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Combined [^{18}F]-Fluorodeoxyglucose Positron Emission Tomography-MR Imaging: A Promising Tool for Diagnostics of Small Bowel Crohn's Disease

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Keywords
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Abstract
Introduction: Diagnostics of small bowel Crohn's disease (CD) can be difficult. Combined positron emission tomography-magnetic resonance enterography (PET-MRE) can be used to evaluate intestinal metabolism, but clinical use has been limited due to accessibility, costs, absence of standardized methods, and diagnostic thresholds. Our aim was to show that combined PET-MRE can be used to diagnose active small bowel CD. ***Methods:*** We performed a fusion PET-MRE scan with [^{18}F]-FDG tracer to 30 patients with suspected small bowel CD in colonoscopy. Standardized uptake values (SUVs) were measured from small bowel. The diagnosis was confirmed with small bowel capsule endoscopy. Clinicians chose appropriate medication to each patient blinded from SUV results. Endoscopic, laboratory, and MRE findings were investigated in relation to SUV. ***Results:*** Fusion PET-MRE outperformed MRE in diagnostic accuracy. Patients diagnosed with CD (N = 24) had higher SUV than patients not diagnosed with CD (N = 6) (3.34 vs. 1.84, p = 0.022). A diagnostic cut-off at SUV at 2.5 could be used (AUROC = 0.81). A higher SUV predicts need for immunosuppressive medication (p = 0.0026) and biologics (p = 0.0005). SUV correlates positively with Simple Endoscopic Score for Crohn's Disease (SES-CD), fecal calprotectin, and CRP and negatively with Hb and serum albumin. ***Conclusion:*** In future, [^{18}F]-FDG PET-MRE can be used in diagnostics of small bowel CD as a safe alternative for capsule endoscopy. High SUV can predict a more progressive disease course and need for more advanced therapies.

Introduction

Crohn's disease (CD) is an inflammatory condition of the gut characterized by relapsing and remitting inflammation of the mucosa. The disease can affect different sites in the gastrointestinal tract from mouth to anal canal. More than 80% of patients get the diagnosis before the age of 40 and have ileal, colonic, or ileocolonic

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inflammation [1]. The precise pathophysiology of CD remains a mystery, but it is thought that the disorder is likely to be related to an aberrant immunological response to intestinal microbiota in genetically susceptible individuals [2–4]. Overall course of CD tends to be progressive leading to chronic damage of the gut fibrosis, malnutrition, malaise, and even malignancies. Up to half of patients with CD also present with strictures, fistulae. The disease pathway can often be altered by medical therapy or surgery; thus, the diagnosis should be established rapidly [5].

With ileal, colonic, or gastric involvement, the diagnostics can be easy as these areas are accessible by conventional endoscopy, which is considered to be the golden standard for evaluation of the mucosa. In 43–60% of patients with established CD and suspected small bowel involvement, the lesions may not be assessed by conventional endoscopy [6]. With small bowel CD, the diagnostics often requires computed tomography (CT) scan or magnetic resonance enterography (MRE) and small bowel capsule endoscopy (SBCE), which are time consuming for both the patient and clinician. CT is also widely used for diagnosis and follow-up of small bowel CD and compared to MRE, CT has similar sensitivity and specificity for detecting active CD inflammation, strictures, fistulae, and abscesses [7, 8] but it has a limited ability to differentiate between active inflammation and chronic inactive fibrosis and the soft tissue contrast is inferior to MRE [9]. MRE can detect transmural damage in advanced disease [10, 11], but in the case of luminal disease the sensitivity is limited [10–12]. Bowel ultrasound is also a feasible technique used to evaluate disease progress but is inferior to MRE in sensitivity and specificity [13]. SBCE is highly sensitive for even small mucosal breaks, but it lacks specificity as over 10% of healthy subjects demonstrate mucosal breaks and erosions in their small bowel [14, 15]. With SBCE, there is also a risk of capsule retention; in general, it is 2.1% and in patients with suspected CD 1.2% [16]. SBCE findings of mucosal lesions of the small bowel are not alone sufficient to establish a diagnosis of CD, but the diagnosis should rely on the patients' symptoms and history together with laboratory, endoscopy, histology, and imaging findings [17]. As the diagnosis of small bowel CD can be difficult, there is an urgent need for new, more specific diagnostic methods.

Positron emission tomography (PET) scans using [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) can be used to assess areas with high rate of glucose metabolism caused by, i.e., inflammation, infections, and malignancies [18, 19]. [^{18}F]-FDG PET imaging has also proven to be sensitive and specific for active lesions in CD [20–26]. The drawback of PET imaging is the lack of anatomical references, but this issue can be solved by fusion technologies where a CT or magnetic resonance imaging (MRI) scan is done simultaneously. PET-CT scanners are more widely available than PET-MRI scanners. However, CT has limited soft tissue contrast, which is a major drawback especially in abdominal lesions. MRI has superior soft tissue contrast compared to CT, and the patients are not exposed to potentially harmful radiation [9]. MRI techniques have improved significantly with faster sequences, stronger gradients, and motion correction enabling detailed anatomic map for fusion imaging with PET scan [27, 28].

