Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1241530

Anatolian Curr Med J 2023; 5(2); 143-147

The effect of proton pump inhibitor use on the biodistribution of FDG in patients undergoing ^{18}F FDG PET/CT imaging

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Cite this article as: Kaplan İ, Güzel Y, Can C, et al. The effect of proton pump inhibitor use on the biodistribution of FDG in patients undergoing ^{18}F FDG PET/CT imaging. Anatolian Curr Med J 2023; 5(2); 143-147.

ABSTRACT

Aim: In this study, we aimed to investigate the effects of proton pump inhibitors (PPIs) administered shortly before intravenous (iv) F-18 fluorodeoxyglucose (FDG) injection on the physiological FDG uptake in the gastrointestinal tract (GIS) of patients undergoing F-18 FDG positron emission tomography/computed tomography (PET/CT) for oncological purposes.

Material and Method: We retrospectively evaluated 350 patients who underwent ^{18}F-FDG PET/CT in our clinic between November 2020 and June 2021. Among these, 178 patients were given iv PPIs before the scan and the remaining 172 patients with similar characteristics were not. FDG uptake in the gastrointestinal tract was analyzed visually and quantitatively.

Results: The mean age of the patients was 51.7±15 years. There was no significant difference between the two groups in terms of age and gender. Quantitative evaluation revealed that the FDG uptakes in the stomach, duodenum, ileum, and transverse colon and their ratio to hepatic uptake were significantly lower in the group receiving iv PPIs ($p<0.05$). In visual evaluation, gastric and ileal uptake were significantly lower in the intravenous PPI group ($p<0.05$).

Conclusion: Our findings indicate that intravenous administration of a PPI before FDG PET/CT imaging can decrease the FDG uptake in the gastrointestinal tract. We think that this practice can reduce false positive findings in the gastrointestinal system and help identifying gastric and intestinal cancers by reducing background activity.

Keywords: Positron emission tomography, proton pump inhibitor, physiological uptake, gastrointestinal tract

INTRODUCTION

^{18}F-FDG PET/CT is a non-invasive diagnostic tool that shows metabolic activity in target tissues and is used to obtain quantitative parameters (1,2). FDG PET/CT is a valuable imaging tool for diagnosis, staging, evaluation of response to treatment and prognosis in oncology (3,4).

Recommended for imaging infection/inflammation as well as cancer diseases (5, 6). In addition, variable degrees of physiological FDG uptake may occur in the brain, salivary glands, thyroid, muscles, GIS, urinary system, adrenal gland, uterus, ovary, adipose tissue, muscles, spleen, and bone marrow (7-9).

FDG uptake may increase in the stomach, small and large intestines physiologically, in benign diseases or due to drug use (10-13). Gastric distention (drinking water) and use of iv buscopan were found to be effective in reducing FDG uptake in the stomach, and oral omeprazole in small and large intestines (14,15). Suspected focal or diffuse FDG uptake in the GIS requires endoscopic examination to rule out malignancy or to accurately stage malignant disease. The operations performed cause cost and time loss.

In this study, we aimed to examine the effect of using iv proton pump inhibitor on the physiological involvement of GIS before ^{18}F-FDG PET/CT imaging.

MATERIAL AND METHOD

The study was carried out with the permission of Diyarbakır Training and Research Hospital Ethics Committee (Date: 21.04.2022, Decision No: 72). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Received: 23.01.2023 **Accepted:** 15.03.2023

Three hundred and fifty patients who had no prior history of gastrointestinal symptoms or oral PPI use and underwent ^{18}F-FDG PET/CT in our clinic between November 2020 and June 2021 were retrospectively included in our study. One hundred and seventy-eight patients received an iv PPI (40 mg of pantoprazole) one hour before the FDG injection. One hundred and seventy-two patients with similar demographic characteristics and diagnoses, who also don't have a history of oral or iv PPI use, were included in the control group. Patients with a history of abdominal surgery, using oral antidiabetic drugs, or using stomach drugs (antiacids, H2 receptor blockers, and PPIs) for any reason were excluded from the study.

