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ORIGINAL ARTICLE

A Negative Correlation Between Blood Glucose Level and ^{68} Ga-DOTA-TOC Uptake in the Pancreas Uncinate Process

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Abstract

Purpose ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process is often found due to physiologic expression of somatostatin receptors (SSTR). We investigated the association of physiologic ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process with blood glucose level.

Methods ^{68} Ga-DOTA-TOC PET scans acquired from 44 patients (male:female = 20:24, age = 50.8 ± 14.8y [mean ± SD]) were retrospectively analyzed. The blood glucose level (BGL) was examined before ^{68} Ga-DOTA-TOC injection. Patients diagnosed with diabetes mellitus and patients with BGL over 200 mg/dl were excluded. ^{68} Ga-DOTA-TOC uptake was measured by the maximum standardized uptake values (SUVmax). Additionally, SSTR-positive volume (SV) in the pancreas uncinate process was measured with two different thresholds: by SUV cutoff of 2.5 ($SV_{2.5}$) and 40% of SUVmax ($SV_{40\%}$). These measurements on ^{68} Ga-DOTA-TOC PET were correlated with BGL.

Results The mean of SUVmax of the pancreas uncinate process was 6.51 ± 2.04. $SV_{2.5}$ was 17.81 ± 7.14 cm^3, and $SV_{40\%}$ was 18.20 ± 8.83 cm^3. A significant negative correlation was found between SUVmax of the pancreas uncinate process and BGL (r = -0.37, p = 0.01). The ratio between SUVmax of the pancreas uncinate process and SUVmean of the pancreas body also showed a significance negative correlation with BGL (r = -0.40, p = 0.01). $SV_{2.5}$ (r = 0.27, p = 0.07) and $SV_{40\%}$ (r = -0.151, p = 0.32) were not significantly correlated with BGL.

Conclusion Physiologic ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process was negatively correlated with BGL. Our results suggested that glycemia could affect physiologic uptake of ^{68} Ga-DOTA-TOC.

Keywords ^{68} Ga-DOTA-TOC · PET · Uncinate · Pancreatic polypeptide cell · Blood glucose level

Introduction

^{68} Ga-1,4,7,10-tetraazacyclo-dodecane-N,N′,N″,N‴-tetraacetic-acid-D-Phe[1]-Tyr[3]-octreotide (DOTA-TOC) is a somatostatin analogue for PET imaging with high binding affinity to human somatostatin receptor type 2 [1]. ^{68} Ga-DOTA-TOC PET has been widely used for the diagnosis of somatostatin receptor (SSTR)-expressing tumors, representatively neuroendocrine tumor (NET). On ^{68} Ga-DOTA-TOC PET, increased uptake in the pancreas uncinate process is often observed, which is deemed due to physiologic expression of SSTR in the uncinate process [2]. This physiologic uptake is a pitfall of ^{68} Ga-DOTA-TOC PET interpretation in NET because it can be misinterpreted as an SSTR-expressing tumor [3].

The reason for the physiologic ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process is believed to be a region-specific uptake related to a cell type known as pancreatic polypeptide (PP) cells, which contain enriched endocrine polypeptide [4]. The PP cells consist of the endocrine pancreas islet and are located predominantly in the pancreas head and uncinate process [5]. PP secreted by the PP cells contains 36 amino acids, which inhibit gallbladder contraction and pancreatic exocrine secretion. The secretion of PP is stimulated by a protein meal, fasting, exercise, and acute hypoglycemia [5, 6], and the secretion is inhibited by glucose load [7]. Thus, it can be assumed that the cellular activity of PP cells is affected by blood glucose level (BGL).

In this study, we hypothesized that BGL affects the metabolic activity of PP cells and, consequently, SSTR

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expression of PP cells. As a pilot study, we retrospectively analyzed ^{68} Ga-DOTA-TOC PET scans that were performed for the diagnosis of NET patients. The purpose of this study was to investigate the association between BGL and ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process.

