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Title: Effect of Diet on Physiological Bowel 18F-FDG Uptake

Running title: Diet and bowel 18F-FDG uptake

Bahar Moasses-Ghafari[1], Babak Fallahi[2], Armaghan Fard Esfehani[2], Mohammad Eftekhari[2], Khaled Rahmani[3], Arash Eftekhari[4], Parham Geramifar[2†]

[1] Kurdistan University of Medical Sciences, Sanandaj, Iran

[2] Research Center for Nuclear Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

[3] Social Determinants of Health Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran

[4] Diagnostic Radiology/Nuclear Medicine, Surrey Memorial Hospital and Jim Pattison Outpatient Care and Surgery Centre, Surrey, British Columbia, Canada

† Corresponding author:

Parham Geramifar,

Email: pgeramifar@tums.ac.ir

Postal address: Research Center for Nuclear Medicine, Shariati Hospital, North Kargar Ave. 1411713135, Tehran, Iran **Tel:** +98-21-88026901 **Fax:** +98-21-88026905

Effect of diet on physiologic bowel ^{18}F-FDG uptake

Abstract

Objective: Intestinal ^{18}F-FDG uptake is variable in whole body PET/CT scan. In cancer patients, in particular those suspected for relapse or metastasis, ^{18}F-FDG absorption might interfere with scan interpretation. This study was conducted in order to evaluate the effect of the diet on intestinal ^{18}F-FDG absorption.

Materials and methods: A total of 214 patients referring for oncologic ^{18}F-FDG PET/CT scan participated in this study. They were randomly divided into two groups and advised to follow one of the following diets 24 hours prior to the study; namely routine diet (RD) or low carbohydrate high fat diet (LCHFD). Small bowel and different parts of colon including caecum, ascending, transverse, descending as well as hepatic and splenic flexure segments were evaluated and visual interpretation of the scan images was made by nuclear medicine experts. Bowel uptake was graded through comparison with that of the liver as absent, mild, moderate and severe.

Results: Significantly higher ^{18}F-FDG uptake was observed in the descending colon (P=0.001) and small intestine (P=0.01) in the group following RD in comparison with the LCHFD group. After omitting patients with bowel cancer from the statistical analysis, no significant differences in the final results were seen.

Conclusion: LCHFD intake from 24 hours prior to ^{18}F-FDG PET imaging resulted in lower ^{18}F-FDG uptake in descending colon and small bowel compared to RD, assisting the interpreting physician by declining the intestinal activity interference for more accurate diagnostic interpretation.

Keywords: Diet, Bowel physiologic 18F-FDG uptake, Oncologic PET/CT imaging

Introduction

Positron emission tomography/computed tomography (PET/CT) is one of the most useful imaging modalities for metabolism studies at the cellular and molecular level. The growing trend of imaging procedures make PET/CT substantially superior for diagnostic purposes, staging, restaging or prognostic evaluation of oncologic patients. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is the most common radioisotope used worldwide for PET/CT scan in malignant diseases (*1*). ^{18}F-FDG distribution based on glucose metabolism can be seen in other organs including brain, myocardium, kidneys, urinary bladder and bowel (*1,2*).

Methods for suppression of myocardial ^{18}F-FDG uptake in oncologic patients has been previously reported (*3-5*). No study, however, has been conducted to determine the effects of diet on bowel ^{18}F-FDG uptake, the importance of which cannot be underestimated in the interpretation of PET/CT results of the abdomen and pelvis.

Previous researchers attempted to find a solution to minimize physiological ^{18}F-FDG uptake throughout the body through mainly focusing on reducing myocardial ^{18}F-FDG uptake by low-carbohydrate high fat (LCHF) diet or prolonged fasting (*4,5*). Although few studies have been carried out to control bowel ^{18}F-FDG uptake, they had focused on the effect of bowel preparation (*6*), and classification of uptake and its potential interfering effect in scan interpretation of abdomen-pelvic (mainly colon) cancer (*7,8*). Therefore, we decided to design a study to evaluate the effect of LCHF diet on intestinal ^{18}F-FDG uptake.

Methods

A total of 214 patients older than 18 years (107 males and 107 females), ranging from (18-84) with suspicion or proven malignancies, were enrolled in the study. The study protocol was evaluated and approved by Institutional Research Ethics Committee and the study plan was fully explained

to the patients and written informed consent was obtained from all. PET/CT was requested in different stages of the disease. Exclusion criteria included serum glucose level more than 200 mg/dl at the time of radiotracer injection, failure to observe fasting, known bowel disease or pathologic bowel ^{18}F-FDG uptake interfering with physiologic bowel activity.