Fusion [^{18}F]-FDG PET-MRI has been documented to be a reliable tool for evaluating intestinal metabolism [19, 29, 30], but its use has been limited due to cost, accessibility, and lack of standardized methods to quantify inflammation. Fusion PET-MRI using [^{18}F]-FDG tracer has been documented to correlate with endoscopic inflammation activity in patients with known or suspected IBD in colon or terminal ileum [31] and is accurate in detecting active lesions and extraluminal disease in small bowel preoperatively [32]. To our knowledge, there is no previous study on fusion PET-MRI on diagnostics of small bowel Cohn's disease. Our study aimed to prove that combined [^{18}F]-FDG PET-MRE can be used to detect active CD inflammation in small bowel in patients with suspected CD. Secondary aim was to compare [^{18}F]-FDG PET-MRE to MRE only in the diagnostics of CD [33].

Materials and Methods

Study Outline

We conducted a prospective study with volunteers who were suspected of small bowel CD in Turku University Hospital. The study plan was approved by the committee of ethics of Hospital District of Southwest Finland. Volunteer patients were recruited from Turku University Hospital's outpatient clinic of gastroenterology between August 2020 and November 2023. A written informed consent was obtained. Study population consists of patients previously referred to gastroenterology for obscure GI symptoms with diarrhea, elevated fecal calprotectin (FC) (>100 μg/g), accidental CT findings (thickened small bowel segment or stricture), or iron deficiency anemia to rule out IBD. All the patients included had colonoscopy done on a routine basis with biopsies from ileum and colon prior to recruitment in the

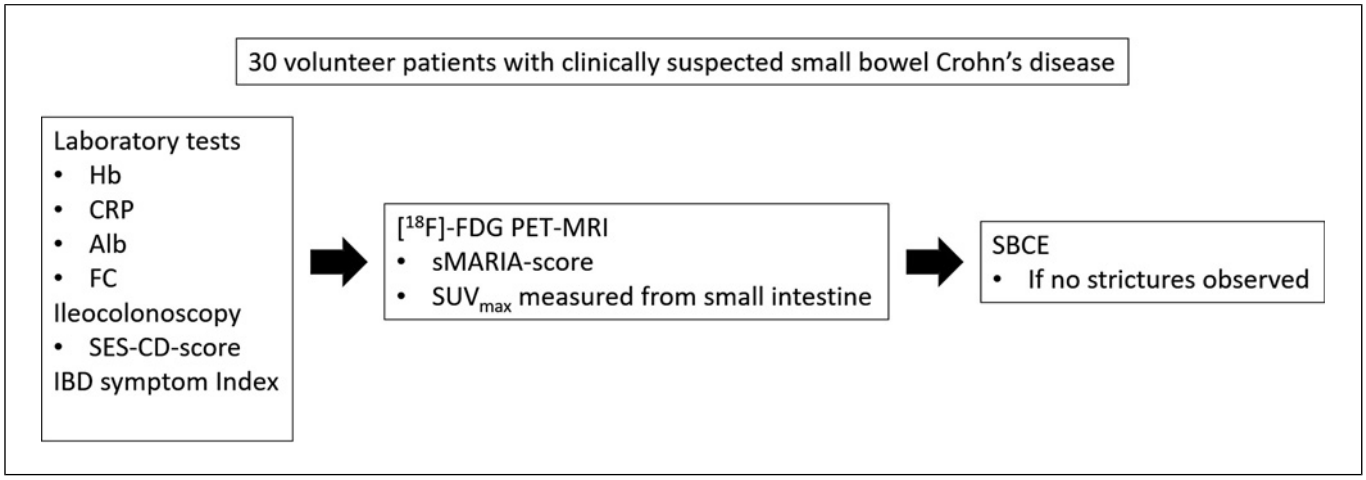

Fig. 1. Study design outline.

study. The clinicians treating these patients referred volunteers with clinical suspicion of small bowel CD to researchers for screening. Inclusion criteria were clinical suspicion of small bowel CD in colonoscopy (Simple Endoscopic Score for Crohn's Disease [SES-CD] ileal subscore >2) or in CT, or unexplainedly elevated FC with GI symptoms. Exclusion criteria were previously known small bowel CD, other findings in colonoscopy explaining symptoms or laboratory findings, use of nonsteroidal anti-inflammatory drug or metformin, unbalanced diabetes, pregnancy, or any other contraindication for PET-MRI scan.

Endoscopic findings of the terminal ileum were graded along the SES-CD score [34]. Fecal and blood samples were collected. The patients filled a validated symptom questionnaire (IBD Symptom Index) with a range from 0 to 22 points [35]. A fusion PET-MRI scan was performed. For patients who had no strictures in the PET-MRI scan, diagnosis was confirmed with SBCE and the SBCE findings graded along the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score validated in several studies [36–38]. The median time between laboratory tests and PET-MRE was 17.5 days (IQR: 7–43.3 days), and the median time between colonoscopy and PET-MRE was 27.5 days (IQR: 17.8–49.8 days). The median time between PET-MRE and SBCE was 41 days (IQR: 35–61 days).

