Diabetology International
https://doi.org/10.1007/s13340-021-00545-y

COMMENTARY

Metformin action in the gut—insight provided by [^{18}F]FDG PET imaging

Hitomi Tsuchida[1] · Yasuko Morita[1] · Munenobu Nogami[2] · Wataru Ogawa[1]

Received: 30 August 2021

Abstract

Suppression of hepatic gluconeogenesis is thought to largely underlie the antidiabetes action of metformin. However, this drug also exerts various effects on the gut, one of which is the enhancement of the uptake of ^{18}F-labeled fluorodeoxyglucose (FDG), a nonmetabolizable glucose derivative, during [^{18}F]FDG positron emission tomography (PET)–computed tomography (CT). Whereas the relevance of this effect to the glucose-lowering action of metformin remains unclear, it is of special interest because it was discovered in humans. Cessation of metformin treatment for several days is required to normalize [^{18}F]FDG uptake in the intestine, suggesting that the enhanced uptake is not a direct effect of the drug in the circulation but rather a prolonged secondary effect. A recent study with state-of-the-art PET–magnetic resonance imaging (MRI), which provides better tissue registration and soft-tissue contrast compared with PET-CT, revealed that metformin-induced accumulation of [^{18}F]FDG occurs primarily in the lumen of the intestine, indicating that the drug promotes excretion of glucose from the circulation into this space. This phenomenon does not necessarily imply that metformin stimulates the removal of glucose from the body in the stool. Instead, it might be related to changes in the abundance and metabolism of the gut microbiota induced by metformin. Further studies of this effect of metformin might shed light on the unanswered questions that still remain concerning the clinical action of this old drug.

Keywords Metformin · Intestine · FDG PET · Glucose excretion · PET-MRI · Gut microbiota

Introduction

Whereas suppression of gluconeogenesis in the liver appears to be of primary importance for the hypoglycemic effect of metformin [1–4], the entire picture of the pharmacological action of this drug remains unclear. One ambiguity in this regard is that the half-life of metformin in the circulation is short, on the order of 2.0 to 6.0 h [5], which is inconsistent with the impression of clinicians for glucose-lowering effect of this drug, suggestive of the operation of a mechanism (or mechanisms) independent of the drug concentration in the circulation. Given that orally administered metformin remains in the intestine for a relatively long period [6], pharmacological effects on the intestine may explain this inconsistency. Several effects of metformin on the intestine have been identified, including suppression of glucose absorption [7, 8], changes in the intestinal flora [9–11], increased secretion of humoral factors such as glucagon-like peptide–1 (GLP-1) [12–14] and growth/differentiation factor 15 (GDF15) [15, 16], and stimulation of neural signaling at the duodenum that also results in the inhibition of hepatic glucose production [17]. How and to what extent these effects on the gut are responsible for the antidiabetes action of metformin remain unknown, however.

Positron emission tomography (PET)–computed tomography (CT) with ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG), a nonmetabolizable glucose derivative, is widely performed to detect malignancy or inflammation, which are associated with increased uptake of glucose, and hence of [^{18}F]FDG, compared with normal tissues. In 2008, Gontier et al. found that the uptake of [^{18}F]FDG in the intestine was enhanced in individuals treated with metformin [18], an observation that was subsequently confirmed by many other investigators [19, 20]

✉ Wataru Ogawa
ogawa@med.kobe-u.ac.jp

[1] Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

[2] Department of Radiology, Kobe University Graduate School of Medicine, Kobe, Japan

Published online: 23 September 2021

and which indicated that metformin promotes the accumulation of glucose in the intestine. Whereas neither the underlying mechanism of this effect nor its relevance to the antidiabetes action of metformin is yet fully understood, the finding that metformin affects glucose handling in the intestine is of particular interest in that it was discovered in humans, whereas many effects of the drug have been identified and characterized in animals and not validated in humans. In this article, we summarize findings concerning metformin action in the gut as revealed by [^{18}F]FDG PET.