Patients were randomly assigned into two groups; one group of routine diet (RD) and the other had a LCHF diet for 24 hours prior to the ^{18}F-FDG PET/CT scan. All patients received the required information and details regarding their diet and were instructed to fast at least 6 hours before the study. Food in LCHF diet included boiled eggs, grilled beef, fried chicken, vegetables, and any carbohydrate containing beverage or meal 24 hours prior to the study were avoided. PET/CT was performed on a Biograph TruePoint 6 (Siemens, Germany), for all patients. PET/CT acquisition was performed approximately 60 minutes after an intravenous administration of 10.6±1.7 mCi (392±63 MBq) ^{18}F-FDG according to body weight (0.14 mCi/kg [5.2 MBq/kg]). PET image reconstruction protocol includes four iterations per 21 subsets, a 5-mm Gaussian post smoothing filter, and a 168 × 168 matrix, using the point-spread-function (PSF) based reconstruction algorithm TrueX. PET imaging protocol was set for 3 min/bed position as default and 4 min/ bed position in cases with body mass index (BMI)>35. Low dose CT (50 mA, 110 -130 kV) was applied for attenuation correction.

Visual evaluation of ^{18}F-FDG uptake was performed by two nuclear medicine physicians grading the uptake levels in small intestine and different parts of the large bowel including ascending, transverse, descending segments, and caecum as well as hepatic and splenic flexures. In cases of disagreement, the third specialist's opinion was the criterion of decision making. The intensity of uptake in small intestine and in different colon segments, comparing to liver activity, Fig. 1, was

classified into four groups namely absent, mild (less than liver), moderate (equal to the liver) and severe (more than liver).

- **Statistical analysis**

Analyses were conducted using SPSS 22 and Independent sample T-test, Chi square or fisher's exact test were used to assess the relationship between the type of diet and investigated outcome including the intensity of ^{18}F-FDG uptake in several bowel regions. P value less than 0.05 was considered as statistically significant.

Results

A total of 214 patients were enrolled in the study and were randomly divided into two groups. A group had RD while the other one thoroughly followed a 24-hour LCHF diet. Baseline data analysis of heart rate (HR), blood pressure (BP), and fasting blood sugar (FBS) besides demographic characteristics of gender, age, height and weight were done to ensure proper randomization of potential confounders in the study groups. *Table 1* shows the state of baseline and demographics characteristic factors in the two groups of the study. The demographic and baseline characteristics of the patients were balanced between groups (Table *1*).

The intensity of ^{18}F-FDG uptake in different segments of colon is presented in the *Table 2*. As detailed in the Table *2*, significantly higher intense ^{18}F-FDG uptake was observed in the descending colon and small intestine following RD as compared with low carbohydrate high fat diet (LCHFD) group.

34 patients with history of colon cancer were removed from the statistical analysis. The intensity of descending colon and small intestinal ^{18}F-FDG uptake in LCHFD group was still lower than RD group, while no remarkable difference of ^{18}F-FDG uptake in other segments of colon was noted between the two groups (Table *3*).

As noted in the Table *2*, significantly higher intense ^{18}F-FDG uptake was observed in the descending colon and small intestine in the group following the RD compared with LCHFD group.

Discussion

Epidemiologic studies have shown that colon cancer is the third most lethal cancer in the world after prostate and lung cancer in men and following breast and lung malignancies in women (*9,10*). Choice of colon cancer treatment depends on multiple factors including basic patient's health status as well as the size, location and extension of tumor. Surgery is the most commonly used therapy depending on the size and extension of the tumor (*9,10*). PET/CT is an appropriate diagnostic tool for the evaluation of the regional or distant tumor extension and accordingly has vital clinical effect on patients' management at different stages of the disease. In cases of suspicion for tumor recurrence or liver metastasis, PET/CT is very effective in deciding the feasibility of surgery. PET/CT is also much more useful than conventional imaging in decision making for monitoring response to the given therapy.

Physiological ^{18}F-FDG absorption in small and large intestines can interfere with accurate interpretation and may lead to masking true lesions or, conversely, causing misdiagnosis and false positive results. The control of intestinal ^{18}F-FDG uptake is expected to reduce possible false positive and false negative results.