Clinicians had access to patients' endoscopy, laboratory, SBCE, and MRE findings but were blinded from PET findings. CD diagnosis was made by clinicians based on these findings and on clinical basis according to ECCO-ESGAR guideline on diagnostics of CD [39]. Patients diagnosed with CD were started with appropriate treatment chosen by clinicians. Patients' medication data were collected prior to and after participating in the study as shown in Figure 1.

PET Imaging

Patients fasted for 6 h before PET imaging. Bowel was prepared by drinking 1,200 mL diluted 3% mannitol in 45 min. Fasting glucose was measured from venous sample. Patients lie prone to optimize small bowel visualization. In total, 4 MBq/kg of [^{18}F]-FDG was injected in antecubital vein (maximum 400 MBq). After injection, a dynamic PET was obtained. A static PET sequence was obtained after [^{18}F]-FDG injection (median 39 min).

MRI Protocol

Imaging was performed on a 3T-PET-MR scanner (SIGNA™ PET/MR, General Electric, Boston, MA, USA). During the imaging, the patients received intravenously 10 mg hyoscine butylbromide (Buscopan®, Boehringer Ingelheim International GmbH, Germany) to reduce bowel motility and 0.1 mmol/kg gadoterate meglumine (Dotarem®, Guerbet, France) as a contrast agent. The MRI sequences were as follows: (1) 2D breath hold (BH) fast imaging employing steady-state acquisition in coronal plane (slice thickness of 4 mm; TE/TR of 1.4 ms/3.7 ms), (2) 2D T2-weighed single-shot fast spin echo in coronal (slice thickness of 4 mm; TE/TR of 90 ms/3,750–4,615 ms) and in axial plane (slice thickness of 6 mm; TE/TR of 90 ms/2,100–2,333 ms), (3) 2D diffusion-weighted imaging with fat saturation in axial plane (b values of b50, b500, and b1000; slice thickness of 6 mm; minimum TE), (4) pre- and post-contrast BH fat-saturated 3D T1 gradient echo in coronal plane with

40 s post-contrast delay (slice thickness 2/4 mm; minimum TE), and (5) post-contrast BH fat-saturated 3D T1 gradient echo in axial plane (slice thickness 2/4 mm; minimum TE).

Image Analyses

Endoscopists, PET-MRE readers, and clinicians were unaware of each other's results. MRE and PET data were co-registered using the lower edge of liver and kidneys as reference. Standardized uptake values (SUVs) were calculated in multiple regions of small intestine and the anatomical localization assessed from the MR images. SUV is a semiquantitative variable which describes radiopharmaceutical accumulation in PET studies [40]. The highest SUV (SUV_{max}) in each area was measured using "Send cursor to max value" function in AW VolumeShare 5 (version 11.3), GE 2005–2010 General Electrics Company software. SUV measurements were done from the wall of intestine; location was confirmed also in both axial and coronal MR slices. Only the segment with highest SUV value was included in analysis (SUV_{max}). MRE scans were analyzed, and the degree of inflammation in small intestine was graded on sMARIA score [41] by an experienced abdominal radiologist. Only the segment with highest sMARIA score was used in analysis.

Statistical Methods

Categorical variables were summarized with counts and percentages, continuous variables with mean and standard deviation if normally distributed, and with median and lower (Q1) and upper quartile (Q3) otherwise. Association between SUV_{max} and SBCE finding was analyzed using one-way ANOVA. Logarithm transformation (natural logarithm) was used in SUV_{max} to fulfill assumption of normality of studentized residuals. Model-based estimates were then back-transformed to the original scale (using formula e^x) to be able to make clinical interpretation. Same analysis method was used for patients who were later treated with oral budesonide only (yes/no), patients treated with immunomodulators (yes/no), and patients treated with biologics (yes/no). If distribution of response variable did not follow distribution, nonparametric Wilcoxon rank sum test was used. When association between two categorical variables was examined, Fisher's exact test or Cochran-Armitage trend test (another variable being ordinal) was performed. To study association between two continuous variables (like log-transformed $SUV_{max,}$ Hb, CRP, etc.), Pearson correlation was used.

With logistic regression model, area under ROC curve was estimated. In addition, Youden index was used to find optimal cut-off point for SUV_{max}. After that, we tested nearby values that could be used more easily in clinical use.

p values (two-tailed) less than 0.05 were considered as statistically significant. The data analysis for this paper was generated using SAS software, version 9.4, of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

A total of 30 patients were recruited for this study and went through [^{18}F]-FDG PET-MRE scan. The patient demographics are shown in Table 1. Twenty-one patients (83.3%) had Montreal L1 disease (restricted to small bowel), and 3 patients 16.7% had L3 disease (ileocolonic). Disease behavior was mostly non-penetrating B1 ($N = 19$, 79.2%), 3 patients (12.5%) had stricturing disease (B2), and 2 patients (8.3%) had penetrating disease (B3). None of the patients had perianal disease. Twenty-one patients (70%) also went through SBCE after [^{18}F]-FDG-PET-MRE.

