Am J Nucl Med Mol Imaging 2021;11(4):271-279
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0130662

Original Article

Utility of FDG PET/CT in assessing bowel inflammation

David Gelston[1], Samantha C Brosler[1], Jennifer Vazquez[1], Olivia Sorci[1], A Huntington Griffith[1], Shampa Chatterjee[4], Anna Buchner[1], Poul F Høilund-Carlsen[2], Abass Alavi[2], Chamith S Rajapakse[1,3]

[1]Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Nuclear Medicine, Odense University Hospital, Odense, Denmark, USA; [3]Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Physiology, University of Pennsylvania, Philadelphia, PA, USA

Received January 23, 2021; Accepted June 14, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Purpose: To develop a methodology for the quantification of gastrointestinal (GI) inflammation as indicated by 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG) uptake on positron-emissions tomography/computed tomography (PET/CT) imaging. This is intended to investigate the feasibility of using standard uptake value (SUV) levels to assess levels of GI inflammation in humans. Methods: 131 participants were injected with a weight-controlled dose of FDG 180 minutes prior to PET/CT scanning. Operator-guided software was used to segment the GI tract and perform (SUV) calculations. Regions of interest (ROIs) were created using CT images and stacked to create three dimensional volumes of interest (VOIs). These VOIs defined 6 sections of the GI tract: esophagus, stomach, descending colon, ascending and transverse colon, bowel below the ilium and small bowel above the ilium. Results: This study found a significant correlation between age and average FDG uptake (avg-SUV) of the GI tract (P=.0003) with the esophagus showing the highest significance. Correlations were found between avg-SUV of the sigmoid segment and the group average (P<.0001), and between the descending colon VOI and the group (P<.0001). Intra-operator reproducibility over 3 trials showed a coefficient of variation (CV) of .63%. Inter-operator CV over 5 randomly selected patients was 5.6% over the entire GI tract. Conclusion: This study shows that FDG-PET/CT imaging is a promising technique for quantifying bowel inflammation, despite the fact that age related inflammation may not be of clinical utility. The fact that we were able to detect these subtle changes indicates this as an avenue for potential future investigation.

Keywords: IBD, radiology, abdominal imaging, PET/CT imaging

Introduction

Inflammatory Bowel Disease (IBD), which includes both Ulcerative Colitis (UC) and Crohn's Disease (CD), currently affects over 3 million Americans. Data from the Crohn's & Colitis Foundation suggests that over 780,000 [1] people suffer from CD in the United States, and 70-80% of them require intestinal surgery within 20 years of diagnosis [2] with a further 30% requiring follow-up surgical intervention [3]. The majority of patients with CD have progressive disease, moving from an initial inflammatory phenotype to stricturing and/or penetrating disease later in life [2]. Therefore, recent emphasis has been placed on early identification and aggressive treatment of CD to modify future disease course, and prevent complications and surgery especially in CD patients with small bowel involvement in which diagnosis may be especially challenging [4]. Unfortunately, none of the existing diagnostic techniques is accurate enough alone, while some are invasive and associated with risks of substantial radiation exposure [5]. These limitations are of special concern in younger populations, which comprise 7-20% of CD patients, as they have a low tolerance to radiologic and endoscopic tests [6-8]. For these reasons, it is critical to investigate new non-invasive modalities that may be useful in diagnosing and monitoring patients with CD especially in patients with small bowel involvement where the access of advanced endoscopic modalities is limited in many center and thus requires referral to tertiary centers for further diagnostic evaluation (double balloon enteroscopy exams).

The hallmark pathologic finding in CD is transmural inflammation of the intestine which can

be both acute and chronic, and is differentiated by cell type [9]. The inflammation in CD can be segmental intervening areas of normal mucosa, and the transmural nature of the inflammation often leads to complications such as fistulas, abscesses, perforations, and strictures, that often require surgical therapy. Although CD has a predilection for the ileum, it can affect any part of the gastrointestinal tract, from mouth to anus. The clinical evaluation of pa tients with CD occurs at various time points in the disease course, as follows: at diagnosis, after treatment, during flares, preoperatively, and postoperatively. Traditional modalities to evaluate patients with CD at these various time points have many shortcomings especially in patients presenting with isolated small bowel involvement.