Following our previous study leading to successful experiences in the suppression of myocardial ^{18}F-FDG uptake by LCHF diet (*5*), we were encouraged to test the effect of diet on intestinal ^{18}F-FDG absorption. Interestingly, the application of LCHFD vs. RD resulted in significant reduction of ^{18}F-FDG uptake in descending colon and small intestine. To the best of our knowledge, no study has been conducted on the effect of the LCHF diet on intestinal absorption so far. Considering the significant prevalence of colon cancer and the role of PET/CT in its management, the results of

such a study ought to be extremely invaluable to improve the image quality of the abdominopelvic cavity in particular. The goal of our study was to investigate the effect of diet on reducing ^{18}F-FDG uptake in the bowel.

In this well-controlled randomized trial study, it was attempted to illustrate the changes of ^{18}F-FDG uptake in the intestinal system when LCHFD was used for patients' preparation. The LCHF diet might not be suitable for vegetarians, but as the focus of the assessment was on carbohydrate restriction along with an LCHF diet, the plant protein foods (e.g. soy) can be used as a substitute for animal proteins in the given food list.

A significant statistical relationship was found between diet and ^{18}F-FDG distribution in descending colon and small intestine and diet can be an effective controllable factor to reduce bowel ^{18}F-FDG uptake.

78.5% of the patients in LCHFD group had no ^{18}F-FDG absorption or had only a mild uptake in descending colon and 94.4% of them also revealed no ^{18}F-FDG uptake or mild absorption in small intestine. In the RD group, 36.4% of patients revealed moderate to severe ^{18}F-FDG absorption (equal or more than the liver activity), while it was only 21.5% in LCHFD group. In general, moderate to severe intestinal ^{18}F-FDG absorption was reported in 16.8% of patients in the RD group and 5.6% in LCHFD group (P =0.01).

The results of the study showed that LCHF regimen 24 hours before the scan shifted the ^{18}F-FDG uptake of small intestine and descending colon from moderate or severe to mild or absent ^{18}F-FDG uptake. In 2015, a study was conducted to evaluate the background bowel ^{18}F-FDG uptake in breast cancer patients on 326 females who underwent ^{18}F-FDG PET scan for primary staging of breast cancer. Indeed, none of the cases had hypertension or diabetes. According to the results colon absorption was categorized as (low or high) on the basis of visual and quantitative assessments.

The average SUVmax values in eight segments of the intestine (duodenum, jejunum, ileum, caecum, hepatic flexure and splenic flexure, descending colon and sigmoid) was reported as total bowel SUVmax (TB SUVmax). Age, FBS, BMI, triglyceride (TG), cholesterol (CHOL), high density lipoprotein (HDL), and low density lipoprotein (LDL) were considered as cardio-metabolic related factors. TB SUVmax had a positive relationship with age, BMI, TG, CHOL, and LDL and had negative relationship with HDL. Multivariate analysis represented that BMI and TG were independent factors associated with bowel ^{18}F-FDG uptake. According to these results, high bowel ^{18}F-FDG uptake in PET scan could be due to changes in lipid metabolism and an increased risk of cardio-metabolic disease in non-diabetic and non-hypertensive patients (*11*), while in our study, the limited use of glucose and increased lipid levels in the diet resulted in a significant reduced ^{18}F-FDG uptake in the small intestine and descending colon.

The first study on the factors potentially influencing intestinal ^{18}F-FDG absorption was conducted in 1998. According to the data in that study, age, sex and bowel habits were effective in ^{18}F-FDG absorption, no relationship, however, was found between free fatty acid level and bowel ^{18}F-FDG uptake. Moreover, female gender, older age and constipation were associated with higher ^{18}F-FDG uptake (*12*).

Insulin increases glucose uptake by enterocytes and consequently increased bowel absorption in diabetic patients (*13-15*). However, a wide range of intestinal ^{18}F-FDG uptake was observed in non-diabetic subjects. Another study concluded that hypoglycemic oral agents such as metformin consumption was considered as a factor causing higher ^{18}F-FDG uptake in colon significantly and to a lesser extent in the small intestine (*13-18*). Furthermore, a study in 2017 revealed that Metformin consumption remarkably increased colonic ^{18}F-FDG absorption, but this increased absorption was independent of increase in energy expenditure or core body temperature. In other

words, there was no relationship between maximal colonic ^{18}F-FDG uptake and energy expenditure or core body temperature (*19*).

With discontinuation of metformin 48 hours before the scan in diabetic patients of this study, the effect of interfering metformin on the bowel ^{18}F-FDG uptake was eliminated and only the effect of diet on bowel ^{18}F-FDG uptake was investigated.