A total of 24 (80%) patients were diagnosed with small bowel CD (CD group), and 6 (20%) had normal findings in SBCE (non-CD group). There was no significant difference in age or sex of the patients between the two groups. SUV_{max} was higher in patients with CD than in patients who had normal SBCE findings (model-based estimated mean values 3.34 vs. 1.84, $p = 0.022$) (Table 1; Fig. 2). ROC curve for SUV_{max} showed AUC of 0.81 and 0.69 for sMARIA (Fig. 3). The sensitivity and specificity for CD were highest at SUV_{max} 2.76. After finding this optimal cut-off, SUV_{max} was also categorized with 2.5 and 3.0 to see whether using a more simple cut-off would work. In fact, using 2.5 cut-off we achieved same agreement in our data, where 22 out of 30 (73%) were categorized correctly. Sensitivity for SUV_{max} was 79.2% and specificity 66.7% (PPV 90.5%, NPV 44.4%). sMARIA in MRE yielded both lower sensitivity (75%) and specificity (50%) (PPV 85.7%, NPV 33.3%). When the results for MRE and SUV_{max} were combined (sMARIA 1 or more or SUV_{max} >2.5 for CD and sMARIA 0 or SUV_{max} <2.5 for non-CD), sensitivity for [^{18}F]-FDG-PET-MRE was 87.5%, specificity 16.7%, PPV 80.8%, and NPV 25%. Sample images comparing MRE and [^{18}F]-FDG-PET-MRE in CD patients are shown in Figure 4.

We found no significant difference between CD and non-CD groups in sMARIA ($p = 0.14$) (Table 1), although a higher sMARIA score was associated with higher SUV_{max}. There was only significant difference in SUV_{max}

Table 1. Patient demographics and differences between patients diagnosed with CD (CD group) and not diagnosed with CD (non-CD group)

Variable	CD	Non-CD	*p* value
N	24	6	
Age, median [Q1–Q3], years	30.5 [22.5–40.0]	39.5 [20.5–47.3]	0.59[1]
Sex (M, F)	14 (58.3%), 10 (41.7%)	5 (83.3%), 1 (16.7%)	0.37[2]
Hb, median [Q1–Q3], g/L	144 [138–150]	150 [138–163]	0.35[3]
CRP <10 mg/L, >10 mg/L	18 (75%), 6 (25%)	6 (100%), 0 (0%)	0.26[1]
Serum alb, median [Q1–Q3], g/L	38.1 [36.5–39.7]	42.3 [39.3–45.3]	0.017[3]
FC, median [Q1–Q3], µg/g	563 [126–1,610]	101 [45–271]	0.13[3]
IBD Symptom Index, median [Q1–Q3]	5 [3–6.3]	2.8 [1.5–4.5]	0.12[3]
SES-CD (terminal ileum), median [Q1–Q3]	3 [3–6]	1.5 [0–3]	0.025[4]
CECDAI, median [Q1–Q3]	4 [2–7.5]	0 [0–2.25]	0.045[1]
sMARIA, median [Q1–Q3]	1 [0.25–2]	0.5 [0–1.25]	0.14[4]
SUV_{max}, median [Q1–Q3]	3.1 [2.4–4.1]	1.9 [1.3–2.8]	0.022[3]

[1]Wilcoxon rank sum. [2]Fisher's exact *t* test. [3]One-way ANOVA. [4]Cochran-Armitage.

between sMARIA scores 0 and 5 ($p \leq 0.001$), but not between lower sMARIA score. However, sMARIA score correlated significantly with SUV_{max} (Table 2).

There were no significant differences between CD and non-CD groups in Hb, CRP (normal vs. abnormal), FC, or IBD Symptom Index ($p = 0.35$, $p = 0.53$, $p = 0.13$, $p = 0.12$, respectively). Serum albumin (alb) was lower in CD group than in non-CD group ($p = 0.017$) (Table 1). Hb and alb had a significant negative correlation with SUV_{max} ($r = -0.51$, $p = 0.0039$; $r = -0.58$, 0.0013). FC and CRP had positive correlations with SUV_{max} ($r = 0.52$, $p = 0.0030$, and $r = 0.60$, $p = 0.0006$) (Table 2).

SES-CD in terminal ileum and CECDAI score were higher in CD group compared to non-CD group ($p = 0.02$ and 0.05) (Table 1). SES-CD in terminal ileum was positively correlated with SUV_{max} ($r = 0.63$, $p = 0.0002$), but CECDAI score did not show a statistically significant correlation with SUV_{max} ($r = 0.23$, $p = 0.32$) (Table 2).

We found no significant difference in SUV_{max} between patients who were later treated with oral budesonide only and patients not diagnosed with CD (3.2 vs. 2.2, $p = 0.16$). SUV_{max} was significantly higher in patients treated with immunomodulators (thiopurines or methotrexate) than in patients not treated with immunomodulators or biologics (3.86 vs. 2.1, $p = 0.0026$). Patients treated with biologics had significantly higher SUV_{max} (5.51) than patients not treated with biologics (2.45), $p = 0.0005$ (Fig. 5). None of the patients in non-CD group were later diagnosed with CD, although 1 patient was diagnosed with ulcerative colitis 12 months after participating in this study. The median follow-up time of the study population was 27.5 months (IQR: 19–35 months). The median time between PET-MR imaging and starting glucocorticoids was 12 days (IQR: 7–39 days), 36 days (IQR: 25–75 days) for immunosuppressants, and 167 days (27–296 days) for biologics.