We hypothesize that positron-emissions tomography/computed tomography (PET/CT) overcomes many of the drawbacks of other modalities and will likely prove to be effective for disease assessment in CD. Both in vitro and in vivo studies have shown that neutrophils (the primary immune cells of acute inflammation) as well as macrophages and lymphocytes (the primary immune cells of chronic inflammation) accumulate high levels of 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG), due to both overexpression of glucose transporters and overproduction of glycolytic enzymes [10-14]. As there is a paucity of data on the use of PET/CT in CD, it is vital to investigate PET/CT in this regard, as the results of such research would likely be of great interest and importance to the scientific community and especially to healthcare providers and their patients. The use of this safe, non-invasive, and well-tolerated diagnostic test may lead to the detection of early disease, which could be treated aggressively, with the goal of modifying the disease's natural course. An increase in metabolic activity, as measured by a rise in average FDG uptake, implies a higher degree of inflammation. Previous studies [15] have established a link between an increase in FDG uptake and an increased inflammatory response, making PET one of the most promising imaging modalities for use in diagnosing and monitoring chronic inflammatory disorders. The primary goal of this study was to develop a methodology for the quantification of gastrointestinal (GI) inflammation as indicated by FDG-PET/CT imaging. This is intended to investigate the feasibility of using standard uptake value (SUV) levels to assess levels of bowel inflammation in humans.

Materials and methods

Study population

The participants for this cross-sectional retrospective study were the same as those who participated in the Cardiovascular Molecular Calcification Assessed by FDG PET/CT (CAMONA) study conducted by Odense University Hospital. The CAMONA study was approved by the Danish National Health Committee on Health Research Ethics, registered at ClinicalTrials.gov (NCT01724749) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Participant selection

The CAMONA study recruited 139 total participants for a prospective heart study. The original study included 89 designated healthy controls and 50 patients who had been referred for coronary CT angiography on the basis of persistent chest pain. This cohort did not present with diagnosable CD allowing for the cross-sectional associations presented in this paper. Of the 139 total participants, 8 were rejected due to poor scan quality or missing scans, and all 131 remaining participants were used to examine associative variables (i.e., age, BMI, SUV). Included in the study were 68 females (ages 21-75, BMI 18-37 kg/m^2) and 63 males (ages 22-75, BMI 13-42 kg/m^2). Inclusion criteria for healthy controls included systolic blood pressure below 160 mm/Hg with diastolic blood pressure below 100 mm/Hg, glycated hemoglobin below 48 mmol/mol, and total serum cholesterol below 6.2 mmol/L. Patient groups were also required to meet this criterion in addition to the angina they experienced upon referral for angiography. Individuals with a history of smoking or cardiovascular disease were not eligible for inclusion.

Study design

131 participants were intravenously injected with a dose of FDG that was controlled for body weight (4 MBq/Kg of body weight). PET/CT scans were conducted 180 minutes following

Table 1. Patient data

Average Blood Values	Participants (n=131)	Normal Values
Gender (No.)	Female n=68	
	Male n=63	
Height (m)	1.72±0.09	
Weight (kg)	80.3±17.8	
Age (years)	48.8±14.2	
BMI (kg/m^2)	26.8±4.5	
Fdg180 Dose (MBq)	172.8±35.5	
Syst. BP (mmHg)	129.0±17.0	120-129
Diast. BP (mmHg)	77.6±9.5	80-84
Pulse (Beats/min)	66.6±12.4	60-100
Total cholesterol (mmol/L)	5.1±0.9	<11
LDL cholesterol (mmol/L)	3.2±0.8	<7.2
HDL cholesterol (mmol/L)	1.4±0.4	1.7-4.2
Triglycerides (mmol/L)	1.10±0.7	1.9-9.4
Fasting plasma Glucose (mmol/L)	5.6±0.7	3.6-5.5
HbA1c (mmol/mol)	35.1±4.7	<42
CRP (mg/L)	2.4±3.1	<3
Fibrinogen (umol/L)	10.6±8.7	8.9-25
White Blood Cell Count (cells/L)	6.1±1.9	3.8-11×10^3 mm^3

Note: Unless otherwise specified, data are means ± SD.

injections, under the same conditions for all individuals (GE Discovery STE, VCT, RX, and 690/710). After performing two ANOVA tests, there was no significant difference found between the average age (P=0.31) or BMI (P=0.23) of participants scanned by each scanner. CT images (140 kV, 30-110 mA, noise index 25, 0.8 seconds per rotation, slice thickness 3.75 mm) were corrected for anatomic orientation. Likewise, PET images were corrected for attenuation due to scattering, and random coincidence.

Average values and ranges for the following biomarkers were collected and computed [**Table 1**: *Patient Data*]: blood pressure, pulse, LDL/HDL/Total cholesterol, triglycerides, homocysteine, fasting plasma glucose, CRP, Fibrinogen, WBC Count. Patient history of cofactors such as smoking, alcohol use, history of hypocholesterolemia, Coronary Heart Disease, Peripheral artery disease, type 1 or type 2 diabetes, or the use of anti-platelet agents, aspirin, or diuretics was analyzed with respect to the inflammatory markers taken from the PET/CT scans.

