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SHORT COMMUNICATION

High and typical ^{18}F-FDG bowel uptake in patients treated with metformin

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Abstract
Purpose This prospective and bi-centric study was conducted in order to determine the impact of antidiabetic treatments (AD) on ^{18}F-FDG bowel uptake in type 2 diabetic patients.
Methods Fifty-five patients with previously diagnosed and treated type 2 diabetes mellitus (group 1) were divided in two subgroups: AD treatment including metformin (n=32; group 1a) and AD treatment excluding metformin (n=23; group 1b). The 95 patients without diabetes mellitus made up controls (group 2). ^{18}F-FDG uptake in small intestine and colon was visually graded and semi-quantitatively measured using the maximum standardized uptake value.
Results ^{18}F-FDG bowel uptake was significantly increased in AD patients (group 1) as compared to controls (group 2) ($p<0.001$). Bowel uptake was significantly higher in AD patients including metformin (group 1a) as compared to AD patients excluding metformin (group 1b) ($p<0.01$), whose bowel uptake was not significantly different from controls (group 2). A metformin treatment was predictive of an increased bowel uptake in the small intestine (odds ratio OR=16.9, $p<0.0001$) and in the colon (OR=95.3, $p<0.0001$), independently of the other factors considered in the multivariate analysis. Bowel uptake pattern in the patients treated with metformin was typically intense, diffuse and continuous along the bowel, strongly predominant in the colon, in both the digestive wall and lumen.
Conclusion This study emphasizes that metformin significantly increases ^{18}F-FDG uptake in colon and, to a lesser extent, in small intestine. It raises the question of stopping metformin treatment before an ^{18}F-FDG PET/CT scan is performed for intra-abdominal neoplasic lesion assessment.

Keywords ^{18}F-FDG PET/CT · Antidiabetic · Metformin · Bowel uptake

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Introduction

Many patients treated with oral antidiabetic medications are referred for an ^{18}F-FDG PET scan for carcinologic reasons. As a rule, an intense ^{18}F-FDG accumulation suggests the presence of malignant tumour. However, increased non-pathological ^{18}F-FDG uptakes are frequently seen. In our experience, we often observed a high and diffuse bowel ^{18}F-FDG uptake in type 2 diabetic patients. Therefore we decided to conduct a prospective and bi-centric study in order to determine whether or not antidiabetic treatments (AD) affect the ^{18}F-FDG bowel uptake.

Material and methods

Patients

One hundred and fifty patients, who underwent an ^{18}F-FDG PET/CT scan between October 2005 and August 2006, were prospectively included in this study.

One hundred and eighteen patients were imaged in the Cancer Research Center René Huguenin, the remaining 32 patients in the University Hospital of Strasbourg. In both institutions, the same imaging material and protocols were used.

For the study purposes, the patients were divided in groups, as described below:

Group 1: Type 2 diabetic patients

Fifty-five patients (33 males, 22 females, mean age 66.6±7.3 years) with a previously diagnosed type 2 diabetes mellitus, treated by oral antidiabetics (AD), in some cases associated with insulin, were included.

Group 1 patients were divided in two subgroups: patients treated with metformin (alone or in association with other antidiabetics) (n=32; group 1a) and patients treated with antidiabetics excluding metformin (n=23; group 1b).

Group 2: Control patients

Ninety-five patients without diabetes mellitus (41 males, 54 females, mean age 55.4±16.2 years) were included.

Exclusion criteria for groups 1 and 2 were patients with type 1 diabetes (insulin dependent), under 18 years old, referred for colorectal and/or peritoneal carcinoma, with a previous history of inflammatory bowel disease, with recent infectious colitis or with gastrointestinal symptoms such as abdominal pain or diarrhoea.

Patients were asked about their medical history and especially if they presented type 2 diabetes mellitus.

Types of antidiabetic treatments, blood glucose level, body weight, age, sex and injected ^{18}F-FDG activity were recorded for each patient.

Patient approval or information was not required for review of patient files and images by our Institutional Review Board.

PET/CT acquisitions

PET/CT studies were performed using a combined PET/CT scanner (Discovery LS, GE Healthcare). Patients were asked to fast for at least 6 h before ^{18}F-FDG injection. Blood glucose level was determined in capillary blood samples before ^{18}F-FDG injection. In our department, the cut-off blood glucose level that contraindicates ^{18}F-FDG injection is 8 mmol/l. PET images were acquired 1 h after injection of 4–5 MBq/kg of ^{18}F-FDG on a 2D mode, from the skull to the mid-thigh, with five to seven bed positions of 4 min each. CT images were used for attenuation correction and fusion; no contrast medium was used. Helical CT was acquired first with the following parameters: 40 mAs, 140 kV and 5-mm section thickness. Whole-body CT was performed in a craniocaudal direction. Immediately afterwards, PET data were collected in a caudocranial direction. The CT data were matched and fused with the PET data.

