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ORIGINAL ARTICLE

Metformin Discontinuation for 48 Hours Reduces Intestinal Fluorodeoxyglucose Uptake in ^{18}F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

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ABSTRACT

Objective: *To evaluate the effect of 48-hour metformin discontinuation on bowel fluorodeoxyglucose (FDG) uptake in a Chinese population undergoing ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging.*

Methods: *All patients with known type 2 diabetes mellitus treated with metformin who had had a previous FDG PET/CT examination performed in our centre, and who were scheduled for a second FDG PET/CT examination within 1 year of the first one, were recruited. These subjects were advised to stop metformin for 48 hours prior to the second examination. The intestinal uptakes were graded visually by a four-point scale and semiquantitatively by maximum standardised uptake value (SUVmax) of small and large bowel segments. Any differences in intestinal uptake, as well as other differences in examination day blood glucose levels between the two successive examinations were compared.*

Results: *In total, 44 patients were included. Metformin discontinuation resulted in a significant reduction in small and large bowel uptake by visual scoring. The SUVmax values were significantly lower in all bowel segments except duodenum. Examination day blood glucose levels after 48-hour metformin discontinuation were <11 mmol/L, in all examinations.*

Conclusion: *Metformin discontinuation for 48 hours prior to scanning significantly reduced intestinal uptake and should be considered as a method to improve PET/CT interpretation.*

Key Words: *Diabetes mellitus; Fluorodeoxyglucose F18; Metformin; Positron-emission tomography; Tomography, X-ray computed*

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Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: The study was approved by the Research Ethics Committee (Kowloon Central / Kowloon East) under Kowloon Central Cluster of Hospital Authority, Hong Kong (Ref KC.KE-19-0048/ER-4).

中文摘要

停用二甲雙胍48小時可降低FDG PET/CT中的腸道FDG攝取

吳官橋、許殷豪、朱競新、龔本霆、歐陽定勤

目的：在接受氟化去氧葡萄糖正電子及電腦雙融掃描（FDG PET/CT）成像的華籍人口中，評估停用二甲雙胍48小時對腸道FDG攝取的影響。

方法：納入所有接受二甲雙胍治療的已知2型糖尿病患者。他們曾於我們中心進行FDG PET/CT檢查，以及將於首次FDG PET/CT檢查後1年內進行第二次FDG PET/CT檢查，建議這些受試者在第二次檢查前48小時停用二甲雙胍。通過視覺評估將腸道FDG攝取程度分為四級，並通過小腸及大腸段的最大標準化攝取值 (SUVmax) 進行半定量。比較兩次連續檢查之間腸道FDG攝取的差異以及檢查日血糖水平的其他差異。

結果：共納入44例患者。視覺評估顯示停用二甲雙胍能顯著減少小腸及大腸FDG攝取。除十二指腸外，所有腸段的SUVmax值均顯著降低。在所有檢查中，停用二甲雙胍48小時後的檢查日血糖水平均<11 mmol/L。

結論：掃描前48小時停用二甲雙胍可顯著降低腸道攝取，可考慮作為改進PET/CT顯示的方法。

INTRODUCTION

Metformin is an oral antihyperglycaemic agent commonly used in non-insulin dependent (type II) diabetes mellitus. It is known to be associated with typically intense, diffuse, and continuous uptake along the bowel in ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT).[1] This can pose difficulty in FDG PET/CT interpretation by obscuring bowel lesions or adjacent extra-intestinal structures. In FDG PET/CT, a particular concern of metformin discontinuation is the effect on blood glucose levels, which, if >11 mmol/L,[2] may delay FDG PET/CT scanning.

Previous studies on metformin discontinuation in non-Chinese populations had different study designs and showed conflicting results in the effect of metformin discontinuation on examination day blood glucose levels.[3,4] The purpose of this study was to evaluate the effect of 48-hour metformin discontinuation on reducing bowel FDG uptake in a Chinese population undergoing FDG PET/CT, and the effect on blood glucose levels.