Quantitative image analysis

An operator guided computer software, PMOD (PMOD Technologies LLC, Switzerland), was used to carry out the segmentation of the bowel and to perform standard uptake value (SUV) calculations. Regions of interest (ROIs) were created using a multi-step process on CT images: manual and rough region selection followed by intensity thresholding for tissue density of -50 Hounsfield units or greater for better anatomical delineation and stacked to create three dimensional volumes of interest (VOIs). Regions of interest were manually selected for in order to avoid the inclusion of surrounding organs in the analysis. These VOIs defined 6 sections of the bowel: the esophagus, stomach, descending colon, ascending and transverse colon, bowel below top of ilium and small bowel above the top of the ilium [**Figure 1**: *Gastrointestinal Segments*]. The VOIs were generated using the CT images for structural clarity, then superimposed on the corresponding PET images. From here, average SUV (avg-SUV) and maximum SUV (SUVmax) were calculated within each VOI. The SUV uptake was not statistically different between the control and test groups (P=0.15). Reproducibility was assessed by calculating the coefficient of variation (CV) in avg-SUV values obtained from segments created by 3 trained operators. Both intra and inter-operator CV was calculated based on the segmentation done by the operators on a set of 5 typical cases.

Full set analysis

Multiple regression analyses were performed to determine the association between age and both avg-SUV and SUVmax, while controlling for BMI, and dosage. BMI, avg-SUV and SUVmax were also associated, controlling for age, and dosage. These analyses were done on the six separate VOIs (the esophagus, stomach, descending colon, ascending and transverse colon, bowel below top of ilium and small bowel above the top of the ilium) as well as the average and maximum SUV of the entire GI tract. Male and female regressions were conducted separately but final regression calculations included all 131 subjects.

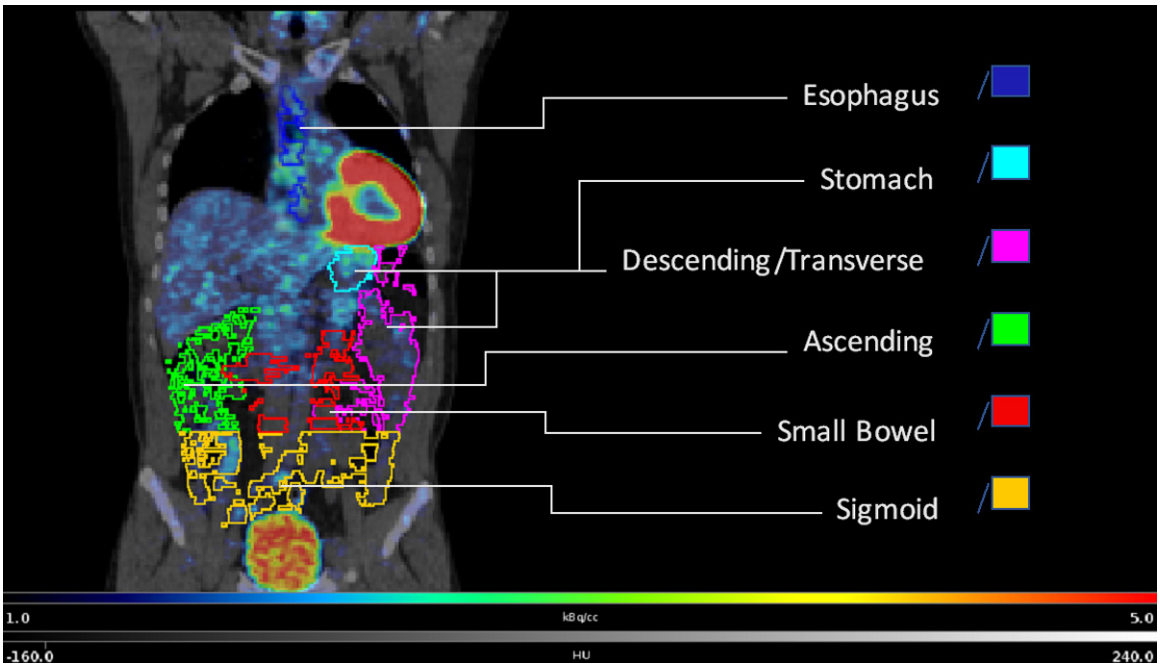

Figure 1. Gastrointestinal segments.