Data analyses

Attenuation-corrected PET images, CT images and PET/CT fused images were displayed using dedicated software (Xeleris workstation, GE Healthcare).

PET/CT images were evaluated visually and semi-quantitatively by two nuclear medicine physicians (EG, CB), who were blinded to the subjects' group status. Both physicians worked separately; then, in case of discrepancies, they reviewed the images together in order to reach a consensus.

Small bowel and colon uptakes were visually assessed and graded according to a four-point scale, as follows (Fig. 1):

- grade 1: lower than the background hepatic activity;
- grade 2: similar to that of the liver;

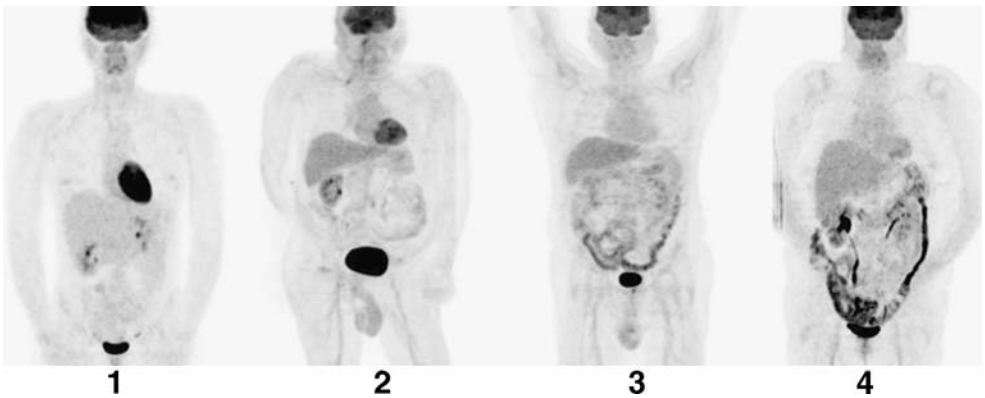

Fig. 1 Visually grading scale (maximal intensity projection images). 1: Uptake less than the background hepatic activity; 2: uptake similar to that of the liver; 3: uptake moderately greater than the hepatic activity; 4: intense and diffuse uptake

– grade 3: moderately higher than the hepatic activity;
– grade 4: intense and diffuse uptake.

A semi-quantitative analysis of ^{18}F-FDG activity was obtained by recording the maximum standardized uptake value (SUVmax) in different bowel segments by placing regions of interest (1-cm diameter circle) on transverse slices. Three measures were made on small bowel segments:

– 1: on the third duodenum, with the pancreas used as a landmark;
– 2: on the jejunum, closed to the mid-height of the descending colon;
– 3: on the distal ileum loop, in the place where it connects with the caecum.

Four measures were made on colic segments:

– 1: on the caecum;
– 2: on the hepatic flexure;
– 3: on the splenic flexure;
– 4: on the descending colon-sigmoid junction.

Semi-quantitative means of SUVmax were calculated for the small bowel (mean small intestine) and the colon (mean colon).

Statistical analyses

Statistical analyses were performed using a SEM statistical package. Before the study, no hypothesis for directional outcome was made. Unpaired tests were used: chi-square test and Yates correction chi-square test for qualitative analyses and the Kruskal-Wallis test for quantitative analyses. A multiple logistic regression step-by-step model, using age, sex, body weight, injected ^{18}F-FDG activity, blood glucose level and type of antidiabetic treatment, were used to assess the contribution of these factors to the intestinal ^{18}F-FDG uptake (the median value was used as a cut-off). Odd ratios (OR) were presented with 95% confidence interval (CI). All reported p values were two-sided, and a p value ≤ 0.05 was considered significant.

Results

^{18}F-FDG bowel uptake was significantly increased in AD patients (group 1) as compared to control subjects (group 2). This increase in ^{18}F-FDG bowel uptake concerned the colon and, to a lesser extent, the small intestine, excepting the duodenum, for both visual ($p<0.001$ for small intestine, $p<0.0001$ for colon) and semi-quantitative evaluations ($p<0.0001$ for small intestine and for colon) (Table 1).