Materials and Methods

Patients

In this retrospective study, 77 patients who underwent ^{68} Ga-DOTA-TOC PET scans at a single institution were evaluated, from December 2020 to January 2021. The demographic and clinical information of the enrolled patients are listed in Table 1. One of 77 patients underwent two serial ^{68} Ga-DOTA-TOC PET scans with 51 days interval, and both exams were included for the analysis. Among of 78 studies, 19 were excluded because of the presence of tumor in the pancreas head and uncinate process or adjacent retroperitoneal lymph node metastasis. Four studies were excluded because those patients had a previous history of pancreatectomy. We excluded patients diagnosed as or suspected of diabetes: Six patients were diagnosed as diabetes, and four patients were suspected of diabetes because BGL was higher than 200 mg/dl. Accordingly, 45 PET scans were included for the analysis. Because diabetes affects neuroendocrine function of pancreas and the study aims at normal physiologic DOTA-TOC uptake, patients with diabetes were excluded.

BGL and ^{68} Ga-DOTA-TOC PET Image Acquisition

All patients were informed that no fasting is required prior to ^{68} Ga-DOTA-TOC PET scan. Right before ^{68} Ga-DOTA-TOC injection, BGL was measured using reflectance photometry method after finger-prick test. Patients were intravenously injected with 185 MBq of ^{68} Ga-DOTA-TOC, and PET/CT of PET/MR scans were performed 60 min after the injection.

PET scans were acquired using PET/CT (Biograph mCT40 or mCT64, Simense Healthcare) or PET/MR scanners (Biograph mMR; Siemens Healthcare, Erlangen, Germany). For PET/CT scans, a low dose CT scan (120 kVp, 50 mAs) was acquired. Afterwards, PET images from vertex to proximal thigh were obtained for 2 min per bed position (6–7 bed positions for a patient), and images were reconstructed by an iterative algorithm (ordered subset expectation maximization, iteration 2, subset 21). For PET/MR scan, the coronal 3D volume-interpolated gradient echo (VIBE) sequence for Dixon-based attenuation correction was acquired. PET was obtained for 2 min per bed position using a three-dimensional acquisition mode. PET images were reconstructed on 172×172 matrices using an iterative algorithm (ordered subset expectation maximization; two iterations and 21 subsets).

Image Analysis and Statistics

The ^{68} Ga-DOTA-TOC PET images were analyzed using Syngo.via software (Siemens Healthcare, Erlangen, Germany). A spherical volume of interest (VOI) was drawn to include physiologic DOTA-TOC uptake in the pancreas uncinate process. A standardized-uptake-value (SUV) was calculated, and SUVmax (highest value of SUV within the VOI) and SUVpeak (maximum average SUV within a 1 cm^3 spherical volume) were obtained. SSTR-positive volume (SV) of physiologic uptake on ^{68} Ga-DOTA-TOC PET in the pancreas uncinate process was measured with two different methods: SUV cutoff of 2.5 ($SV_{2.5}$) and 40% of SUVmax ($SV_{40\%}$).

Table 1 Demographic and clinical data of 44 study participants

Characteristics ($n = 44$)	
Age (years)	53.5 [7–74]‡
Sex	M:F = 20:24 (45.5%:54.5%)
Diagnosis	Pancreas NET: 6 (13.64%)
	Rectal NET: 13 (29.55%)
	Other gastrointestinal NET: 2 (4.55%)
	NET, from unknown origin: 2 (4.55%)
	Pheochromocytoma/paraganglioma: 6 (13.64%)
	Other tumors (including meningioma): 15 (34.09%)
Blood glucose level (mg/dL)	102.5 [70–145]‡

‡The values are reported as median [minimum value–maximum value]