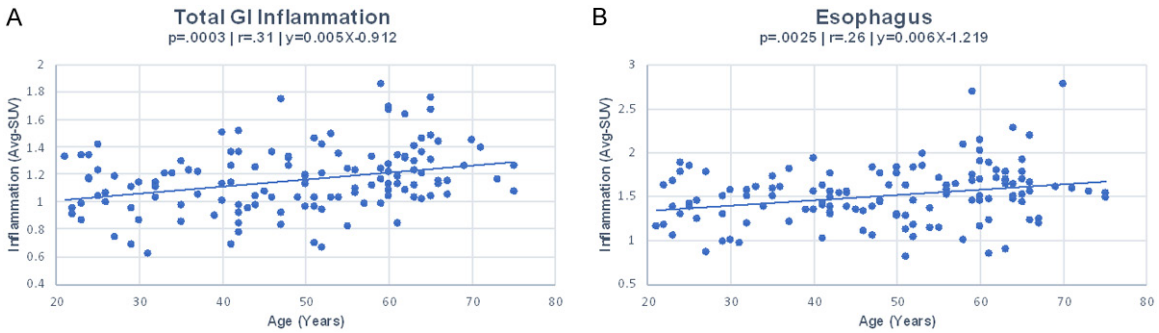

Figure 2. A. Total gastrointestinal Avg-SUV vs age. B. Esophageal Avg-SUV vs age.

Power and sample size considerations

All power calculations were conducted in PASS (NCSS, Version 16) assuming a 5% type I error rate and using two-sided hypothesis tests, and assuming 10% missing data due to subject motion and other image quality assessments. Given these data expect to have 85% power to detect group differences in average SUV.

Results

This study found a significant correlation bet ween age and average FDG uptake (avg-SUV) of the whole bowel (P=.0003) [**Figure 2A**: *Total bowel inflammation vs age*]. This correlation was improved when correcting for BMI for the whole bowel with partial-P=.0001. No significant correlation was found between age and SUVmax. In addition, no significant correlation was found between BMI and avg-SUV. The esophagus showed the highest significance with age (P=.0025) [**Figure 2B**: *Esophagus inflammation vs age*] even when corrected for BMI. Additionally, significant correlations were found between the descending colon VOI and the group average (P<.0001) [**Figure 3A**: *Descending colon inflammation vs total bowel*] as well as avg-SUV of the sigmoid segment and the group (P<.0001) [**Figure 3B**: *Sigmoid colon inflammation vs total bowel*], indicating that these segments are predictive of overall avg-

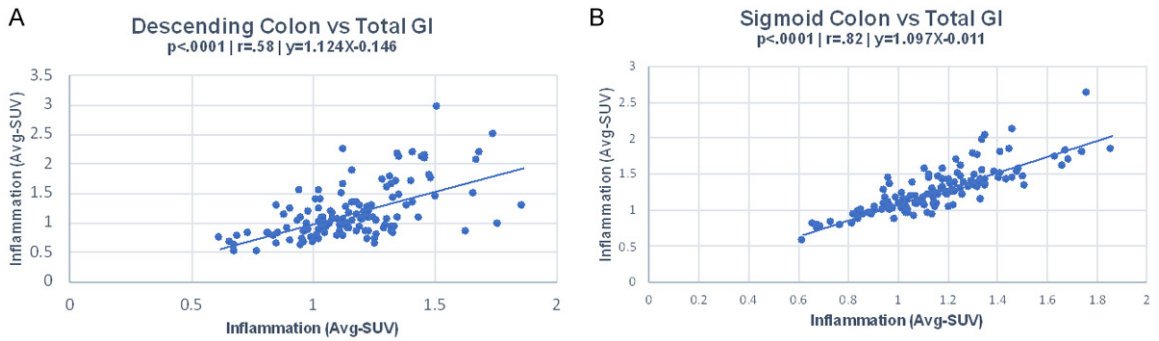

Figure 3. A. Descending colon vs total gastrointestinal Avg-SUV. B. Sigmoid colon vs total gastrointestinal Avg-SUV.