Antidiabetes medications and intestinal [^{18}F]FDG uptake during [^{18}F]FDG PET-CT

As the application of [^{18}F]FDG PET to the detection of malignant tumors became more common, radiologists noticed that some individuals with type 2 diabetes manifested nonpathological enhancement of [^{18}F]FDG uptake in the intestine. Gontier et al. first investigated the relation between treatment with antidiabetes drugs and [^{18}F]FDG uptake in individuals who underwent [^{18}F]FDG PET-CT [18]. They thus performed a prospective study to compare [^{18}F]FDG uptake in the intestine between nondiabetic subjects and patients with type 2 diabetes treated with or without metformin. They found that intestinal [^{18}F]FDG uptake was greater in type 2 diabetic patients treated with metformin than in those treated without metformin or in the nondiabetic subjects. This enhanced accumulation of [^{18}F]FDG in the metformin-treated individuals was observed in both the small and large intestine [18] (Fig. 1).

A subsequent retrospective analysis of [^{18}F]FDG PET-CT images of diabetic and nondiabetic subjects revealed that metformin use was associated with enhanced accumulation of [^{18}F]FDG in all compartments of the intestine analyzed (whole colon, ileum, cecum, and transverse, descending, and sigmoid colon), whereas sulfonylurea administration was associated with enhanced [^{18}F]FDG accumulation in the ileum and transverse colon [19]. A randomized controlled study confirmed the stimulatory effect of metformin on intestinal [^{18}F]FDG uptake. Koffert et al. thus randomly assigned newly diagnosed type 2 diabetic subjects to groups treated with metformin, rosiglitazone, or placebo and subjected these individuals to [^{18}F]FDG PET-CT before and 26 weeks after the onset of treatment [20]. They found that treatment with metformin increased [^{18}F]FDG accumulation in the small and large intestine by a factor of 2 and 3, respectively, whereas rosiglitazone induced only a small increase (~ 15%) in [^{18}F]FDG accumulation in the small intestine.

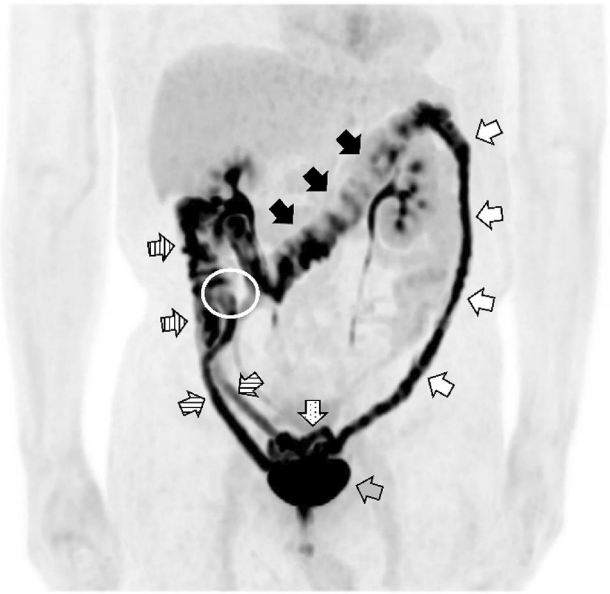

Fig. 1 Representative [^{18}F]FDG PET-MRI image of a metformin-treated individual. The image was obtained from a 56-year-old man with type 2 diabetes who was taking 1,500 mg of metformin daily. Arrows with vertical stripes indicate the ascending colon, black arrows the transverse colon, white arrows the descending colon, horizontal-striped arrows the ileum, the dotted arrow the sigmoid colon, the grey arrow the bladder, and the white circle the terminal ileum

Discontinuation of metformin and intestinal [^{18}F]FDG accumulation

Given that exaggerated [^{18}F]FDG uptake hinders accurate image evaluation, the effect of discontinuation of metformin on such uptake was studied. Özülker et al. performed [^{18}F]FDG PET-CT with the same type 2 diabetic individuals on two separate occasions: during treatment with metformin and after cessation of the drug for 3 days [21]. The uptake of [^{18}F]FDG in both the small and large intestine as assessed by a visual score was reduced after cessation of metformin treatment. Compartment-specific analysis based on the maximum standardized uptake value (SUV_{max}), a semiquantitative index, revealed that [^{18}F]FDG uptake was decreased after metformin cessation in the ileum and colon but not in the duodenum and jejunum. A prospective study also showed that the high intestinal [^{18}F]FDG uptake in both the small and large intestine of individuals treated with metformin was markedly attenuated 2 days after drug cessation [22].