^{18}F-FDG PET/CT imaging protocol

All patients were asked to fast and cease iv glucose intake at least six hours before FDG imaging. Blood glucose was confirmed to be ≤ 140 mg/dL using fingerstick method, and 3.5-5.5 MBq/kg of ^{18}F-FDG was intravenously injected. One hour after the injection, CT images (120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64x0.625 mm collimation, pitch 1.4, 0.5 s rotation time, 3.3 mm slice thickness, 512x512 matrix) from the vertex to the middle of the thigh were obtained using the Discovery IQ 4 ring 20-cm axial FOV PET/CT device (GE Healthcare, Milwaukee, WI, USA) in the supine position. Then, PET images were obtained at 2.5 minutes per bed position (3D FOV 20 cm, ordered subset expectation-maximization algorithm [OSEM] 5 iterations/12 subset, full width at half maximum [FWHM] 3 mm).

Evaluation of Images

All ^{18}F-FDG PET/CT images were evaluated by two nuclear medicine specialists with at least 10 years of experience using Advantage Workstation software version AW 4.7 (GE Healthcare Milwaukee, WI, USA). FDG uptake was assessed both visually and quantitatively in the liver, stomach (cardia, fundus, body, antrum, and pylorus), duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum separately. In visual assessment, uptakes were scored as grade 1 (uptake<liver), grade 2 (uptake=liver), and grade 3 (uptake > liver). In quantitative assessment, maximum standardized uptake value (SUVmax) of the gastrointestinal segments and their ratio to hepatic SUVmax were calculated.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used for statistical analyses. Normality of univariate data was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov test. Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define continuous variables. Mann-Whitney U test was used to compare two independent and non-normally distributed groups. Visual data was analyzed with chi-squared test. $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 51.7±15 years and the median age was 53 years (18-92). Fifty percent (175) of the patients included in the study were male. There was no significant difference between the two groups in terms of age and gender. The underlying diseases of the PPI group and control group are summarized (**Table 1**).

Table 1. Demographic characteristics and underlying diseases of patients with and without proton pump inhibitors

Patient Groups	PPI Group	Control Group	p value
Male	92	83	0.296
Female	86	89	
Age (range)	52 (20-87)	53.5 (18-92)	0.766
Underlying diseases			
Lung ca	30	37	
Breast ca	28	33	
Malignant lymphoma	18	15	
Head-neck tumors (Thyroid ca, Larynx ca, etc)	14	17	
Cancer of unknown origin	20	3	
Colorectal ca	15	22	
Gynecological ca	15	10	
Stomach ca	11	3	
Multiple myeloma	3	1	
Malignant mesothelioma	5	1	
Male genitourinary ca	6	4	
Small intestine tumors	5	3	
Thymoma	1	1	
Renal cell carcinoma	4	4	
Skin ca (Malignant melanom-Squamous cell carcinoma)	5	1	
Esophagus ca	1	5	
Soft tissue sarcoma	2	3	
Pancreatic ca	1	5	
Hepatocellular carcinoma	0	1	

PPI: proton pump inhibitor, cancer: ca

The SUVmax values measured in the stomach and intestinal segments of the patients with and without intravenous PPI use before the scan, the ratios of these values to the hepatic SUVmax, and the p values obtained are summarized in **Table 2**. FDG uptake in the cardia, fundus, gastric body, duodenum, and transverse colon were significantly lower in the group using iv PPIs ($p=0.011$, $p<0.001$, $p=0.004$, $p<0.001$, and $p=0.003$, respectively).The ratios of cardia/liver, fundus/liver, gastric body/liver, antrum/liver, pylorus/liver, duodenum/liver, and ileum/liver SUVmax were also significantly lower in the iv PPI group ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.006$, $p=0.002$, $p=0.037$, and $p<0.000$, respectively) (**Table 2**).

Visual evaluation revealed that the FDG uptakes in gastric cardia, fundus, body, antrum, pylorus, and ileum were significantly lower in the intravenous PPI group (p=0.0006, p<0.001, p=0.002, p=0.040, and p<0.001, respectively) (**Figure 1** and **2**). No significant difference was observed in other intestinal segments (**Table 3**).

Table 2. Quantitative comparison of patients with and without proton pump inhibitors.