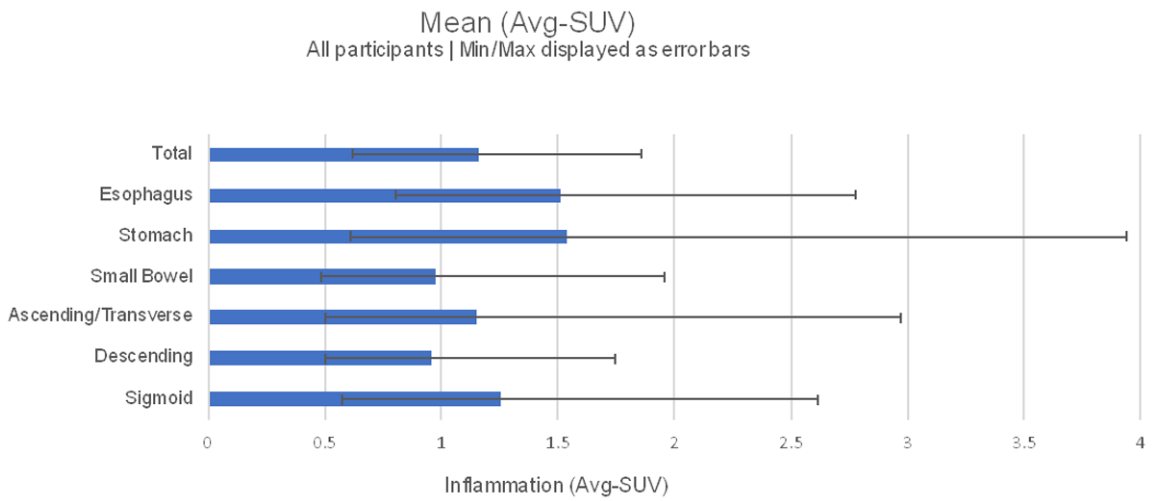

Figure 4. Mean, min and max Avg-SUV for all participants.

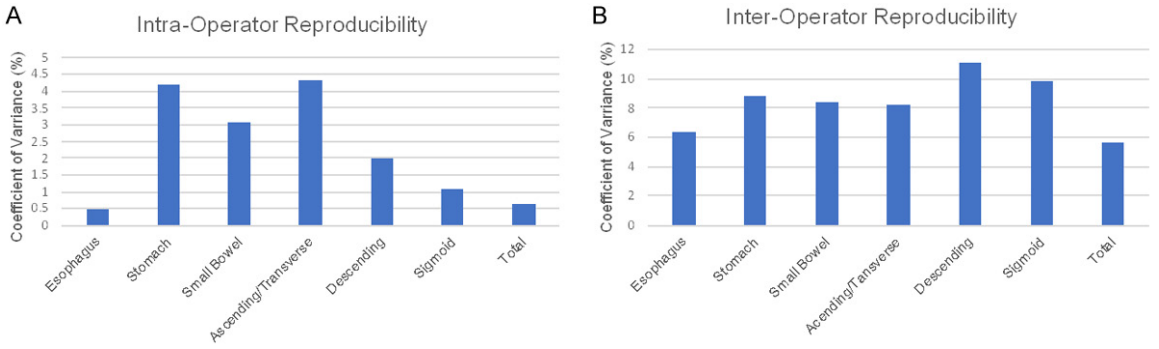

Figure 5. A. Intra-Operator reproducibility. B. Inter-Operator reproducibility.

SUV values. No significant correlation between C-Reactive Protein (CRP) values and avg-SUV or SUVmax was found. The mean of Avg-SUV measurements for all participants is shown in [**Figure 4**: *Mean, Min and Max Avg-SUV all participants*] with error bars representing the minimum and maximum values.

Reproducibility

Intra-operator reproducibility measured over 3 trials showed total coefficient of variation (CV) of .63% [**Figure 5A**: *Intra-Operator CV*]. Inter-operator CV over 5 randomly selected patients calculated for each VOI and for the entire GI

tract by 3 trained operators range from 6.3% to 11% in the descending colon and stomach, respectively. The inter-operator CV of the entire GI tract was 5.6% [**Figure 5B**: *Inter-Operator CV*].

Discussion

These results support the assertion that FDG PET/CT is an effective imaging modality with respect to the detection and quantification of age-related increase in gastrointestinal inflammation. The noted correlation between age and Avg-SUV was likely improved when corrected for BMI due to the previously documented increases in inflammatory response with high BMI. Our protocol was able to generate statistically significant data in line with the current literature of potential use in future investigations of GI inflammation. This suggests the possibility of using PET/CT in the diagnosis of conditions such as Crohn's Disease. A variety of endoscopic and radiologic modalities are available for the evaluation of disease activity in CD including ileocolonoscopy, flexible sigmoidoscopy, upper endoscopy (including push enteroscopy), deep enteroscopy (both antegrade and retrograde with single- or double-balloon technology), capsule endoscopy, barium studies (small bowel follow through [SBFT] or enteroclysis, upper GI series, and barium enema), CT with or without enterography (CTE) or enteroclysis, and magnetic resonance enterography (MRE) or enteroclysis. Many of these imaging techniques such as all endoscopic procedures are considered invasive and requiring anesthesia assistance and are associated with significantly increased risk. Plasma or stool based inflammatory markers, specifically C-reactive protein (CRP) and fecal calprotectin, represent systemic inflammation and imperfectly correlated to localized inflammatory pathologies; indeed studies have shown low to moderate correlation between CRP levels and disease activity in small bowel CD [16, 17]. Therefore, CRP and other laboratory markers can be employed only in conjunction with other detection modalities. Thus, there is a need for the introduction of more available and less invasive technologies in patients with chronic inflammatory GI conditions such as Crohn's disease with small bowel/ileocolonic involvement which require frequent follow ups to demonstrate healing or activity stage. With respect to chronic inflammatory diseases, PET has been successfully used to identify inflammation in patients with rheumatoid arthritis [18], sarcoidosis [19], atopic asthma [20], and fibrosing alveolitis [21]. In addition, FDG-PET has been utilized it in a number of studies investigating infection and inflammation [22-27].