In addition, SUVmean of the normal pancreas body uptake was measured using VOI drawn in the center of pancreas body entirely within the pancreatic tissue, located in anterior aspect of abdominal aorta and posterior to stomach lower body wall. SUVmean of blood pool (BP SUVmean) was also measured using the VOI drawn on the center of the ascending aorta, without inclusion of the aortic wall activity. Figure 1 depicted the measurement of SUV parameters in pancreas uncinate process, pancreas body, and blood pool using VOIs. The ratio between SUVmax of the uncinate process and SUVmean of the normal pancreas body was calculated. Also, the ratios between SUVmax of the uncinate process over BP SUVmean were calculated. The continuous variables were represented by mean ± SD. The correlation was analyzed by Pearson correlation, and a p value of 0.05 or lower was considered to be statistically significant. Statistical analyses were performed by IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Patient Characteristics

The mean age of 44 patients was 50.8 years (SD, 14.8; range, 7–71). Among 44 patient, 22 (50%) patients were diagnosed with neuroendocrine tumors, of which 9 patients with pancreatic NET, 8 patients with rectal NET, and 5 patients with other or unknown origins. Twelve patients (27%) were diagnosed as pheochromocytoma or paraganglioma. Other 10 (23%) patients were diagnosed with other tumors except NET including meningioma. Demographics and diagnosis of patients were summarized in Table 1. BGL of 44 patients were 107.5 ± 37.5 mg/dL (70–145 mg/dL), and the distribution of BGL is shown in Fig. 2.

^{68} Ga-DOTA-TOC PET Parameters of Physiologic Uncinate Process Uptake

The mean SUVmax of the pancreas uncinate process was 6.51 ± 2.04, and SUVpeak was 5.90 ± 1.51. The mean $SV_{2.5}$ was 17.8 ± 7.1 cm^3, and $SV_{40\%}$ was 18.2 ± 8.8 cm^3. The distributions of SUVmax and SUVpeak of the pancreas uncinate process are shown in Fig. 2.

A significant negative correlation was found between BGL and SUVmax of the pancreas uncinate process (r = -0.37, p = 0.01). SUVpeak also showed a significant negative correlation with BGL (r = -0.33, p = 0.03). The ratio between SUVmax of the pancreas uncinate process and SUVmean of the normal pancreas body showed a significant negative correlation with BGL (r = -0.40, p = 0.01), and the ratio between SUVmax of the pancreas uncinate process and BP SUVmean also showed a significant negative correlation with BGL (r = -0.34, p = 0.02). However, two volume measurements on ^{68} Ga-DOTA-TOC PET were not significantly correlated with BGL: r = 0.274 and p = 0.068 for the correlation between $SV_{2.5}$ and BGL and r = -0.15 and p = 0.32 for the correlation between $SV_{40\%}$ and BGL. There was no significant correlation between patient age and SUVmax of the pancreas uncinate process (r = -0.17, p = 0.27). Representative cases with high and low BGL are shown in Fig. 3. The result of correlation analysis between BGL and ^{68} Ga-DOTA-TOC PET parameters is shown in Fig. 4.

Discussion

Our analyses were aimed to know which factors affect physiologic uptake of ^{68} Ga-DOTA-TOC in the pancreas uncinate process. PP is a hormone regulating pancreatic endocrine and exocrine secretion and hepatic glycogen level and also known to suppress the excretion of somatostatin [8]. The excretion of PP is stimulated by a protein meal, fasting, exercise, and hypoglycemia, whereas its excretion is suppressed by hyperglycemia. PP is excreted by PP cells mainly located