	PPI (+)			PPI (-)			p
	n	Mean+SD	Med (Min-Max)	n	Mean+SD	Med (Min- Max)	
Cardia SUVmax	178	2.5+1.0	2.3(0.6-6.2)	172	2.7+1.0	2.7(0.7-6.7)	0.011
Cardia/Liver SUVmax ratio	178	0.7+0.3	0.6(0.2-1.6)	172	0.8+0.3	0.8(0.2-2.4)	0.000
Fundus SUVmax	178	2.2+1.2	2.2(0.0-7.4)	172	2.8+1.1	2.7(0.5-5.7)	0.000
Fundus/Liver SUVmax ratio	178	0.6+0.3	0.6(0.0-1.9)	172	0.8+0.4	0.8(0.1-2.3)	0.000
Gastric Body SUVmax	178	2.6+1.3	2.5(0.4-6.8)	172	2.9+1.1	2.9(0.6-6.1)	0.004
Gastric Body/Liver SUVmax ratio	178	0.7+0.3	0.7(0.1-1.6)	172	0.9+0.3	0.8(0.2-1.8)	0.000
Antrum SUVmax	178	2.5+1.4	2.2(0.2-6.5)	172	2.5+1.2	2.4(0.5-6.0)	0.242
Antrum/Liver SUVmax ratio	178	0.6+0.3	0.6(0.1-1.8)	172	0.7+0.3	0.7(0.2-1.8)	0.006
Pylorus SUVmax	178	2.4+1.1	2.2(0.7-7.5)	172	2.5+1.1	2.4(0.4-5.5)	0.242
Pylorus/Liver SUVmax ratio	178	0.6+0.3	0.6(0.2-2.5)	172	0.7+0.3	0.7(0.1-1.8)	0.002
Duodenum SUVmax	178	2.6+0.9	2.5(0.9-6.3)	172	2.3+0.8	2.1(0.7-4.7)	0.000
Duodenum/Liver SUVmax ratio	178	0.7+0.2	0.6(0.2-1.5)	172	0.6+0.2	0.6(0.1-1.6)	0.037
Jejunum SUVmax	178	2.9+1.0	2.8(1.1-8.6)	172	2.7+0.8	2.6(0.8-5.4)	0.067
Jejunum/Liver SUVmax ratio	178	0.8+0.3	0.7(0.4-2.5)	172	0.8+0.2	0.8(0.3-1.7)	0.120
Ileum SUVmax	178	3.6+2.3	2.9(1.0-17.7)	172	3.7+2.1	3.3(0.9-16.3)	0.063
Ileum/Liver SUVmax ratio	178	1.0+0.6	0.8(0.2-5.0)	172	1.1+0.6	1.0(0.3-4.3)	0.000
Cecum SUVmax	178	2.8+1.8	2.4(0.5-10.8)	172	2.7+1.9	2.1(0.7-13.3)	0.054
Cecum/Liver SUVmax ratio	178	0.8+0.5	0.6(0.1-2.9)	172	0.8+0.5	0.6(0.2-2.9)	0.519
Asc.Col. SUVmax	178	3.1+2.1	2.4(0.8-13.3)	172	2.8+2.1	2.1(0.7-12.6)	0.067
Asc.Col./Liver SUVmax ratio	178	0.8+0.6	0.7(0.2-3.2)	172	0.8+0.6	0.6(0.2-3.3)	0.728
Trans.Col. SUVmax	178	2.6+1.8	2.2(0.7-12.7)	172	2.6+2.7	1.7(0.5-18.7)	0.003
Trans.Col./Liver SUVmax ratio	178	0.7+0.5	0.6(0.2-2.7)	172	0.7+0.7	0.5(0.2-4.9)	0.153
Desc.Col. SUVmax	178	2.4+1.8	1.9(0.4-13.7)	172	2.4+2.2	1.6(0.5-16.0)	0.195
Desc.Col. /Liver SUVmax ratio	178	0.6+0.5	0.5(0.1-3.9)	172	0.7+0.6	0.5(0.1-4.2)	0.976
Sig. Col. SUVmax	178	3.3+2.3	2.7(0.6-14.2)	172	3.5+2.9	2.8(0.4-23.6)	0.779
Sig. Col. /Liver SUVmax ratio	178	0.9+0.6	0.7(0.2-4.0)	172	1.0+0.8	0.8(0.2-5.5)	0.106
Rectum SUVmax	178	3.0+2.0	2.4(0.7-13.5)	172	2.8+2.2	2.4(0.6-20.5)	0.174
Rectum/Liver SUVmax ratio	178	0.8+0.5	0.7(0.2-3.4)	172	0.8+0.6	0.7(0.2-4.5)	0.831