^{18}F-FDG bowel uptake was significantly higher in subjects treated with AD including metformin (group 1a), as compared to subjects treated with AD excluding metformin (group 1b) ($p<0.01$) (Table 2).

Table 1 Bowel uptake in patients treated with AD (group 1) and control patients (group 2): visual analysis, semi-quantitative measures and p value

	Grades of uptake	Group 1 (n=55)	Group 2 (n=95)	p value
Visual analysis				
Small intestine	1–2	44 (80%)	94 (98.9%)	<0.001*
	3–4	11 (20%)	1 (1.1%)	
Colon	1–2	26 (47.3%)	84 (88.4%)	<0.0001*
	3–4	29 (52.7%)	11 (11.6%)	
Semi-quantitative measures				
		SUVmax mean± ST(median)	SUVmax mean± ST(median)	
Duodenum		2.13±0.75 (2.1)	1.93±0.65 (2.0)	*NS***
Jejunum		2.61±1.24 (2.2)	1.96±0.59 (1.9)	<0.0001*
Ileum		3.50±2.39 (2.5)	1.77±0.57 (1.6)	<0.0001*
Caecum		4.01±2.46 (3.2)	2.32±1.35 (1.9)	<0.0001*
Hepatic flexure		3.93±2.37 (3.5)	2.06±1.43 (1.7)	<0.0001*
Splenic flexure		4.09±3.07 (3.2)	1.88±1.49 (1.4)	<0.0001*
Colo-sigmoid jonction		5.81±4.21 (4.6)	2.62±1.40 (2.2)	<0.0001*
Mean small intestine		2.75±1.08 (2.5)	1.89±0.43 (1.9)	<0.0001*
Mean colon		4.47±2.68 (4.0)	2.23±1.17 (1.9)	<0.0001*

AD: antidiabetics treatment, * statistically significant values, **not significant.

^{18}F-FDG bowel uptake was significantly higher in patients treated with AD including metformin (group 1a) than the control group (group 2) ($p<0.0001$ for small intestine and colon with visual and semi-quantitative evaluations). On the other hand there was not a significant difference between patients treated with AD excluding metformin (group 1b) and the control group (group 2) (for small intestine and colon with both evaluations).

The typical increase of ^{18}F-FDG bowel uptake due to metformin was intense, diffuse and continuous along the bowel, strongly predominant in colon in both the digestive wall and lumen (Fig. 2).

Metformin treatment was predictive of an increase of ^{18}F-FDG bowel uptake in small intestine [OR=16.9, 95% CI=(4.3–66.5) $p<0.0001$] and colon [OR=95.3, 95% CI=(10.6–853) $p<0.0001$], independently of the other factors included in the multivariate analysis (body weight, injected ^{18}F-FDG activity, blood glucose level, sex, age and type of treatment).

Discussion

Intestinal and colonic non-specific ^{18}F-FDG uptake is quite frequent on ^{18}F-FDG imaging and often relates to a physiologic origin. The mechanisms of this uptake are unclear, and several hypotheses have been suggested, including uptake by the smooth muscles, by the lymphoid tissue and the superficial mucosal cells and also ^{18}F-FDG excretion in the stool.

Table 2 Bowel uptake in subjects treated with AD including metformin (group 1a) and excluding metformin (group 1b): visual analysis, semi-quantitative measures and p value

	Grades of uptake	Group 1a (n=32)	Group 1b (n=23)	p value
Visual analysis				
Small intestine	1–2	21 (66%)	23 (100%)	=0.005*
	3–4	11 (34%)	0 (0%)	
Colon	1–2	7 (22%)	19 (83%)	<0.0001*
	3–4	25 (78%)	4 (17%)	
Semi-quantitative measures				
		SUVmax	SUVmax	
Mean small intestine		3.27	2.03	<0.0001*
Mean colon		5.98	2.37	<0.0001*

AD: antidiabetics treatment, *statistically significant values, **not significant.