Additionally, the significant correlation between Avg-SUV of the sigmoid and descending colon with total GI Avg-SUV may obviate the need for total assessment as these VOIs are predictive of the level of SUV in the entire GI tract. With regards to the use of PET/CT in the treatment of CD, a number of preliminary studies have shown promising results for this new technique [28, 29]. The first study prospectively evaluated 95 ileocolonic segments in 22 adult CD patients, using an endoscopic score as the standard of reference, and calculated that PET/CT had an overall sensitivity of 73% for the detection of endoscopic lesions but a sensitivity of 100% for the detection of severe endoscopic lesions [30]. This study did not include any biopsy confirmations. A subsequent study including 7 adult CD patients and 20 control subjects with solitary pulmonary nodules reported an 81% correlation between PET activity and clinical disease activity in the CD patients; in the control subjects, only 2% of all bowel segments examined showed significant FDG uptake [28]. Of note, the authors discovered that the use of intravenous contrast in a subset of patients did not provide any additional information.

Our study found no correlation between CRP and SUV values. The lack of correlation is likely due to the fact that circulating levels of blood CRP represents a systemic inflammatory response while this study only investigated a site-specific form of inflammation. Often plasma CRP levels in subjects are either masked or enhanced due to pathologies such as infection or underlying chronic inflammation in the cardiovascular system [31], and cannot be an independent marker of localized inflammation [31]. The correlation between age and elevated CRP values has been previously established [32], and this coincides with the correlation between avg-SUV and age found in this study. Another preliminary study on the functional and structural age-related changes found on PET/CT found no significant changes to Mean SUV in

the adult patients studied [33]. These results align with those of our study, though it should be mentioned that Meier et al used a representative ROI to obtain SUV values while our study used VOIs containing the entire organ. In general, previous research has not shown any significant age-related changes in small bowel function and though there are some studies the indicate an inverse relationship, the lack of clinically significant changes is due to the reserve capacity of the organ. Moreover the reduced functional activity noted by Meier is secondary to the age-related reduction in myenteric neuron density [34].

There are a few limiting factors of this study, such as it is possible that PET/CT could identify inflammation that is not verifiable with another marker, and since such findings could represent either a true positive or a false positive, a subsequent prospective study would need to be performed to determine their authenticity. An additional limitation of this study is related to the non-specificity of FDG imaging. Intestinal uptake in FDG imaging comes from both normal physiological uptake and inflammation. Some normal physiologic uptake of FDG tracer in the gastrointestinal tract is present in all patients. However, the majority of the uptake with intestinal diseases including tumors arises due to inflammation (or infection). Therefore, we can consider the normal physiologic uptake as the baseline level and uptake above that level as due to inflammation. That said, a limiting factor of this study is the extent to which FDG uptake as a result of inflammation versus normal physiological uptake can be differentiated. It is also possible natural movement within the bowels may result in unavoidable misregistration on the scans. Another limitation of this study is that our patient cohort consisted of patients not identified as individuals with inflammatory bowel disease but presenting with cardiac complains. Thus, we were not able to correlate the level of inflammatory changes in the GI tract with patient's gastrointestinal symptoms. However, the PET Scan availability for the detection of inflammatory changes in the colon and in the esophagus is promising and it may be related to other inflammatory conditions in the study patients including GERD related inflammation, functional GI disorders, other types of colitis. Further studies need to include patients with known inflammatory GI conditions such as Crohn's disease and explore imaging accuracy for detecting pathological sites and discriminating between fibrotic and inflammatory strictures, assessing the response to therapy while correlating the PET Scan results with the patients' clinical presentation and endoscopic assessment. No information on ulcerative colitis or Crohn's disease was collected at the time of the study.