Lee et al. retrospectively analyzed [^{18}F]FDG PET-CT images of type 2 diabetic subjects obtained < 24 h, 24 to 48 h, or 48 to 72 h after cessation of metformin treatment and compared the intestinal [^{18}F]FDG uptake of these subjects with that of control individuals who did not take

metformin [23]. Compared with that in the control subjects, [18F]FDG uptake was enhanced from the ileum to the rectosigmoid colon, from the transverse to the rectosigmoid colon, and from the descending to the rectosigmoid colon in the individuals who had stopped metformin administration for < 24 h, 24 to 48 h, or 48 to 72 h, respectively. Schreuder et al. found that [18F]FDG uptake in the descending and rectosigmoid colon of type 2 diabetic subjects who had stopped metformin for > 48 h (but < 72 h) was still greater than that for individuals not treated with metformin, with the uptake in the transverse and rectosigmoid colon being greater in subjects who had stopped metformin for < 48 h than in those who had stopped the drug for > 48 h [24].

The normalization of [18F]FDG uptake observed after cessation of metformin administration thus provided additional evidence that the enhanced uptake apparent in metformin-treated individuals is triggered by the drug. However, the finding that such normalization remains incomplete for up to 72 h after drug discontinuation indicates that the enhancement of [18F]FDG uptake is the result not of a direct effect of metformin in the circulation but of an unidentified and prolonged secondary effect of the drug. How long it takes metformin to induce this intestinal effect remains unknown. Whereas administration of the drug for 26 weeks enhanced [18F]FDG uptake in the intestine [20], no human study has been performed with a shorter administration period. Metformin administration in drinking water for 48 h had no effect on intestinal [18F]FDG uptake in mice, whereas that for 1 month did enhance the uptake [25].

Compartment of [18F]FDG accumulation in the intestinal tract: wall or lumen?

Animal experiments have shown that treatment with metformin stimulates glucose utilization in the small intestine via anaerobic metabolism [26]. Moreover, lactic acid production in the portal vein is increased in humans taking metformin [27]. These observations suggested that metformin might increase the uptake and utilization of glucose in enterocytes, and that the enhanced accumulation of [18F]FDG detected in the intestine of metformin-treated individuals by PET-CT reflects glucose uptake by these cells. Treatment with metformin was indeed found to result in the accumulation of [18F]FDG in the wall of the small intestine in rats [20].

In human studies, repeat acquisition of [18F]FDG PET-CT images after ingestion of food revealed that radioactivity in the intestine appeared to move along the intestinal tract [28], and feces obtained after such imaging were found to contain radioactivity at a level corresponding to 3.8% to 54.5% of that in blood [29]. These observations thus indicated that intravenously administered [18F]FDG is transferred into the intestinal lumen. In addition, Gontier et al. showed that the accumulation of [18F]FDG in subjects taking metformin was localized, at least in part, to the intestinal lumen [18]. However, it is difficult to accurately discriminate [18F]FDG accumulation in the intestinal wall from that in the lumen by PET-CT, given that the PET and CT images are obtained sequentially and the occurrence of peristalsis hinders their precise superposition.

PET–magnetic resonance imaging (MRI) is a recently introduced imaging modality that enables simultaneous acquisition of metabolic information with PET and morphological information with high soft-tissue contrast by MRI. PET-MRI thus yields an accurate registration between PET and MRI images [30] and offers diagnostic advantages over PET-CT for the organs that move such as heart, lungs, liver, digestive tracts and skin [31]. Taking advantage of the benefits of PET-MRI, we studied the accumulation of [18F]FDG, with discrimination between the intestinal wall and lumen, in diabetic individuals [32] (Fig. 2). We found that [18F]FDG accumulation in the lumen of the ileum and the right and left hemicolon was greater in subjects treated with metformin than in those not treated with the drug. In contrast, [18F]FDG accumulation in the wall of any compartment of the intestine examined did not differ significantly between the two treatment groups [32]. Further examination of the relation between [18F]FDG accumulation in the intestinal lumen and various clinical parameters of subjects who underwent PET-MRI after taking metformin revealed that the dose of metformin