PPI (+): patients using proton pump inhibitors, PPI (-): patients not using proton pump inhibitors, n: number of cases, SD: standard deviation, Med: median, Min: minimum, Max: maximum, SUVmax: maximum standardized uptake value, Asc.Col: ascending colon, Trans.Col: transverse colon; Desc.Col: descending colon, Sig. Col: sigmoid colon

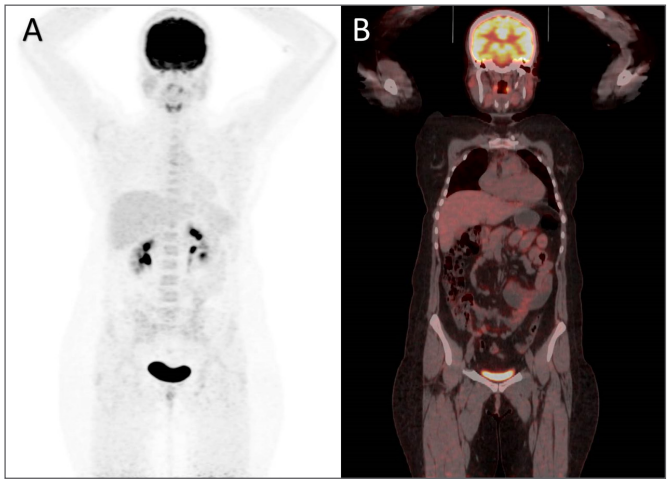

Figure 1. 32 year old woman with breast cancer using iv PPI before imaging; FDG uptake in the stomach and intestines was less than in the liver (Visual score: Grade 1).

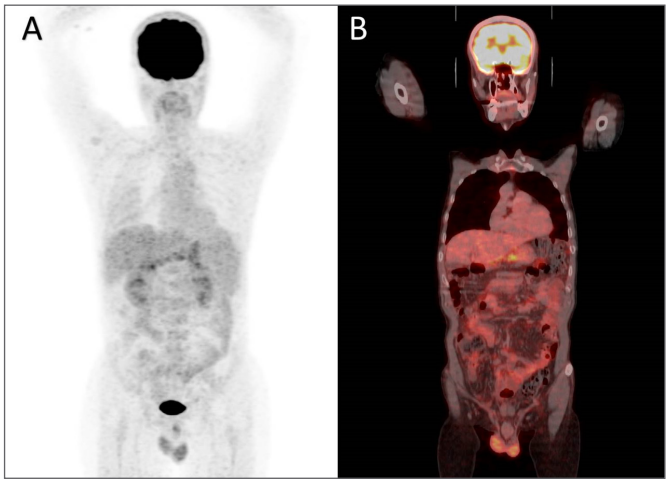

Figure 2. 50 year old man with hepatocellular carcinoma who did not use iv PPI before imaging; FDG uptake in stomach was higher than liver (Visual score: Grade 3).

Table 3. A visual comparison of patients with and without proton pump inhibitors.

	Visual score	PPI (+)	PPI (-)	Total	p
Cardia	1	129	92	221	<0.001
	2	40	61	101	
	3	9	19	28	
Fundus	1	133	93	226	<0.001
	2	37	49	86	
	3	8	30	38	
Gastric Body	1	121	85	206	0.002
	2	43	60	103	
	3	14	27	41	
Antrum	1	129	106	235	0.041
	2	34	51	85	
	3	15	15	30	
Pylorus	1	148	109	251	<0.001
	2	14	47	58	
	3	11	16	21	
Duodenum	1	131	145	282	0.199
	2	31	23	59	
	3	5	4	9	
Jejunum	1	125	114	239	0.600
	2	42	48	90	
	3	11	10	21	
İleum	1	109	63	172	<0.001
	2	36	61	101	
	3	33	44	77	
Cecum	1	129	121	250	0.431
	2	25	20	45	
	3	24	31	55	
Asc.Col.	1	119	118	237	0.810
	2	20	20	40	
	3	39	34	73	
Trans.Col.	1	143	133	276	0.796
	2	14	15	29	
	3	21	24	45	
Desc.Col.	1	142	139	281	0.745
	2	17	15	32	
	3	19	18	37	
Sig. Col.	1	116	92	208	0.062
	2	23	40	63	
	3	39	40	79	
Rectum	1	124	110	234	0.602
	2	29	37	66	
	3	25	25	50	