The conclusions of this study are limited by the amount of clinical data available on each patient, and as such only BMI and Age were tested against FDG uptake. In 2017, Bahler et al found that drugs such as Metformin [35] and other physiologic activity in the bowel can affect FDG uptake and therefore hamper interpretation. These potential cofactors were not taken into consideration in this study, as a 72 hr discontinuation of Metformin is recommended to obtain normal images [36]. Reproducibility is another limitation of this study design, with a measured inter-operator variance of 5.6% this would suggest that the best data would be obtained from a small number of well-trained operators to minimize this variance.

Conclusion

We investigated the effect of FDG inflammation on Age as a way of testing the feasibility of using these methods in future studies. In active disease states we would expect the increases in FDG PET/CT inflammation to be even more pronounced than the age-related changes. This study shows that the FDG-PET/CT imaging modality is a promising technique for detecting small changes in bowel inflammation, despite the fact that age related inflammation may not be of clinical utility. The fact that we were able to detect these subtle changes indicates this as an avenue for potential future investigation. Future studies are needed to investigate the link between inflammation caused by IBD and FDG uptake seen in PET/CT. Correlation of PET/CT with transmural inflammation would enable physicians to treat for true mucosal (transmural histologic) healing, not just endoscopic mucosal healing. Overall, we believe the findings from the proposed study could pave the way for a paradigm shift in CD imaging of patients with suspected CD with small bowel involvement or for monitoring the response to therapy without

the need for application of more advanced invasive endoscopic studies.

Disclosure of conflict of interest

None.

Address correspondence to: Samantha C Brosler, 1 Founders Building, MRI Education Center, 3400 Spruce Street, Philadelphia, PA, USA. Tel: 214-449-7660; E-mail: broslers@seas.upenn.edu

References

[1] IBD Factbook. Crohn's and colitis foundation of America %U http://www.crohnscolitisfoundation.org/assets/pdfs/updatedibdfactbook.pdf; 2014.

[2] Cosnes J, Gower-Rousseau C, Seksik P and Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011; 140: 1785-94.

[3] Munkholm P, Langholtz E, Davidsen M and Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995: 30: 669-706.

[4] Van Assche G, Vermier S and Rutgeerts P. The potential for disease modification in Crohn's disease. Nat Rev Gastroenterol Hepatol 2010: 7: 79-85.

[5] Brenner DJ and Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007; 357: 2277-84.

[6] Tolia V, Peters JM and Gilger MA. Sedation for pediatric endoscopic procedures. J Pediatr Gastroenterol Nutr 2000; 30: 477-85.

[7] Montanari F, Viola L and Amarri S. Sedation in pediatric digestive endoscopy. Pediatr Med Chir 2001; 23: 45-9.

[8] Masselli G, Mastroiacovo I, De Marco E, Francione G, Casciani E, Polettini E and Gualdi G. Current tecniques and new perpectives research of magnetic resonance enterography in pediatric Crohn's disease. World J Radiol 2016; 8: 668-82.

[9] Osterman MT and Lichtenstein GR. Inflammatory bowel disease. AGA Press 2011; 6: 361-402.

[10] Osman S and Danpure HJ. The use of 2-[18F] fluoro-2-deoxy-D-glucose as a potential in vitro agent for labelling human granulocytes for clinical studies by positron emission tomography. Int J Rad Appl Instrum B 1992; 19: 183-90.

[11] Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N and Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992; 33: 1972-80.

[12] Yamada S, Kubota K, Kubota R, Ido T and Tamahashi N. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. J Nucl Med 1995; 36: 1301-6.

[13] Sugawara Y, Braun DK, Kison PV, Russo JE, Zasadny KR and Wahl RL. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. Eur J Nucl Med 1998; 25: 1238-43.

[14] Mochizuki T, Tsukamoto E, Kuge Y, Kanegae K, Zhao S, Hikosaka K, Hosokawa M, Kohanawa M and Tamaki N. FDG uptake and glucose transporter subtype expressions in experimental tumor and inflammation models. J Nucl Med 2001; 42: 1551-5.

[15] Love C, Tomas M, Tronco G and Palestro C. FDG PET of infection and inflammation. Radiographics 2005; 25: 1357-68.

[16] Lochhead P, Khalili H, Ananthakrishnan AN, Richter JM and Chan AT. Association between circulating levels of c-reactive protein and interleukin-6 and risk of inflammatory bowel disease. Clin Gastroenterol Hepatol 2016; 14: 818-24, e6.

[17] Florin TH, Paterson EW, Fowler EV and Radford-Smith GL. Clinically active Crohn's disease in the presence of a low C-reactive protein. Scand J Gastroenterol 2006; 41: 306-11.