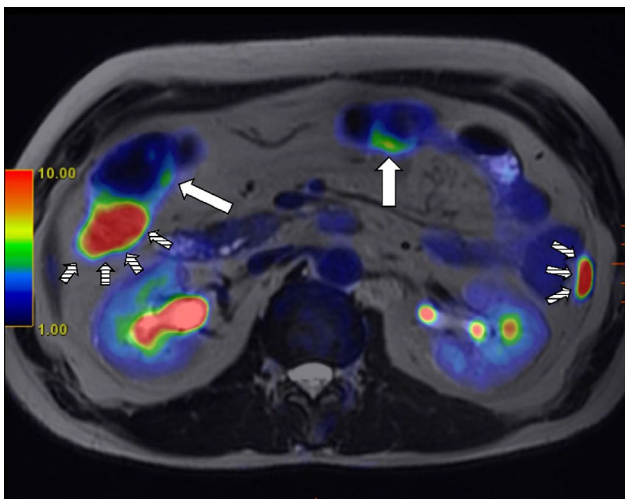

Fig. 2 Representative images of FDG accumulation at the wall and lumen of the intestine obtained with [18F]FDG PET-MRI. The image was obtained from the same individual described in Fig. 1. The color scale on the left side of the images represents SUV range between 1.0 and 10.0. White arrows indicate the intestinal wall and horizontal-striped arrows the intestinal lumen

was positively correlated with luminal [^{18}F]FDG accumulation in the large intestine [33].

Glucose in the intestinal lumen—How does it arrive and where does it go?

The study by Morita et al. [32] suggested that metformin stimulates the excretion of glucose into the intestinal lumen (the compartment containing stool). This phenomenon is thus similar to the excretion of glucose from the body into urine stimulated by SGLT2 (sodium-glucose cotransporter 2) inhibitors. However, it is unlikely that all the glucose excreted into the intestinal lumen is passed out from the body in the stool. When glucose is administered into the large intestine, it is not absorbed as glucose but as metabolites generated by gut microbiota [34]. Short-chain fatty acids (SCFAs) are key molecules in the symbiotic relation between the host and gut microbiota, and they exert various physiological actions including beneficial effects on host metabolism [35]. Metformin administration has been shown to increase the amount of SCFAs in stool [11] or serum [36], although the mechanism by which metformin affects SCFA production is unknown. It is possible that glucose excreted into the intestinal lumen in response to metformin treatment serves as a substrate for and thereby increases SCFA production by the gut microbiota [37]. Moreover, given that changes in energy source affect the composition of the intestinal flora [35], the excretion of glucose into the intestinal lumen might contribute to the metformin-induced changes in such composition (Fig. 3).

The mechanism by which glucose is excreted into the intestinal lumen in response to metformin administration is unknown. In general, ingested glucose is taken up by enterocytes via SGLT1 expressed at the apical surface of these cells and is then transported from the cells to the circulation by glucose transporter 2 (GLUT2) expressed at the basolateral surface. However, exposure of enterocytes to high glucose concentrations in the intestinal lumen induces the translocation of GLUT2 to the apical surface of the cells, which likely contributes to the efficient uptake of large amounts of glucose after meals [38]. Of note, metformin has also been shown to promote the translocation of GLUT2 to the apical surface of enterocytes both in vivo [39] and ex vivo [40] in a manner dependent on 5'-AMP–dependent protein kinase (AMPK) [41]. Given that the glucose transport activity of GLUT2 is bidirectional, the metformin-induced translocation of GLUT2 to the apical surface of enterocytes might contribute to glucose excretion into the intestinal lumen. A recent study revealed that Roux-en-Y gastric bypass, a widely adopted bariatric-metabolic surgery, promoted glucose excretion into the intraluminal space of the intestine in rats, an effect likely mediated by up-regulation of GLUT1 in enterocytes [42]. GLUT1 might thus also participate in the glucose excretion into the intraluminal space induced by metformin. Whichever GLUT isoform is involved in this process, the transport mode of each is passive and dependent on the concentration gradient of glucose. An amount of glucose sufficient to generate a concentration gradient would thus need to be transferred from the circulation to enterocytes to support glucose excretion into the intestinal