Metformin (dimethylbiguanide) is the only oral biguanid used in the treatment of type 2 diabetes mellitus. Its main gluco-regulatory effects involve suppression of hepatic glucose output, increased peripheral glucose utilization, reduced fatty acid utilization and increased glucose turnover, especially in the splanchnic bed [1]. This drug accumulates preferentially in the villous lacteals of small intestine in rodents, independently of the route of administration [2]. The intestine wall cells are exposed to much higher concentrations of metformin for much longer periods than other cell types [3, 4]. In metformin-treated insulin-resistant obese rats, metformin enhances glucose transfer from the vascular compartment into cells of the intestinal mucosa and increases glucose utilization: the digestive tract is the only tissue responsible for a large glucose utilization enhancement [5]. In rats under hyperglycaemic hyperinsulinaemic conditions, metformin can produce more than a 60% increase in glucose utilization by the intestine [6].

The intracellular action of metformin seems to result from an increased anaerobic glucose metabolism to lactate [3, 4, 7] and an activation of AMP-activated protein kinase (AMPK), inducing an up-regulation of glucose transporters, notably type GLUT-1, GLUT-2 and GLUT-4 [4, 8, 9].

In our study, visual analysis of ^{18}F-FDG bowel uptake in patients treated with metformin shows that it is partially localised in the digestive lumen, suggesting that part of ^{18}F-FDG is excreted in the stool as previously hypothesized by Kim et al. [10]. This hypothesis has to be verified by measuring the stool radioactivity after ^{18}F-FDG injection.

Conclusion

This study shows that metformin significantly increases ^{18}F-FDG uptake in colon and to a lesser extent in small intestine. This increase is typically intense, diffuse and continuous along the bowel, strongly predominant in colon in both digestive wall and lumen. It cannot be confused

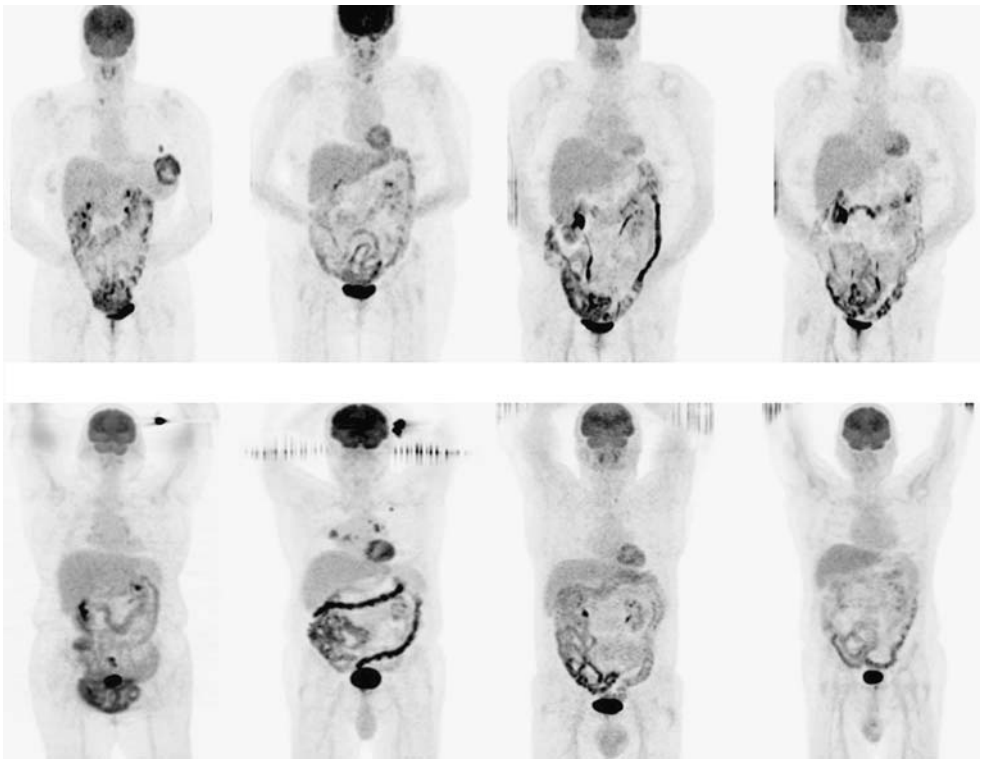

Fig. 2 Maximal intensity projection images of eight patients who took metformin the morning before their ^{18}F-FDG PET/CT scan

with malignant focal bowel uptake, but it can mask an actual neoplasic bowel ^{18}F-FDG focal uptake and can induce false-negative results.

Our findings raise the question of stopping metformin treatment before an ^{18}F-FDG imaging in case of a suspected intra-abdominal neoplasic lesion (peritoneal carcinomatosis, colic or gynaecological neoplasm) and of replacing it, if possible, by another antidiabetic medication to keep the patient's blood glucose level in normal range.

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