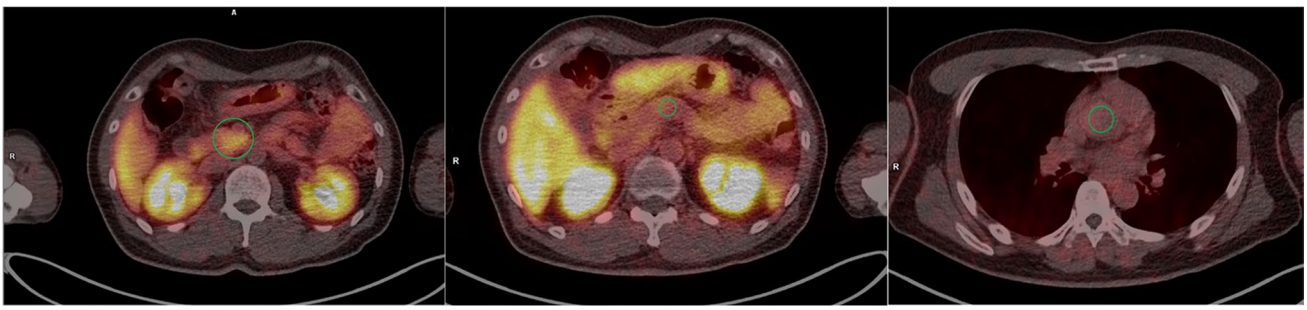

Fig. 1 Measurement of SUV parameters in pancreas uncinate process (left), pancreas body (middle) and blood pool (right) using VOIs

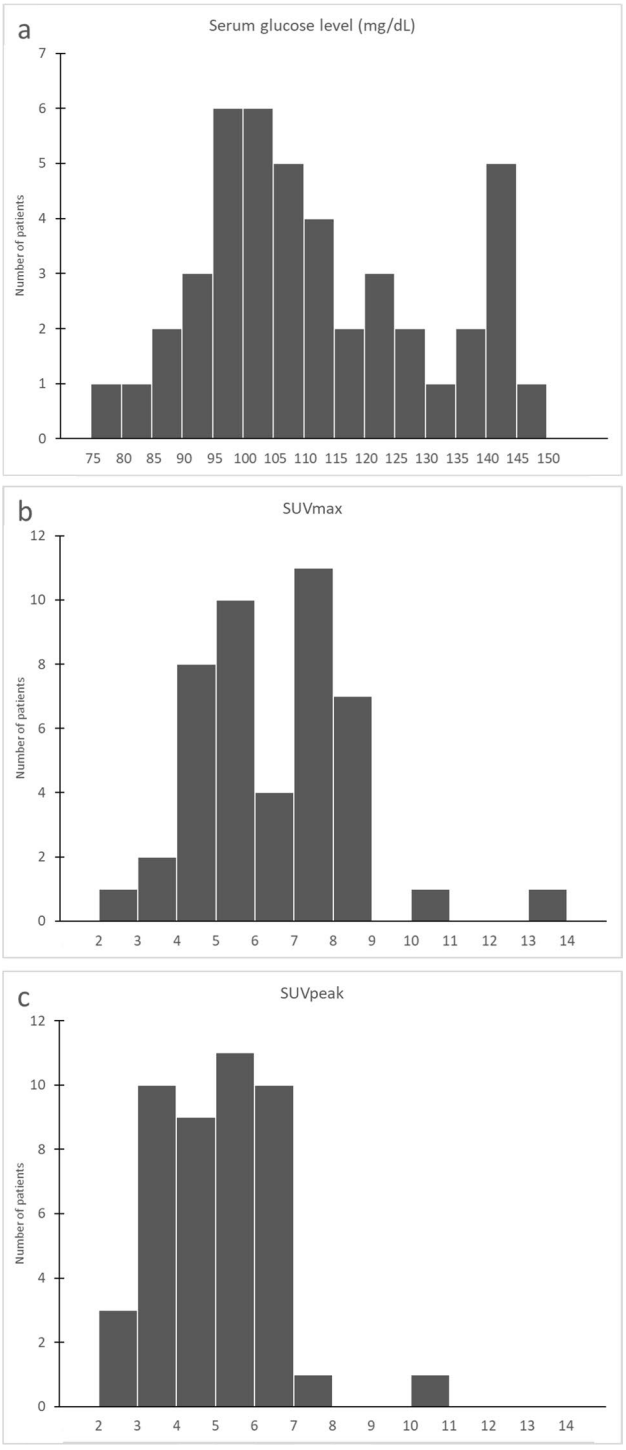

Fig. 2 Distribution of analyzed variables in 45 analyzed ^{68} Ga-DOTA-TOC PET studies. **a** Distribution of BGL. **b** Distribution of SUVmax of focal DOTA-TOC avid portion in the pancreas head/uncinate process. **c** Distribution of SUVmean of focal DOTA-TOC avid portion in the pancreas head/uncinate process

in the uncinate process of pancreas [5] and express somatostatin receptor (SSTR) [9, 10] which can be evaluated by ^{68} Ga-DOTA-TOC PET. Thus, we assumed that the uptake of ^{68} Ga-DOTA-TOC could be associated with functional activity of PP cells. Because PP is affected by glycemic conditions, we evaluated whether glycemia was associated with ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process.