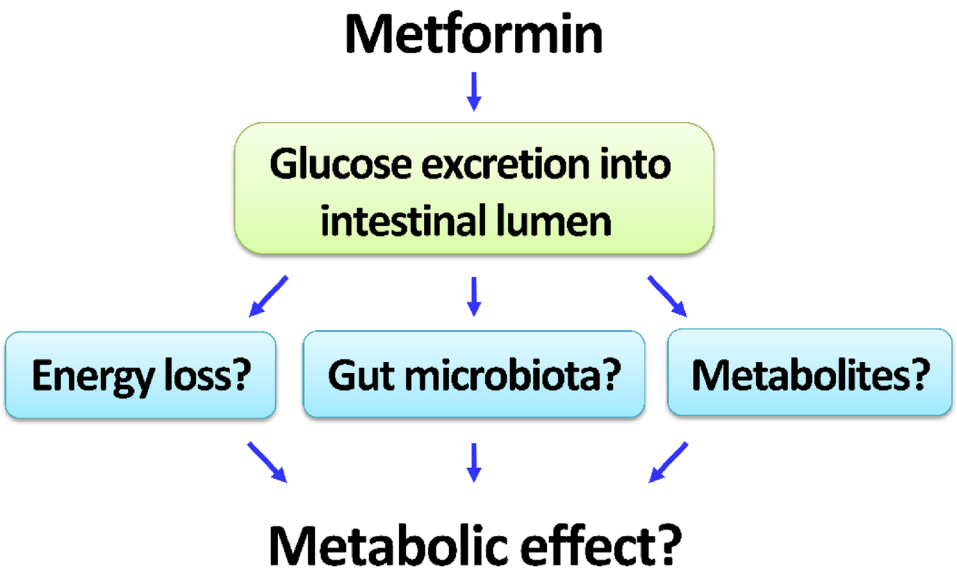

Fig. 3 Possible effects of metformin-induced glucose excretion into the intestinal lumen. Glucose excretion into the intestinal lumen induced by metformin may contribute to energy loss and changes in the abundance and metabolism of the gut microbiota, and thereby to the effects of the drug on host metabolism

lumen, but the mechanism responsible for the establishment of such a gradient remains unknown.

Conclusion

More than a decade after the discovery that metformin induces the accumulation of [^{18}F]FDG in the intestine, the application of PET-MRI, a state-of-the-art imaging modality, showed that the drug promotes excretion of the glucose derivative into the intestinal lumen. Although many questions remain regarding the clinical relevance of this phenomenon, it is of special interest because it was discovered and has been characterized in humans. Given that metformin increases luminal glucose accumulation in the large intestine [32, 33] and that the large intestine contains much greater abundance and diversity of microbiota than other compartments of the gastrointestinal tract [43], it is possible that metformin influences the functions of gut microbiota through the effect. Further studies are warranted to provide greater insight into various aspects of metformin treatment, including the apparent inconsistency between the duration of its clinical action and its pharmacokinetics as well as the mechanisms by which it affects the abundance and metabolism of the gut microbiota and additional mechanisms by which it modulates glucose metabolism.

Declarations

Conflicts of interest WO has received lecture fees from Dainippon-Sumitomo Pharma, Novartis, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, and Abbott Japan as well as research funding from Noster, Nippon Boehringer Ingelheim, Boehringer Ingelheim Pharma GmbH & Co. KG, Nippon Eli-Lilly, Novo Nordisk Pharma, Abbott Japan, Abbott Diabetes Care UK Ltd, Dainippon-Sumitomo Pharma. WO has received subsidies or donations from Kowa Pharmaceutical, Novo Nordisk Pharma, Astellas, Dainippon-Sumitomo Pharma, Ono Pharmaceutical, Takeda Pharmaceutical, Abbott Japan, Novartis, Daiichi Sankyo, Nippon Eli-Lilly, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim. The remaining authors (HT, YM, and MN) declare that they have no conflict of interest.