Recently the probability of the role of intestinal bacteria in luminal ^{18}F-FDG uptake has been raised and treatment with riphaximin before PET scan has been proposed to reduce luminal ^{18}F-FDG uptake. Riphaximin is likely to cause different degrees of ^{18}F-FDG uptake through changing the population of intestinal bacteria and by the alteration of the flora and host metabolism (*20*). Another study evaluated the effect of administration of N-butylscopolamine to decrease bowel artifacts during ^{18}F-FDG PET. The results revealed that it could potentially improve the quality of PET scan images and their reporting as well (*21*).

Randle Cycle described a biochemical mechanism that maintain a cellular fuel metabolism balance between glucose and free fatty acid oxidation. Thus, decreasing glucose oxidation in the presence of free fatty acids. The significance of the glucose-fatty acid cycle is that it may introduce a new aspect in more precise hormonal control by adding a nutrient-mediated modification(*22*). This fact has been proven that the consumption of each nutrient (glucose vs. fatty acid) inhibits the utilization of the other in isolated myocardial and skeletal muscle but no corresponding data did exist to justify the effect of nutrient shift on the smooth muscles of the intestine. The result of our previous study about the factors affecting myocardial ^{18}F-FDG uptake, demonstrated that in 107 patients with LCHF diet, there was a significant statistical relationship between descending colon ^{18}F-FDG absorption and myocardial ^{18}F-FDG uptake (P =0.001) (*5*). However, in spite of a

meaningful shift in ^{18}F-FDG absorption of the descending colon and small intestine, ^{18}F-FDG didn't show significant shift from moderate/high to mild or absent uptake.

Conclusion

Management of physiologic bowel ^{18}F-FDG uptake can play a key role in accurate colon pathologies identification by effectively deterring the occurrence of false positive or false negative results. Patient preparation using LCHFD for 24 hours prior to ^{18}F-FDG PET imaging resulted in lower ^{18}F-FDG uptake in descending colon and small intestine and consequently better quality of the images in particular for precise characterization and interpretation of abdominopelvic findings in ^{18}F-FDG PET/CT images.

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Table 1 Summary of Demographics and Baseline characteristics of study subjects

Variable	RD, Mean ± SD	LCHFD, Mean ± SD	P value
Age (years)	47.73 ± 15.73	47.46±15.59	0.8
Weight (kg)	72.57±14.85	70.57±14.16	0.6
Height (cm)	167.90±9.79	166.67±9.66	0.9
SBP (mmHg)	119.95±15.68	116.93±13.94	0.7
DBP (mmHg)	79.04±8.81	77.51±7.80	0.3
FBS (mg/dl)	95.21±18.73	93.69±17.13	0.6
HR (bpm)	80.35±9.24	80.67±9.06	0.5
^{18}F-FDG injected dose (mCi)	10.56±1.82	10.67±1.66	0.6
Gender, n (%)			0.7
Male	55 (51.4)	52 (48.6)	
Female	52 (48.6)	55 (51.4)	

SBP=systolic blood pressure; DBP= diastolic blood pressure; FBS=fasting blood sugar; HR=heart rate;

Table 2 ^{18}F-FDG distribution patterns in bowel regions

Pattern of ^{18}F-FDG distribution	No ^{18}F-FDG uptake		Mild ^{18}F-FDG uptake		Moderate ^{18}F-FDG uptake		Severe ^{18}F-FDG uptake		P value
	RD	LCHFD	RD	LCHFD	RD	LCHFD	RD	LCHFD	
Caecum	0	0	83(77.57)	84(78.50)	1 (0.93)	0	23(21.50)	23(21.50)	0.6
Ascending colon	66(61.68)	72(67.29)	17(15.89)	23(21.50)	19 (17.76)	9 (8.41)	5 (4.67)	3 (2.80)	0.1
Transverse colon	89(83.18)	97(90.65)	9 (8.41)	7 (6.54)	8 (7.48)	3 (2.80)	1 (0.93)	0	0.2
Descending colon	9 (8.41)	31(28.97)	59(55.14)	53(49.53)	29(27.10)	18(16.82)	10 (9.34)	5 (4.67)	<0.001
Hepatic flexure	0	0	92(85.98)	92(85.98)	0	1 (0.93)	15(14.02)	14(13.08)	0.5
Splenic flexure	0	1 (0.93)	90((84.11)	87(81.31)	0	0	17(15.89)	19(17.76)	0.5
Small intestine	18(16.82)	28(26.17)	71(66.36)	73(68.22)	18(16.82)	5(4.67)	0	1(0.93)	0.01