METHODS

Patient Recruitment

This was a prospective single-centre study with all patients recruited from January 2019 to July 2019 who were referred to our PET/CT centre for ongoing assessment of various neoplastic conditions. Inclusion criteria were patients with type II diabetes being treated with metformin as monotherapy or as part of polydrug therapy, and who had undergone a previous FDG PET/CT in our centre within the past year.

Exclusion criteria were patients with known gastrointestinal malignancy, previous bowel resection, or other intra-abdominal pathology that might affect bowel uptake, e.g., an enterovesical fistula that might cause the appearance of urinary excretion of FDG into the bowel (Table 1).

Patients were instructed to stop taking metformin for 48 hours prior to undergoing the second FDG PET/CT study in our centre. Patients were interviewed on arrival to PET/CT centre by nursing staff to confirm metformin stoppage. Patients were also reminded to resume metformin after PET/CT study was completed.

Patients' blood glucose levels were checked and FDG was only injected if they measured <11 mmol/L, in accordance with local protocol and international guidelines.[3] Other parameters, including body weight, age, sex, metformin daily dosage, injected ^{18}F-FDG activity, and uptake time were recorded for each patient.

Table 1. Excluded conditions (n = 8) and frequency of occurrence.

Excluded condition	Frequency
Known gastrointestinal malignancy	3 (2 colorectal cancers; 1 GIST)
Previous bowel surgery	1 (colostomy)
Other intra-abdominal pathology which affected bowel uptake	1 (enterovesical fistula)
Failure to comply with metformin stoppage in the second PET/CT study	3 (2 stopped metformin only for 24 h; 1 did not stopped taking metformin in the second PET/CT study)

Abbreviations: GIST = gastrointestinal stromal tumour; PET/CT = positron emission tomography/computed tomography.

^{18}F-fluorodeoxyglucose Positron Emission Tomography and Computed Tomography Acquisition

The two PET/CT studies were performed in each patient using the same integrated PET/CT scanner (Discovery 710, General Electric, Milwaukee [WI], United States) at Queen Elizabeth Hospital, Hong Kong. Patients were instructed to fast for at least 6 hours before ^{18}F-FDG injection. Blood glucose levels were measured and the FDG PET/CT was only performed if blood glucose level was <11 mmol/L. Patients were injected with 370 MBq (for normal-weight patients) or 555 MBq (for patients with body weight >80 kg) according to department protocol. Actual dose administered ranged from 347 to 609 MBq, as measured by dose calibrator. Acquisition commenced 60 minutes after FDG administration. CT scanning for anatomical localisation and attenuation correction was performed with the following parameters: 120-kV tube voltage, 120-mA tube current, 0.5-s gantry rotation time, and 0.984 pitch. The PET images were acquired in three-dimensional mode, from skull to mid-thigh with 2 minutes for each bed position. The PET raw data were processed using ordered subset expectation maximisation, point spread function modelling, and time-of-flight (four iterations with 18 subsets and 5.5-mm cut-off frequency). The data were reconstructed with 3.75-mm section thickness in a 256- × 256-mm matrix and processed through a standard filter.

Image Analysis

Attenuation-corrected PET images, maximal intensity projection images, CT images, and PET/CT fused images were generated and displayed using a dedicated workstation, AW VolumeShare 7 (AW 4.7 Ext. 8 Software, General Electric). The FDG uptake was graded both visually and semiquantitatively over different bowel segments by an observer with 5 years of experience in PET/CT.

Visual Analysis

A four-point score scale described by Gontier et al[1] was used for visual assessment of the small and large bowel FDG uptake: Grade 1 (lower than hepatic activity); Grade 2 (similar to hepatic activity); Grade 3 (moderately higher than hepatic activity); and Grade 4 (diffuse and intense uptake).