Research Involving Human Participants and/or Animals This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, Inzucchi SE, Schumann WC, Petersen KF, Landau BR, Shulman GI. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes. 2000;49:2063–9.
2. Hunter RW, Hughey CC, Lantier L, Sundelin EI, Peggie M, Zeqiraj E, Sicheri F, Jessen N, Wasserman DH, Sakamoto K. Metformin reduces liver glucose production by inhibition of fructose-1-6-bisphosphatase. Nat Med. 2018;24:1395–406.
3. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature. 2013;494:256–60.
4. Madiraju AK, Qiu Y, Perry RJ, Rahimi Y, Zhang XM, Zhang D, Camporez JG, Cline GW, Butrico GM, Kemp BE, Casals G, Steinberg GR, Vatner DF, Petersen KF, Shulman GI. Metformin inhibits gluconeogenesis via a redox-dependent mechanism in vivo. Nat Med. 2018;24:1384–94.
5. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 1996;30:359–71.
6. Wilcock C, Bailey CJ. Accumulation of metformin by tissues of the normal and diabetic mouse. Xenobiotica. 1994;24:49–57.
7. Ikeda T, Iwata K, Murakami H. Inhibitory effect of metformin on intestinal glucose absorption in the perfused rat intestine. Biochem Pharmacol. 2000;59:887–90.
8. Czyzyk A, Tawecki J, Sadowski J, Ponikowska I, Szczepanik Z. Effect of biguanides on intestinal absorption of glucose. Diabetes. 1968;17:492–8.
9. de la Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, Velásquez-Mejía EP, Carmona JA, Abad JM, Escobar JS. Metformin is associated with higher relative abundance of mucin-degrading akkermansia muciniphila and several short-chain fatty acid-producing microbiota in the gut. Diabetes Care. 2017;40:54–62.
10. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, Prifti E, Vieira-Silva S, Gudmundsdottir V, Pedersen HK, Arumugam M, Kristiansen K, Voigt AY, Vestergaard H, Hercog R, Costea PI, Kultima JR, Li J, Jørgensen T, Levenez F, Dore J. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528:262–6.
11. Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, Ståhlman M, Olsson LM, Serino M, Planas-Fèlix M, Xifra G, Mercader JM, Torrents D, Burcelin R, Ricart W, Perkins R, Fernàndez-Real JM, Bäckhed F. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23:850–8.
12. Migoya EM, Bergeron R, Miller JL, Snyder RN, Tanen M, Hilliard D, Weiss B, Larson P, Gutierrez M, Jiang G, Liu F, Pryor KA, Yao J, Zhu L, Holst JJ, Deacon C, Herman G, Thornberry N, Amatruda J, Williams-Herman D, Wagner JA, SinhaRoy R. Dipeptidyl peptidase-4 inhibitors administered in combination with metformin result in an additive increase in the plasma concentration of active GLP-1. Clin Pharmacol Ther. 2010;88:801–8.
13. Bahne E, Sun EWL, Young RL, Hansen M, Sonne DP, Hansen JS, Rohde U, Liou AP, Jackson ML, de Fontgalland D, Rabbitt P, Hollington P, Sposato L, Due S, Wattchow DA, Rehfeld JF, Holst JJ, Keating DJ, Vilsbøll T, Knop FK. Metformin-induced glucagon-like peptide-1 secretion contributes to the actions of metformin in type 2 diabetes. JCI Insight. 2018;3:e93936.
14. DeFronzo RA, Buse JB, Kim T, Burns C, Skare S, Baron A, Fineman M. Once-daily delayed-release metformin lowers plasma glucose and enhances fasting and postprandial GLP-1 and PYY: results from two randomised trials. Diabetologia. 2016;59:1645–54.
15. Coll AP, Chen M, Taskar P, Rimmington D, Patel S, Tadross JA, Cimino I, Yang M, Welsh P, Virtue S, Goldspink DA, Miedzybrodzka EL, Konopka AR, Esponda RR, Huang JT, Tung YCL, Rodriguez-Cuenca S, Tomaz RA, Harding HP, Melvin A, Yeo GSH, Preiss D, Vidal-Puig A, Vallier L, Nair KS, Wareham NJ, Ron D, Gribble FM, Reimann F, Sattar N, Savage DB, Allan BB,