Discussion

To our knowledge, this is the first study to show that [^{18}F]-FDG PET-MRE can be used for diagnostics of small bowel CD as the patients diagnosed with CD had significantly higher SUV_{max} than patients not diagnosed with CD. [^{18}F]-FDG PET-MRE increases diagnostic accuracy of small bowel CD compared to MRE only as sensitivity was higher. Distinguishing between normal findings and mild inflammation was difficult based on MRE findings only as there was no difference in sMARIA score between CD- and non-CD groups, but severe MRE findings (sMARIA >4) correlated with increased SUV_{max}. We suspect that imaging findings in MRE persist longer after unspecific ileitis, whereas glucose uptake and thus SUV_{max} decrease faster after resolution of inflammation. This would explain why there was no significant difference in sMARIA between patients with and without small bowel CD. This emphasizes

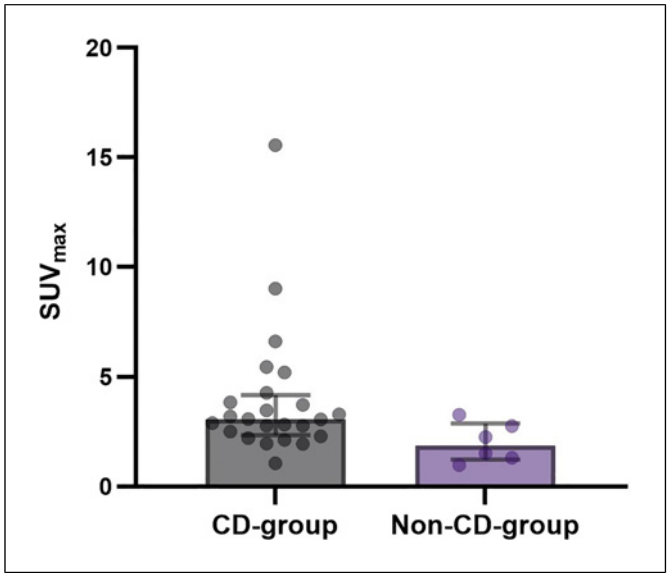

Fig. 2. Highest SUV_{max} of the patients diagnosed with CD (CD group) ($N = 24$) and not diagnosed with CD (non-CD group [$N = 6$], $p = 0.022$. Scatter plot of the median and lower and upper quartile calculated directly from data.

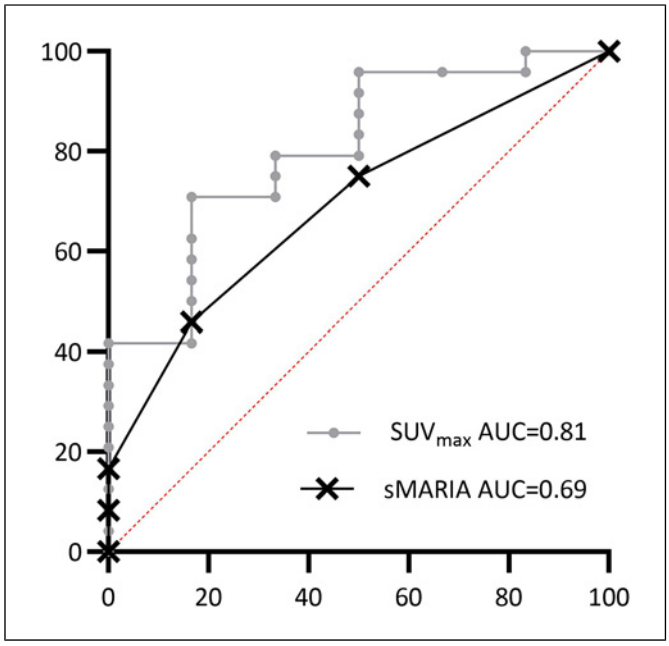

Fig. 3. ROC of highest SUV_{max} and sMARIA score.

that [^{18}F]-FDG PET-MRE can aid in diagnostics of small bowel CD in case of luminal mild CD giving more confidence in differentiating between self-resolving ileitis and chronic inflammation caused by CD.

There was a clear correlation between the endoscopic finding (SES-CD score of terminal ileum) of the patients and SUV_{max} which further supports the ability of [^{18}F]-FDG PET-MRE to be used in assessing the grade of inflammation in small bowel CD. The ROC curve showed sensitivity of 81% for SUV_{max}, and the sensitivity and specificity were the highest at SUV_{max} 2.76, but we found equal accuracy at SUV_{max} 2.5 which could be used as a diagnostic threshold for small bowel CD in future.