[18] Palmer WE, Rosenthal DI, Schoenberg OI, Fischman AJ, Simon LS, Rubin RH and Polisson RP. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995; 196: 647-55.

[19] Lewis PJ and Salama A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J Nucl Med 1994; 35: 1647-9.

[20] Taylor IK, Hill AA, Hayes M, Rhodes CG, O'Shaughnessy KM, O'Connor BJ, Jones HA, Hughes JM, Jones T, Pride NB and Fuller RW. Imaging allergen-invoked airway inflammation in atopic asthma with [18F]-fluorodeoxyglucose and positron emission tomography. Lancet 1996; 347: 937-40.

[21] Pantin CF, Valind SO, Sweatman M, Lawrence R, Rhodes CG, Brudin L, Britten A, Hughes JM and Turner-Warwick M. Measures of the inflammatory response in cryptogenic fibrosing alveolitis. Am Rev Respir Dis 1988; 138: 1234-41.

[22] Saboury B, Salavati A, Brothers A, Basu S, Kwee TC, Lam MG, Hustinx R, Louis E, Torigian DA and Alavi A. FDG PET/CT in Crohn's disease: correlation of quantitative FDG PET/CT parameters with clinical and endoscopic sur-

rogate markers of disease activity. Eur J Nucl Med Mol Imaging 2014; 41: 605-14.
[23] Basu S, Chryssikos T, Moghadam-Kia S, Zhuang H, Torigian DA and Alavi A. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. Semin Nucl Med 2009; 39: 36-51.
[24] Basu S, Torigian D and Alavi A. The role of modern molecular imaging techniques in gastroenterology. Gastroenterology 2008; 135: 1055-61.
[25] El-Haddad G, Zhuang H, Gupta N and Alavi A. Evolving role of positron emission tomography in the management of patients with inflammatory and other benign disorders. Semin Nucl Med 2004; 34: 313-29.
[26] Hustinx R, Smith RJ, Benard F, Rosenthal DI, Machtay M, Farber LA and Alavi A. Dual time point fluorine-18 fluorodeoxyglucose positron emission tomography: a potential method to differentiate malignancy from inflammation and normal tissue in the head and neck. Eur J Nucl Med 1999; 26: 1345-8.
[27] Zhuang H and Alavi A. 18-fluorodeoxyglucose positron emission tomographic imaging in the detection and monitoring of infection and inflammation. Semin Nucl Med 2002; 32: 47-59.
[28] Meisner RS, Spier BJ, Einarsson S, Roberson EN, Perlman SB, Bianco JA, Taylor AJ, Einstein M, Jaskowiak CJ, Massoth KM and Reichelderfer M. Pilot study using PET/CT as a novel, noninvasive assessment of disease activity in inflammatory bowel disease. Inflamm Bowel Dis 2007: 13: 993-1000.
[29] Palatka K, Kacska S, Lovas S, Garai I, Varga J and Galuska L. The potential role of FDG PET-CT in the characterization of the activity of Crohn's disease, staging follow-up and prognosis estimation: a pilot study. Scand J Gastroenterol 2018; 53: 24-30.
[30] Louis E, Ancion G and Colard A. Noninvasive assessment of Crohn's disease intestinal lesions with 18FFDG PET/CT. J Nucl Med 2007: 48: 1053-9.
[31] Sproston NR and Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018; 9: 754.
[32] Velissaris D, Pantzaris N, Koniari I, Koutsogiannis N, Karamouzos V, Kotroni I, Skroumpelou A and Ellul J. C-reactive protein and frailty in the elderly: a literature review. J Clin Med Res 2017; 9: 461-5.
[33] Meier JM, Alavi A, Iruvuri S, Alzeair S, Parker R, Houseni M, Hernandez-Pampaloni M, Mong A and Torigian DA. Assessment of age-related changes in abdominal organ structure and function with computed tomography and positron emission tomography. Semin Nucl Med 2007; 37: 154-72.
[34] Phillips RJ and Powley TL. As the gut ages: timetables for aging of innervation vary by organ in the Fischer 344 rat. J Comp Neurol 2001; 434: 358-77.
[35] Bahler L, Holleman F, Chan MW, Booij J, Hoekstra JB and Verberne HJ. 18F-FDG uptake in the colon is modulated by metformin but not associated with core body temperature and energy expenditure. PLoS One 2017; 12: e0176242.
[36] Lee SH, Jin S, Lee HS, Ryu JS and Lee JJ. Metformin discontinuation less than 72 h is suboptimal for F-18 FDG PET/CT interpretation of the bowel. Ann Nucl Med 2016; 30: 629-36.