O'Rahilly S. GDF15 mediates the effects of metformin on body weight and energy balance. Nature. 2020;578:444–8.
16. Yang M, Darwish T, Larraufie P, Rimmington D, Cimino I, Goldspink DA, Jenkins B, Koulman A, Brighton CA, Ma M, Lam BYH, Coll AP, O'Rahilly S, Reimann F, Gribble FM. Inhibition of mitochondrial function by metformin increases glucose uptake, glycolysis and GDF-15 release from intestinal cells. Sci Rep. 2021;11:2529.
17. Duca FA, Côté CD, Rasmussen BA, Zadeh-Tahmasebi M, Rutter GA, Filippi BM, Lam TK. Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats. Nat Med. 2015;21:506–11.
18. Gontier E, Fourme E, Wartski M, Blondet C, Bonardel G, Le Stanc E, Mantzarides M, Foehrenbach H, Pecking AP, Alberini JL. High and typical 18F-FDG bowel uptake in patients treated with metformin. Eur J Nucl Med Mol Imaging. 2008;35:95–9.
19. Bahler L, Stroek K, Hoekstra JB, Verberne HJ, Holleman F. Metformin-related colonic glucose uptake; potential role for increasing glucose disposal?-A retrospective analysis of (18) F-FDG uptake in the colon on PET-CT. Diabetes Res Clin Pract. 2016;114:55–63.
20. Koffert JP, Mikkola K, Virtanen KA, Andersson AD, Faxius L, Hällsten K, Heglind M, Guiducci L, Pham T, Silvola JMU, Virta J, Eriksson O, Kauhanen SP, Saraste A, Enerbäck S, Iozzo P, Parkkola R, Gomez MF, Nuutila P. Metformin treatment significantly enhances intestinal glucose uptake in patients with type 2 diabetes: Results from a randomized clinical trial. Diabetes Res Clin Pract. 2017;131:208–16.
21. Ozülker T, Ozülker F, Mert M, Ozpaçaci T. Clearance of the high intestinal (18)F-FDG uptake associated with metformin after stopping the drug. Eur J Nucl Med Mol Imaging. 2010;37:1011–7.
22. Oh JR, Song HC, Chong A, Ha JM, Jeong SY, Min JJ, Bom HS. Impact of medication discontinuation on increased intestinal FDG accumulation in diabetic patients treated with metformin. AJR Am J Roentgenol. 2010;195:1404–10.
23. Lee SH, Jin S, Lee HS, Ryu JS, 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.
24. Schreuder N, Klarenbeek H, Vendel BN, Jager PL, Kosterink JGW, van Puijenbroek EP. Discontinuation of metformin to prevent metformin-induced high colonic FDG uptake: is 48 h sufficient? Ann Nucl Med. 2020;34:833–9.
25. Massollo M, Marini C, Brignone M, Emionite L, Salani B, Riondato M, Capitanio S, Fiz F, Democrito A, Amaro A, Morbelli S, Piana M, Maggi D, Cilli M, Pfeffer U, Sambuceti G. Metformin temporal and localized effects on gut glucose metabolism assessed using 18F-FDG PET in mice. J Nucl Med. 2013;54:259–66.
26. Pénicaud L, Hitier Y, Ferré P, Girard J. Hypoglycaemic effect of metformin in genetically obese (fa/fa) rats results from an increased utilization of blood glucose by intestine. Biochem J. 1989;262:881–5.
27. Schommers P, Thurau A, Bultmann-Mellin I, Guschlbauer M, Klatt AR, Rozman J, Klingenspor M, de Angelis MH, Alber J, Gründemann D, Sterner-Kock A, Wiesner RJ. Metformin causes a futile intestinal–hepatic cycle which increases energy expenditure and slows down development of a type 2 diabetes-like state. Mol Metab. 2017;6:737–47.
28. Wang K, Chen YC, Palmer MR, Tal I, Ahmed A, Moss AC, Kolodny GM. Focal physiologic fluorodeoxyglucose activity in the gastrointestinal tract is located within the colonic lumen. Nucl Med Commun. 2012;33:641–7.