As small bowel CD cannot be diagnosed with laboratory tests or symptoms alone, unsurprisingly we found no significant differences in laboratory parameters except in serum alb, which was lower in CD patients. Hb and alb are often decreased in more severe CD, and they both had a negative correlation with SUV_{max}. Elevated CRP and higher FC correlated positively with SUV_{max}. These findings further support our conclusion that [^{18}F]-FDG PET-MRE is a valuable and reliable tool for evaluating the severity of small bowel CD. As SUV_{max} is correlated with FC, one could question the benefit of [^{18}F]-FDG PET over MRE and FC, but in addition to being nonspecific inflammatory marker of intestine, the location where FC is secreted and thus the location of inflammation cannot be deducted from FC results only.

In addition to aiding the diagnostics, [^{18}F]-FDG PET-MRI could be used to predict the need for immunosuppressive or biologics, as SUV_{max} was significantly higher in those patients compared to patients who had no CD or had a mild course of disease and only needed oral budesonide. This could guide the clinician on choosing the right treatment earlier which usually leads to better disease outcome and possibly decreases the risk of overtreating patients with a mild disease, as CD medication is not entirely free of risks and especially novel biologic therapies are expensive [42, 43]. Furthermore, making a difference between a chronic inactive stricture and active inflammation is vital for clinicians on choosing between operative treatment vs. medical treatment. [^{18}F]-FDG PET-MRE can provide beneficial information in evaluating the inflammation activity of a stricture [33]. In future, it is possible to use [^{18}F]-FDG PET-MRE to evaluate response to treatment, but this needs further research as studies on this are relatively few with small series [44, 45]. However, in this study setting, we have not investigated whether SUV_{max} has impact on treatment as the clinicians treating the patients were blinded from PET results. As glucose uptake is increased early in the presence of inflammation, [^{18}F]-FDG PET can detect active lesions before formation of fibrotic damage. Even though statistical analysis of combined [^{18}F]-FDG PET-MRE showed inferior specificity compared to both PET

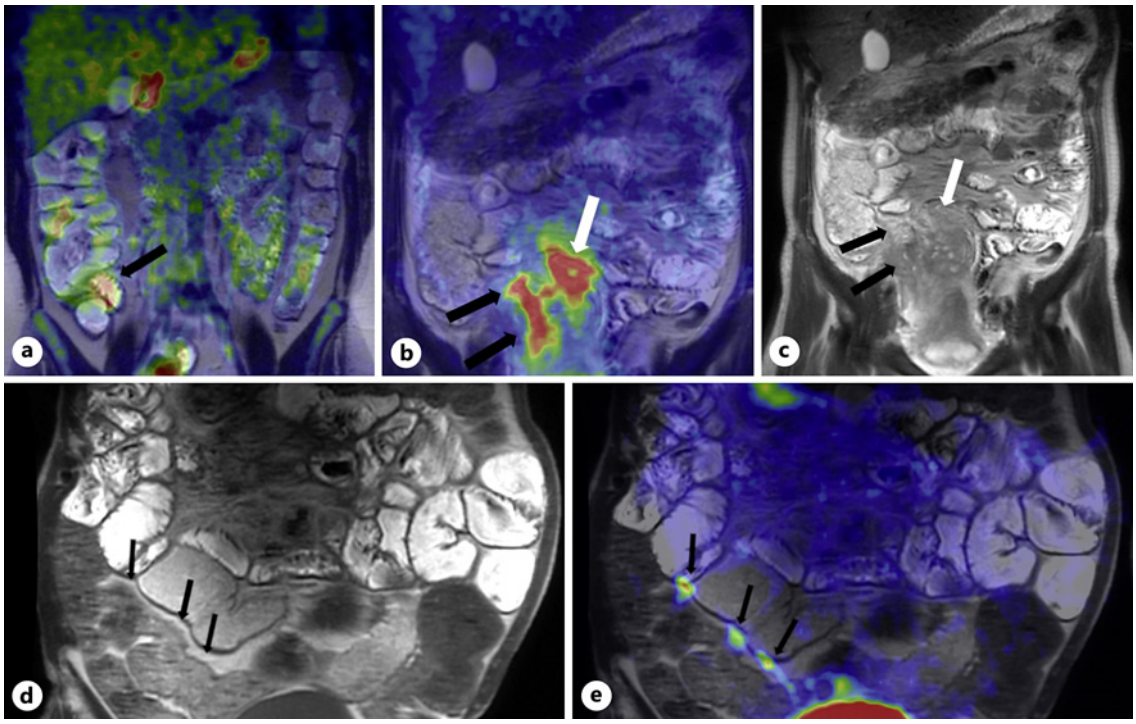

Fig. 4. a 31-year-old female with active CD inflammation in ileum (black arrow) in fused [^{18}F]-FDG PET-MRI. **b** 22-year-old male with active CD inflammation in ileum and intra-abdominal phlegmon. Markedly increased FDG-uptake of ileum terminale (black arrow) and the adjacent mesenteric phlegmon together with early abscess formation (white arrow). Findings are visually better delineated with PET fusion image (**b**) compared to conventional T2W MRI (**c**). **d** 60-year-old male with active CD inflammation in proximal ileum beyond the reach of a colonoscope. In T2W MRI, the inflammation is not visible in the bowel wall, but in FDG-PET-MRI (**e**) there is clear FDG accumulation in actively inflamed lesion (black arrows).