Table 3 ^{18}F-FDG distribution patterns in bowel regions after exclusion of patients with the history of colon cancer

Pattern of ^{18}F-FDG distribution	No ^{18}F-FDG uptake		Mild ^{18}F-FDG uptake		Moderate ^{18}F-FDG uptake		Severe ^{18}F-FDG uptake		P value
	RD	LCHFD	RD	LCHFD	RD	LCHFD	RD	LCHFD	
Caecum	0	0	74(76.29)	66(79.52)	1 (1.03)	0	22 (22.68)	17 (20.48)	0.6
Ascending colon	61 (62.89)	56(67.47)	14 (14.43)	18 (21.69)	17 (17.53)	6 (7.23)	5 (5.15)	3(3.61)	0.1
Transverse colon	80 (82.47)	76(91.57)	8 (8.25)	5 (6.02)	8 (8.25)	2 (2.41)	1 (1.03)	0	0.2
Descending colon	8 (8.25)	24(28.92)	53 (54.64)	44 (53.01)	26 (26.80)	11(13.25)	10 (10.31)	4 (4.82)	<0.001
Hepatic flexure	0	0	82 (84.54)	73 (87.95)	0	1 (1.20)	15 (15.46)	9 (10.84)	0.37
Splenic flexure	0	1 (1.20)	81 (83.51)	68 (81.93)	0	0	16 (16.49)	14 (16.87)	0.5
Small intestine	17 (17.53)	22(26.51)	62 (63.92)	56 (67.47)	18 (18.56)	4 (4.82)	0	1 (1.20)	0.02

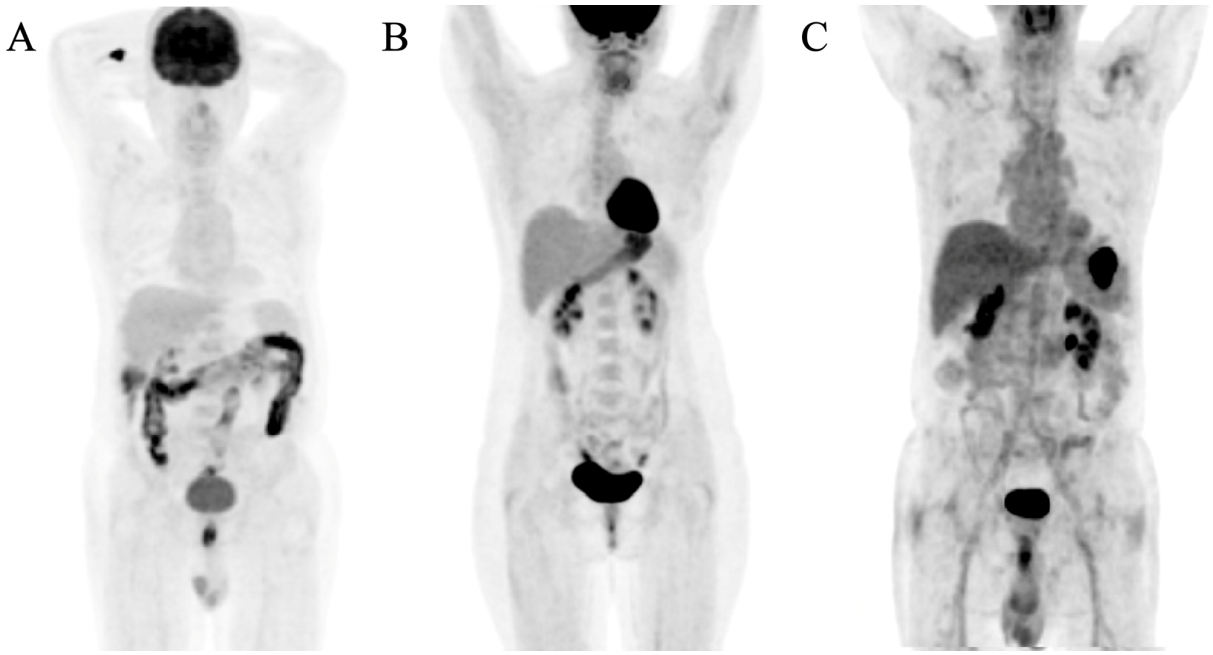

Figure 1. Grading the bowel uptake by comparing it to that of the liver as: (a) severe, more than liver, (b) moderate, equal to the liver, and (c) mild, less than liver.

Graphical Abstract