Semiquantitative Analysis

Semiquantitative analysis of the FDG uptake over different bowel segments was performed using maximum standardised uptake value (SUVmax). The SUVmax was measured using a region of interest of 1 cm in diameter over the predefined anatomical locations, including: horizontal portion of duodenum using the pancreatic head as landmark; jejunum measured at mid-height of descending colon; distal ileum adjacent to the ileocaecal valve; caecum; hepatic flexure; splenic flexure; and junction between descending colon and sigmoid colon.

Statistical Analysis

Statistical analysis was performed using SPSS (Windows version 22.0; IBM Corp, Armonk [NY], United States). A paired-sample t test was used for comparison of visual analysis scores and SUVmax measurements between the two successive PET/CT studies. A p value <0.05 was considered significant.

RESULTS

Patient Characteristics

In total, 44 patients were recruited. Two patients who stopped metformin only for 24 hours and one patient who did not stop taking metformin in the second PET/CT study were excluded. A total of 41 patients (23 men, 18 women) with mean age of 67.2 ± 10.7 years were included in the final analysis. Patients' parameters including weight, body mass index, and metformin daily dose between the two scans were unchanged. The injected doses (402.1 MBq ± 54.1 vs. 409.7 MBq ± 51.7; p = 0.299) and time between injection and imaging between the two scans showed no statistically significant difference (Table 2).

Effect of Metformin Discontinuation on Intestinal Fluorodeoxyglucose Uptake

Small and large bowel FDG uptakes were significantly reduced in the second FDG PET/CT study with metformin stoppage for 48 hours, measured by visual

Table 2. Summary of patient and imaging parameters.

Patient and imaging parameters	FDG PET/CT on metformin	FDG PET/CT off metformin	p Value
Weight, kg	64.3 ± 14.1	63.2 ± 13.5	0.053
BMI, kg/m^2	24.6 ± 4.5	24.2 ± 4.4	0.068
Injected dose of FDG, MBq	402.1 ± 54.1	409.7 ± 51.7	0.299
Uptake time, min	60.1 ± 3.0	59.5 ± 2.9	0.331
Examination day blood glucose level, mmol/L	6.8 ± 1.6 (4.1-11.0)*	7.8 ± 1.8 (4.8-11.0)*	0.003

Abbreviations: BMI = body mass index; FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.
* Data are shown as mean ± standard deviation (range).

Table 3. Results of the semiquantitative analysis (SUVmax) of bowel uptakes in the two consecutive PET/CT studies before and after stopping metformin.*

Bowel segments	Continued metformin	Stopped metformin for 48 h	p Value
Duodenum	2.38 ± 1.04	2.14 ± 0.40	0.125
Jejunum	3.21 ± 1.69	2.57 ± 0.78	0.028
Distal ileum	5.47 ± 2.41	2.79 ± 0.99	<0.001
Caecum	6.54 ± 3.39	2.93 ± 1.24	<0.001
Hepatic flexure	5.80 ± 3.14	2.82 ± 1.45	<0.001
Splenic flexure	4.96 ± 2.04	3.17 ± 1.63	<0.001
Sigmoid colon	7.92 ± 2.64	5.83 ± 2.31	<0.001

Abbreviations: PET/CT = positron emission tomography/computed tomography; SUVmax = maximum standardised uptake value.
* Data are shown as mean ± standard deviation of the SUVmax.