Table 2. Correlations between highest SUV_{max} (transformed to natural logarithm) and other variables

Variable	*r* of SUV_{max}	*p* values
Hb	−0.51	0.0039
CRP	0.60	0.0006
Alb	−0.58	0.0013
FC	0.52	0.003
IBD Symptom Index	0.26	0.19
SES-CD (terminal ileum)	0.63	0.0002
CECDAI	0.23	0.31
sMARIA (highest)	0.59	0.0007

finding or MRE finding alone, this fusion technique enables localization of exact anatomical structures (i.e., thickened wall of ileum) for measuring SUV which has synergistic advantage over MRE alone, as quantitative information on inflammation can be measured from PET sequences. Furthermore, the exact location of inflammation can be identified to target biopsies, medical or surgical treatment. In addition, the extent and severity of the disease can be evaluated in a single study.

There are a few studies in using [^{18}F]-FDG tracers in PET imaging in detecting active CD inflammation in PET-CT scans, but there are no clear diagnostic thresholds previously established [46]. Catalano et al. [47] found out that for patients with known CD sensitivity of [^{18}F]-FDG PET-MRI was higher than MRE alone (88% vs. 80%) and specificity of [^{18}F]-FDG PET-MRI was superior to MRE (91% vs. 83%). Compared to this, the sensitivity of MRE alone in our study was 75%, but specificity was only 50%. We suspect that this is due to the patient population having suspicion of CD instead of being healthy controls and the patients in non-CD group probably had some other type of unspecific inflammation. In the METRIC study, the sensitivity of presence of CD in small bowel was 96% (95% CI: 89–99%) and specificity 83% (95% CI: 68–95%) [13], but the patients were already diagnosed recently with CD explaining better accuracy. In

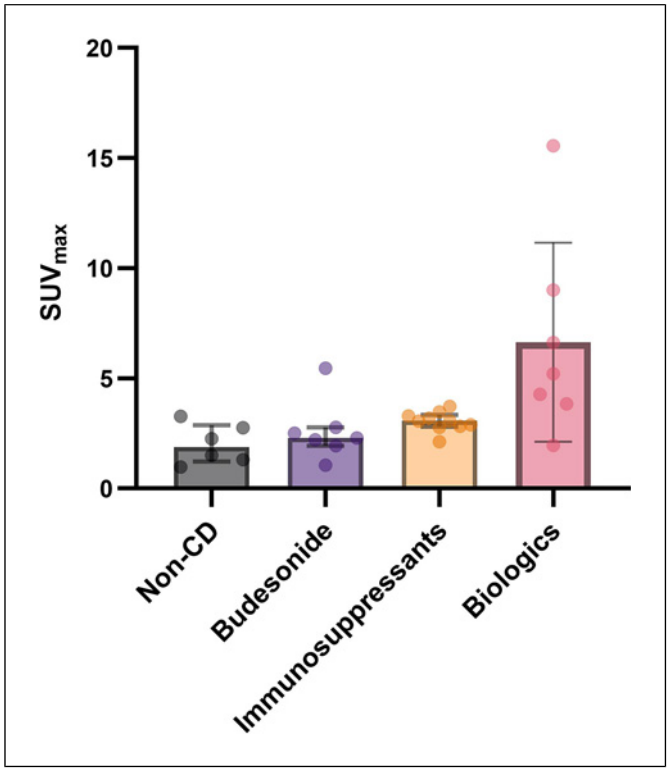

Fig. 5. Highest SUV_{max} of the patients by medical therapy started after imaging compared to non-CD group. Scatter plot of the median and lower and upper quartile calculated directly from data.

a meta-analysis by Liu et al. [48], the sensitivity for MRE was 86% and specificity 93%; however, the data were from heterogenous studies. Adding PET data to MRE, the accuracy improved as specificity was better (66.7%) and sensitivity was better than MRE only (87.5%). The fact that the study population consisted of mainly patients with mild CD (79.2% of the patients had Montreal B1-disease) probably biases the results explaining the poor specificity for both MRE and [^{18}F]-FDG PET-MRE, compared to other studies [13, 47, 48]. In a study comparing SBCE and MRE findings, the sensitivity for small bowel lesions was only 44.7% for MRE, which is considerably lower than our results for combined PET-MRE, probably due to patient population without strictures and thus a milder disease [12].