29. Kim S, Chung JK, Kim BT, Kim SJ, Jeong JM, Lee DS, Lee MC. Relationship between Gastrointestinal F-18-fluorodeoxyglucose accumulation and gastrointestinal symptoms in whole-body PET. Clin Positron Imaging. 1999;2:273–9.
30. Brendle CB, Schmidt H, Fleischer S, Braeuning UH, Pfannenberg CA, Schwenzer NF. Simultaneously acquired MR/PET images compared with sequential MR/PET and PET/CT: alignment quality. Radiology. 2013;268:190–9.
31. Nogami M, Zeng F, Inukai J, Watanabe Y, Nishio M, Kanda T, Ueno YR, Sofue K, Kono AK, Hori M, Ohnishi A, Kubo K, Kurimoto T, Murakami T. Physiological skin FDG uptake: A quantitative and regional distribution assessment using PET/MRI. PLoS ONE. 2021;16:e0249304.
32. Morita Y, Nogami M, Sakaguchi K, Okada Y, Hirota Y, Sugawara K, Tamori Y, Zeng F, Murakami T, Ogawa W. Enhanced release of glucose into the intraluminal space of the intestine associated with metformin treatment as revealed by [18F]Fluorodeoxyglucose PET-MRI. Diabetes Care. 2020;43:1796–802.
33. Ito J, Nogami M, Morita Y, Sakaguchi K, Komada H, Hirota Y, Sugawara K, Tamori Y, Zeng F, Murakami T, Ogawa W. Dose-dependent accumulation of glucose in the intestinal wall and lumen induced by metformin as revealed by 18F-labelled fluorodeoxyglucose positron emission tomography-MRI. Diabetes Obes Metab. 2021;23:692–9.
34. Long CL, Geiger JW, Kinney JM. Absorption of glucose from the colon and rectum. Metabolism. 1967;16:413–8.
35. Cummings JH, Macfarlane GT. Role of intestinal bacteria in nutrient metabolism. JPEN J Parenter Enteral Nutr. 1997;21:357–65.
36. Mueller NT, Differding MK, Zhang M, Maruthur NM, Juraschek SP, Miller ER 3rd, Appel LJ, Yeh HC. Metformin affects gut microbiome composition and function and circulating short-chain fatty acids: a randomized trial. Diabetes Care. 2021;44:1462–71.
37. Marounek M, Rada V, Benda V. Biochemical characteristics and fermentation of glucose and starch by rabbit caecal strains of Bifidobacterium globosum. Folia Microbiol. 1998;43:113–6.
38. Koepsell H. Glucose transporters in the small intestine in health and disease. Pflugers Arch. 2020;472:1207–48.
39. Ait-Omar A, Monteiro-Sepulveda M, Poitou C, Le Gall M, Cotillard A, Gilet J, Garbin K, Houllier A, Château D, Lacombe A, Veyrie N, Hugol D, Tordjman J, Magnan C, Serradas P, Clément K, Leturque A, Brot-Laroche E. GLUT2 accumulation in enterocyte apical and intracellular membranes: A study in morbidly obese human subjects and ob/ob and high fat-fed mice. Diabetes. 2011;60:2598–607.
40. Sakar Y, Meddah B, Faouzi MA, Cherrah Y, Bado A, Ducroc R. Metformin-induced regulation of the intestinal D-glucose transporters. J Physiol Pharmacol. 2010;61:301–7.
41. Walker J, Jijon HB, Diaz H, Salehi P, Churchill T, Madsen KL. 5-aminoimidazole-4-carboxamide riboside (AICAR) enhances GLUT2-dependent jejunal glucose transport: a possible role for AMPK. Biochem J. 2005;385:485–91.
42. Kwon IG, Kang CW, Park JP, Oh JH, Wang EK, Kim TY, Sung JS, Park N, Lee YJ, Sung HJ, Lee EJ, Hyung WJ, Shin SJ, Noh SH, Yun M, Kang WJ, Cho A, Ku CR. Serum glucose excretion after Roux-en-Y gastric bypass: a potential target for diabetes treatment. Gut. 2020. https://doi.org/10.1136/gutjnl-2020-321402.
43. Martinez-Guryn K, Leone V, Chang EB. Regional Diversity of the Gastrointestinal Microbiome. Cell Host Microbe. 2019;26:314–24.