assessed; qualitative PET interpretations and, in particular, semi-quantitative analyses helped to identify patients with active inflammation (17).

In 2010, Das et al. reported promising results by using FDG-PET/CT colonography for the assessment of extent and activity of the disease in patients with UC (18).

In the same year, Groshar et al. used FDG-PET/CT enterography in patients with CD and found that semi-quantitative PET analysis may allow an objective, reliable indication of the grade and severity of inflammation activity in abnormal segments of the bowel detected by CT enterography (19), as confirmed by the prospective study of Shyn et al. (20).

Also Ahmadi et al. reported the value of FDG-PET/CT enterography in assessing the disease activity in patients with CD. These authors highlighted the role of FDG-PET in determining the degree of inflammation in abnormal small bowel segments on CT enterography. In particular, FDG-PET added to CT enterography did not identify additional abnormal segments when compared to CT enterography alone. Nevertheless, abnormal segments on CT enterography that did not accumulate FDG were significantly associated with failure of medical therapy (21).

The usefulness of FDG-PET/CT in assessing the treatment response in patients with IBD was evaluated by Spier et al.; these authors demonstrated that the metabolic activity assessed by FDG-PET decreased with successful treatment of inflammation in active IBD and correlated with clinical improvement (22).

Lapp et al. tested the clinical utility of FDG-PET/CT in comparison to standard workup (including history, physical examination, laboratory tests, colonoscopy and/or cross-sectional imaging) in patients with known or suspected IBD. The authors found that FDG-PET/CT was very useful in diagnosis and management of IBD; compared with standard workup, all the patients evaluated had superior results when therapeutic decisions were based on PET/CT (23).

More recently, Lenze et al. evaluated different noninvasive imaging methods (including FDG-PET/CT, MR enteroclysis and transabdominal US) for the detection and differentiation of inflammatory and fibrotic stenoses in patients with CD in comparison to endoscopic and histologic evaluation. Detection rates of the strictures were not significantly different between FDG-PET/CT, MR enteroclysis, and US; nevertheless, these techniques did not accurately differentiate inflamed from fibrotic strictures. Only a combination of these techniques resulted in a 100% detection rate of strictures

requiring surgery or endoscopic dilation therapy, suggesting the combination of these methods as an alternative to endoscopy at least in the group of patients not able to perform an adequate bowel preparation (24).

Lastly, Holtmann et al. demonstrated in their prospective study that FDG-PET is able to detect mucosal inflammation in CD with high sensitivity (90%) and specificity (92.6%) and to enable proper assessment of inflammatory activity in stenoses (25).

#### *FDG PET and PET/CT in the assessment of IBD in pediatric patients*

First of all, in 1999, Skehan et al. demonstrated that FDG-PET may be a useful technique for the detection of intestinal inflammation also in children with IBD, particularly when conventional studies are technically unsuccessful (26).

In 2005, Lemberg et al. confirmed that FDG-PET may be useful noninvasive tool for identifying and localizing active intestinal inflammation in children with IBD (FDG-PET correctly identified active inflammation in 80% of children with IBD). Also if PET may not be able to replace conventional studies, these authors underlined that this functional method may be useful when conventional studies cannot be performed or fail to be completed (27).

These findings were confirmed by a retrospective study of Löffler et al. who found a high sensitivity (98%) and accuracy (83%) but a moderate specificity (68%) of FDG PET in assessing disease activity in children with IBD and recommended this functional method especially for the assessment of small bowel involvement in children with IBD (28).

Recently, Däbritz et al. reported a high per segment-based sensitivity (82%), specificity (97%) and accuracy (91%) of FDG-PET and PET/CT for assessment of IBD in children. Interestingly, the co-registration of CT did not improve the diagnostic informative value (29).

#### *General remarks and future perspectives*

FDG-PET and PET/CT have great potentialities as non-invasive tools for the assessment of patients with IBD. There is still limited evidence on these imaging methods both in adult and in pediatric IBD patients, but there is a good correlation between PET findings and disease activity (11-29).

FDG-PET, even if low specific, can be particularly useful as a marker of the whole inflammatory burden and may have a role in the initial evaluation of patients with IBD and for early evaluation of therapy efficacy (30).

In patients with an established diagnosis of IBD, FDG PET and PET/CT may provide information about disease, location and extent within the intestinal tract, allowing early recognition of disease relapse and possible complications of the disease in association with clinical symptoms, physical exam and laboratory data (30).

The use of FDG-PET/CT for malignancy surveillance in this high-risk population group may be an added value in the follow-up of IBD patients.

Based on literature data, the role of FDG-PET and PET/CT in the assessment of IBD seems to be promising but currently these diagnostic imaging methods are not routinely used in patients with IBD (4). Whether the information derived from PET imaging justifies the additional radiation exposure, as compared to other imaging modalities, also requires additional investigation. Furthermore, larger clinical trials and cost-effectiveness studies on the use of FDG-PET and PET/CT in patients with IBD are needed to strengthen the usefulness of these functional imaging methods in this setting. Similarly, it is conceivable that further developments of molecular imaging such as hybrid PET/MRI will provide relevant information on IBD.

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