PPI (+): patients using proton pump inhibitors, PPI (-): patients not using proton pump inhibitors, n: number of cases, SD: standard deviation, Med: median, Min: minimum, Max: maximum, SUVmax: maximum standardized uptake value, Asc.Col: ascending colon, Trans.Col: transverse colon; Desc.Col: descending colon, Sig. Col: sigmoid colon

DISCUSSION

Similar to our study, Yamamoto et al. (15) used iv PPIs in their study on rats. However, probably due to very small size of rats, the measurements were obtained by removing the relevant GI segment of the rats and taking measurements on a gamma counter instead of scanning images on a PET/CT device. In this study, observed no effect of iv PPI use on the physiological FDG uptake in the esophagus and stomach, while the FDG activity in the small intestines and colon were significantly decreased. However, in our study, we observed that the use of iv PPIs decreases the FDG uptake in the duodenum and transverse colon along with many gastric segments. In addition to the SUVmax measurements, we also calculated the GI segment/hepatic SUVmax ratios in our study. This way, a statistically more significant difference was obtained, especially in the stomach segments and ileum. In the study of Yamamoto et al. (15), the change in the stomach may have been overlooked since the ratio of the measurements to the liver could not be evaluated. In our study, no statistical difference was observed in the antrum and pylorus when only the difference in FDG uptake was examined, but the evaluation of the GI segment/liver SUVmax ratio revealed a difference in the antrum and pylorus. In addition, because Yamamoto et al. (15) could not evaluate the ratio of their SUVmax measurements to the liver, a dose difference that could be caused by a possible extravasation of the FDG dose given to the rats could be missed. Yamamoto et al (15). also observed that iv PPIs decreased the FDG uptake in the small intestines and colon. We, on the other hand, divided the small intestine and colon into segments within themselves and found that the use of an iv PPI reduced the FDG uptake in the duodenum, ileum, and transverse colon.

Domeki et al. (16) used oral rabeprazole in a human study and investigated its effect on the physiological FDG uptake in the stomach and colon. Similar to our study, the investigators observed that the PPI significantly reduced the physiological FDG uptake in the stomach and colon, but especially in the stomach. Domeki et al. (16) attributed this impact, which was more evident in the stomach, to the mucosal absorption of the orally administered PPI. However, our study showed that direct mucosal absorption may not be an accurate pathophysiological explanation. As a matter of fact, our study showed that iv PPI administration significantly decreased the physiological FDG uptake, especially in the stomach. Domeki et al. (16) did not evaluate small intestinal segments in their study. They also did not assess the stomach and colon segments separately. Another limitation of that study is that the GI segment/liver SUVmax ratio was not evaluated. In addition, for this study, patients were required to use the PPI orally for 3 nights before the study. Since three days of medication use is required for imaging with oral PPI, it loses its applicability when urgent and early scans are required. IV administration of a PPI before FDG PET/CT, however, is a very practical and reliable method.

In this study, we aimed to identify the effects of intravenous PPI use on the physiological FDG uptake in the stomach and intestines. There are studies in the literature reporting that PPIs exhibit inhibitory activity on intestinal peristalsis with their anticholinergic effects (17, 18). Our findings may be due to this anticholinergic impact of PPIs. However, previous studies have shown that PPIs also have an anti-inflammatory effect (19-21). The decreased FDG uptake observed in the PPI group in our study may be due to suppression of inflammation. Even though we did not include patients with gastric or intestinal symptoms to avoid this bias, we were not able to exclude an inflammatory condition endoscopically. However, considering that the purpose of FDG PET/CT is to distinguish between malignant and benign conditions, even if PPIs have an anti-inflammatory effect, it is obvious that it will contribute to this major purpose.

The limitations of our study are that it is retrospective.

CONCLUSION

Our findings indicate that intravenous administration of a PPI before FDG PET/CT imaging can decrease the FDG uptake in the gastrointestinal tract. We think that this practice can reduce false positive findings in the gastrointestinal system and help identifying gastric and intestinal cancers by reducing background activity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diyarbakır Training and Research Hospital Ethics Committee (Date: 21.04.2022, Decision No: 72).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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