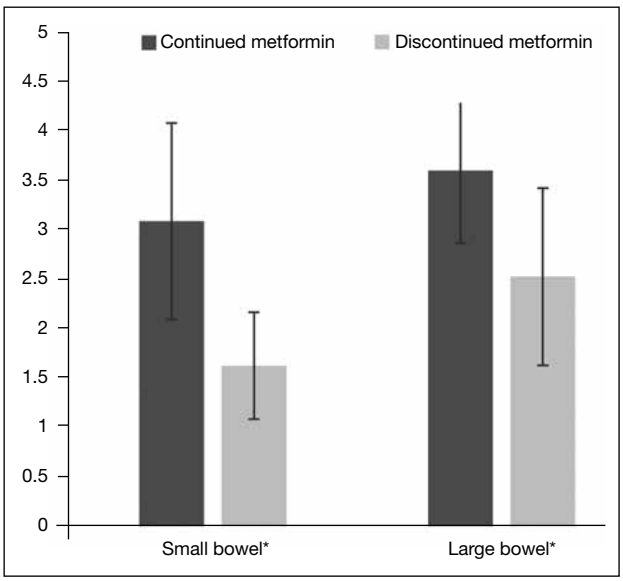

Figure 1. Histogram plot showing mean visual analysis scores between the two successive FDG PET/CT examinations. Error bars indicate standard deviations. Asterisks indicate statistical significance.
Abbreviation: FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.

scoring and SUVmax. Significant differences in visual scoring of the bowel uptake were found in small bowel (3.10 ± 1.00 vs. 1.63 ± 0.73) and large bowel (3.61 ± 0.54 vs. 2.54 ± 0.90). For semiquantitative analysis, there was a significantly lower SUVmax over all the predefined bowel segments except at the duodenum (Table 3, Figure 1).

Effect of Metformin Discontinuation on Examination Day Blood Glucose Level

Metformin daily dosage among the patients recruited ranged from 500 to 2000 mg/d and were not changed between the two PET/CT studies. A mean increase in examination day blood glucose level of 1.07 mmol/L was found when metformin was withheld for 48 hours. All patients in this study had blood glucose levels <11 mmol/L after discontinuation of metformin and did not require injection of short-acting insulin.

Illustrative Case with Focal Bowel Uptake after Metformin Discontinuation

In a patient with history of renal cell carcinoma, there was focal uptake in the caecum in the second FDG PET/CT study performed after metformin discontinuation (Figure 2). This focal uptake was not discernible in the first FDG PET/CT with the presence of metformin-related intense bowel activity. The large bowel uptakes were scored Grade 4 and Grade 1, respectively, in the two consecutive PET/CT studies according to the visual analysis score.

DISCUSSION

The exact mechanism of how metformin affects intestinal glucose uptake and, hence, bowel FDG uptake, is not entirely known. Ethnic differences in response to metformin therapy have been reported.[5-7] Thus a local population study to evaluate the effect of metformin on bowel FDG uptake is warranted before implementing changes in our imaging protocol. To the best of our