We found a correlation between blood glucose level (BGL) and ^{68} Ga-DOTA-TOC uptake in the pancreas uncinate process. While a significant negative correlation between BGL level and SUV parameters of ^{68} Ga-DOTA-TOC uptake was found, volume measurements defined by PET showed no significant correlation with BGL. Our findings imply that BGL could affect SSTR expression in the PP cells enriched in the pancreas uncinate process. Since SSTR is not fixed on cell membrane and is a dynamic structure capable of functions such as internalization, trafficking, and recycling [11, 12], rapid molecular response in SSTR expression could be triggered by glycemic conditions. Of note, volume measurements were not correlated with BGL. It suggested the tissue volume of PP cell rich islets in the pancreas could not be rapidly changed according to the glycemic condition. Moreover, it implied that glycemic conditions affect the functional activity of PP cells which might be represented by SSTR expression rather than increased volume of PP cell enriched region.

The result of this study provides important information during the interpretation of ^{68} Ga-DOTA-TOC PET scans. Currently, there are no agreed protocols about fasting or glucose level measurement prior to ^{68} Ga-DOTA-TOC PET exam. Our results suggested the consideration of new protocols for controlling blood glucose levels particularly for PET study to evaluate pancreas tumors. More specifically, post-prandial status prior to PET or oral glucose intake before the PET study may attribute to standardize and reduce the pancreas uncinate process uptake and avoid clinical misinterpretation. Further studies in a larger cohort and also a prospective study of how physiologic uptake changes with glycemic controlled protocols are needed. In addition, our results could be applied to noninvasive assessment of functional activity of PP cells in the pancreas, though further biological evidence of the association of binding of ^{68} Ga-DOTA-TOC with functional activity of PP cells. As the role of PP cells in pathophysiology of endocrine-related disorders is still unknown, clinical implications would be studied as future work.