The strength of this study is the prospective design. In addition to PET imaging, the patients underwent all the standard diagnostic measures. The clinicians treating the patients were unaware of the PET findings but had access to all the other results to avoid bias in both diagnostics and further treatment. The [^{18}F]-FDG PET-MR imaging was done in a single session providing accurate anatomical information from MRI sequences to PET images and enabling a direct comparison between the modalities. To improve accuracy, we used mannitol preparation and butylbromide as it is known that bowel distension can decrease false-positive signals in glucose uptake [49]. The MRE and PET images were analyzed by different investigators. MRE sequences were analyzed using previously validated and widely used easily replicable and reliable sMARIA score. In order to improve the reliability, the images could have been analyzed by more clinicians blinded from the other. To optimize the accuracy in mild disease, a larger number of patients could have provided more information. In future, a study comparing SUV_{max} results from CD patients to healthy controls might aid in determining a cut-off value between normal findings and small bowel CD. The time difference between colonoscopy, [^{18}F]-FDG PET-MRE, and SBCE can distort the results, as the degree of inflammation may have changed between these exams. The median time between colonoscopy and [^{18}F]-FDG PET-MRE can be considered sufficient for healing of biopsy sites, which could have caused increased FDG uptake and hence SUV_{max} or caused false-positive findings in SBCE. The median time between initiating glucocorticoids was 12 days post-PET-MRE, which may have an impact on SBCE findings, possibly reducing inflammation and thus CECDAI score. Immunomodulators usually have a slower effect, and biologics were mostly started after SBCE (median 167 days after PET-MRE vs. median 41 days between PET-MRE and SBCE). The reason we found nonsignificant correlation with CECDAI and SUV_{max} may be also due to the fact that SUV_{max} only represents the inflammation in single most active location whereas CECDAI score is multiplied if multiple segments are involved. The number of patients who underwent SBCE was also small (n = 21), which may explain the nonsignificant result. The diagnosis for CD was established based on endoscopic and MRE findings for patients who did not go through SBCE due to contraindications (strictures or symptoms suggesting for small bowel stenosis).

[^{18}F]-FDG PET-MRI can be thought as a safe procedure in diagnostics, the main risk being radiation dose. Due to improved imaging techniques, the doses have significantly decreased though [50]. The radiation exposure can be justified in case of unclear diagnosis provided that FDG-PET-MRE is not repeated too often for a single patient. The procedure does not involve bowel preparation other than mannitol solution which is easier for the patient compared to SBCE or ileocolonoscopy. In the presence of strictures in small bowel, fusion imaging can be done safely without the risk of capsule retention. Fusion imaging can be safely used also in severe acute

phase of the CD, without the risk of perforation in endoscopy [23, 32, 51]. The adverse effects in our study experienced by patients were few, and 1 patient reported diarrhea after the imaging which could be caused by mannitol solution. One patient had abdominal pain after injection of butylbromide, which subsided spontaneously.

The main limitation still for [^{18}F]-FDG PET-MRE is not being completely specific for inflammation caused by CD, but also infections, unspecific enteritis of tumors, can cause increase in SUV values in small bowel. In mild luminal CD, the diagnostic accuracy may not be sufficient, but these data show that moderate and severe disease can be diagnosed with confidence when combining PET and MRE data. Background noise in PET images is a confounding factor. The interpretation should also consider the location of higher SUV signal compared to adjacent tissues or that of liver [22, 51]. A PET scan can be considered negative for CD when the uptake is mild and diffuse and positive when segmental changes are present, and the glucose uptake is significantly increased [52]. Major drawback of [^{18}F]-FDG PET-MRE is naturally also limited availability and costs, as these fusion devices are relatively few and the imaging costs more than MRE only [52].

Previously, the indications for fusion imaging for CD have been evaluating the activity and extent of the disease. Early postoperative relapses can be predicted with fusion imaging, and the technique can be useful in differential diagnostics between inflammatory and fibrotic strictures [33]. Extraintestinal manifestations can also be identified and assessed with fusion techniques [47].

To conclude, fusion [^{18}F]-FDG PET-MRI can be used in diagnostics of small bowel disease at a better accuracy than MRI alone. The results may help clinicians to differentiate between self-resolving unspecific ileitis and small bowel CD more reliably than conventional MRE. SUV_{max} measured from patients' small bowel predicts the progression of the disease and need for immunosuppressive or advanced therapies. It is possible to use fusion [^{18}F]-FDG PET-MRI imaging as a safe alternative for SBCE in diagnostics of small bowel. A cut-off in SUV_{max} at 2.5 could be used as a diagnostic threshold for small bowel CD.

Statement of Ethics

The study plan was approved by the committee of ethics of Hospital District of Southwest Finland, Approval No. ETMK 49/2019. Written informed consent was obtained from patients participating in this study.

Conflict of Interest Statement

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Author Contributions

Conceptualization, methodology, and project administration: Jukka Koffert; formal analysis: Juho Mattila and Eliisa Löyttyniemi; investigation, resources, writing – original draft preparation, and visualization: Juho Mattila; data curation: Juho Mattila and Johanna Kallio; writing – review and editing: Jukka Koffert, Johanna Kallio, Eliisa Löyttyniemi, and Pirjo Nuutila; supervision: Jukka Koffert and Pirjo Nuutila; funding acquisition: Juho Mattila, Jukka Koffert, and Pirjo Nuutila. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Study data were collected from Turku University Hospital electronic patient database. Anonymized research data sets will be preserved and made accessible through the Finnish Social Science Data Archives once the whole project is finalized. Further inquiries can be directed to the corresponding author.

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