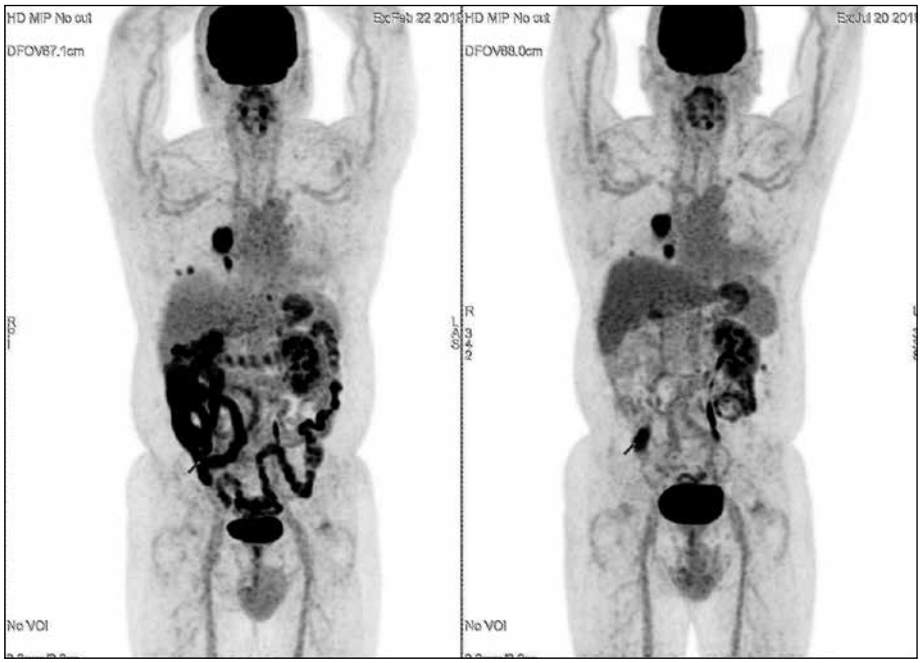

Figure 2. A case of renal cell carcinoma of the right kidney with lung metastases in a 64-year-old man was referred for follow-up FDG PET/CT. MIP image of the FDG PET-CT study on metformin (a) showing intense small and large bowel activity of grade 4 by the visual score scale. MIP image of the second FDG PET-CT study after metformin discontinuation showed focal uptake in the caecum of SUVmax 6.7, now discernible with reduced large bowel uptake of grade 1. The patient was advised to undergo colonoscopy for evaluation.
Abbreviations: FDG PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; MIP = maximal intensity projection; SUVmax = maximum standardised uptake value.

knowledge, this is the first study in a Chinese population that examined the effect of metformin discontinuation on intestinal FDG uptake. Our study showed that metformin discontinuation for 48 hours is effective in reducing bowel FDG uptake in our local population with results comparable to those of prior studies.[8,9]

In FDG PET/CT study a practical consideration in suspending metformin is the potential effect on blood glucose levels on the day of the examination. According to the European Association of Nuclear Medicine procedure guidelines for tumour imaging, a FDG PET/CT study should be delayed or rescheduled if the blood glucose level is >11 mmol/L. This would create problems in PET centre scheduling and, more importantly, a delay in diagnosis. Contrary to previous study[6] which asked patients to stop all antihyperglycaemic drugs, we specifically asked patients to suspend only metformin, whilst continuing other glucose-lowering medication(s). Slightly higher examination day blood glucose levels were observed with metformin discontinuation, but all patients had blood glucose levels <11 mmol/L, thus allowing timely performance of FDG PET/CT studies.

One merit of performing FDG PET/CT after metformin discontinuation is that the reduced bowel uptake facilitates potential bowel lesion detection, as illustrated by a case in our study where an incidental focal colonic uptake in the caecum was only detected in the second FDG PET/CT performed after metformin discontinuation. The identification of focal colonic uptake is of important clinical significance in FDG PET/CT, as the reported pooled risk of malignant or pre-malignant lesions appearing as focal colonic uptake on FDG PET/CT was 68% in a meta-analysis[9] and the authors stated that further investigation is warranted whenever focal colonic uptake is detected. Similar findings regarding focal colonic uptake and underlying colonic polypoid lesion detection in FDG PET/CT have also been reported in our centre, with a prevalence of focal colonic uptake of 4.8%, comparable to previous studies.[10,11] It has been suggested that increased bowel activity (SUVmax >5.9) encountered without discontinuing metformin would obscure focal colonic uptake detection and hinder appropriate management, such as colonoscopy or virtual colonoscopy according to an evidence-based review.[12] Further study is warranted to evaluate the true incidence of focal colonic uptake after metformin discontinuation.

There are limitations to our study. First, this was a single-centre study with a relatively limited number of patients recruited. Second, it was a single-observer non-blinded study, making it prone to observer bias. However, we adopted the visual scale taking the liver uptake as an internal reference, which is relatively consistent even

in the presence of diffuse liver disease.[13-15] We also predefined anatomical localisations of bowel segments to reduce sampling bias and achieve higher reproducibility.

CONCLUSION

In summary, discontinuation of metformin for 48 hours prior to FDG injection and scanning significantly reduced bowel FDG uptake, which may facilitate bowel lesion detection. It is an effective and feasible preparation for FDG PET/CT studies and should be considered in diabetic patients treated with metformin.

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