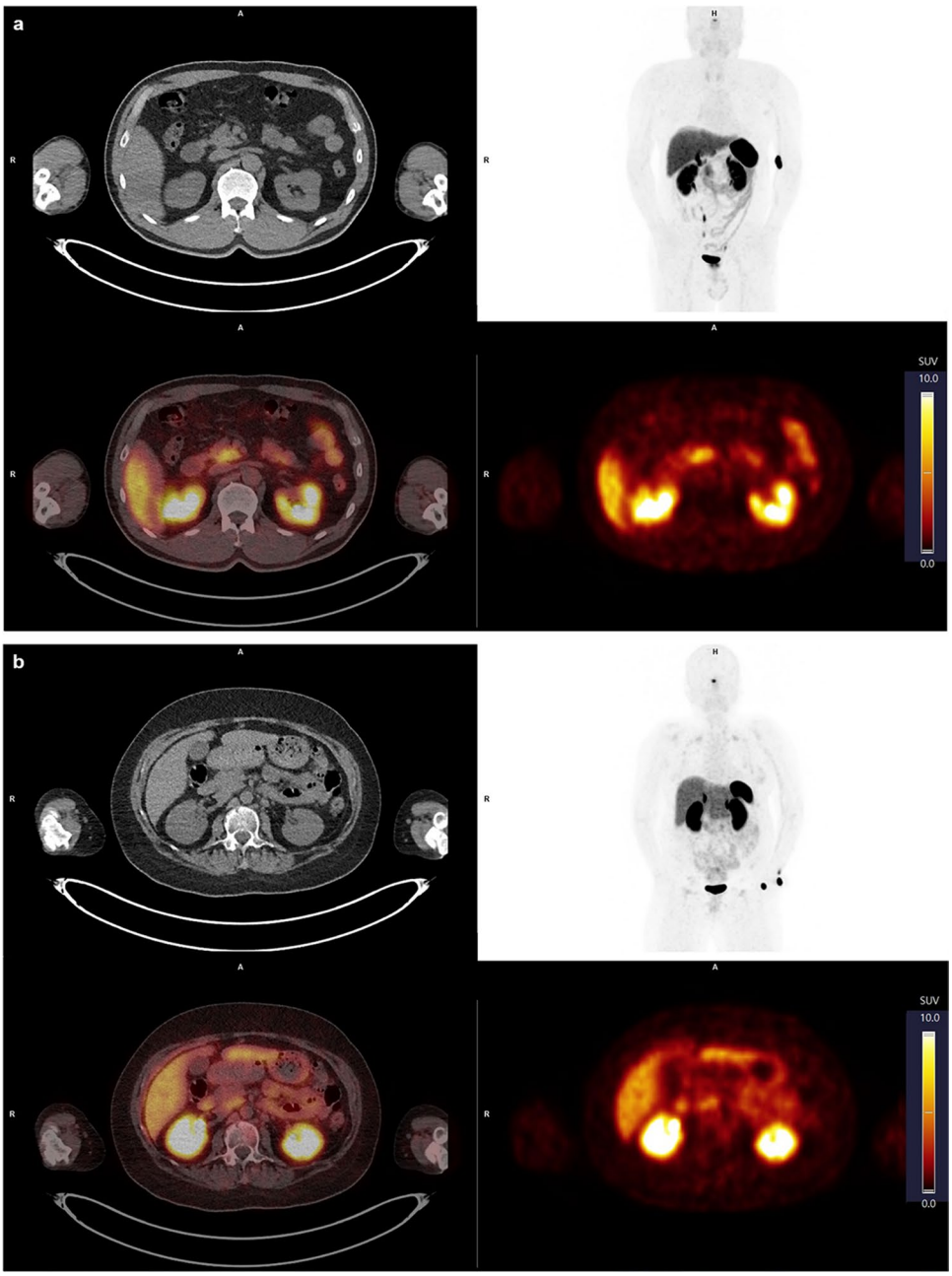

Fig. 3 Comparison of two ^{68}Ga-DOTA-TOC PET/CT images with different serum glucose level and ^{68}Ga DOTA-TOC PET parameters of focal DOTA-TOC avid portion in the pancreas head/uncinate process. **a** ^{68}Ga-DOTA-TOC PET/CT image of a 59-year-old male patient diagnosed with paraganglioma. Serum glucose level measured before isotope injection was 93 mg/dL, and ^{68}Ga-DOTA-TOC PET parameters of focal DOTA-TOC avid portion in the pancreas head/uncinate process were 8.37 for SUVmax and 27.57cm^3 for $SV_{2.5}$, respectively. **b** ^{68}Ga-DOTA-TOC PET/CT image of a 64-year-old male patient diagnosed with phosphaturic mesenchymal tumor. Serum glucose level measured before isotope injection was 145 mg/dL, and ^{68}Ga-DOTA-TOC PET parameters of focal DOTA-TOC avid portion in the pancreas head/uncinate process were 5.44 for SUVmax and 17.547cm^3 for $SV_{2.5}$, respectively

There were some limitations in this study. Firstly, the patients were retrospectively recruited. Thus, the subjects were heterogeneous and were relatively small group ($N = 44$). Furthermore, patients had uncontrolled diet with various interval between last meal and ^{68}Ga-DOTA-TOC PET exams. And the BGL measurement by finger-prick test has lower accuracy compared to the testing blood sample acquired from the peripheral vein with hexokinase method. A prospective study of subjects with controlled postprandial status and intravenous sampling for BGL measurement will be required for understanding of ^{68}Ga-DOTA-TOC uptake in the pancreas uncinate process and blood glucose level.

Conclusion

Physiologic DOTA-TOC uptake of the pancreas uncinate process is negatively correlated with serum blood glucose level. Our results suggested that hypoglycemic condition

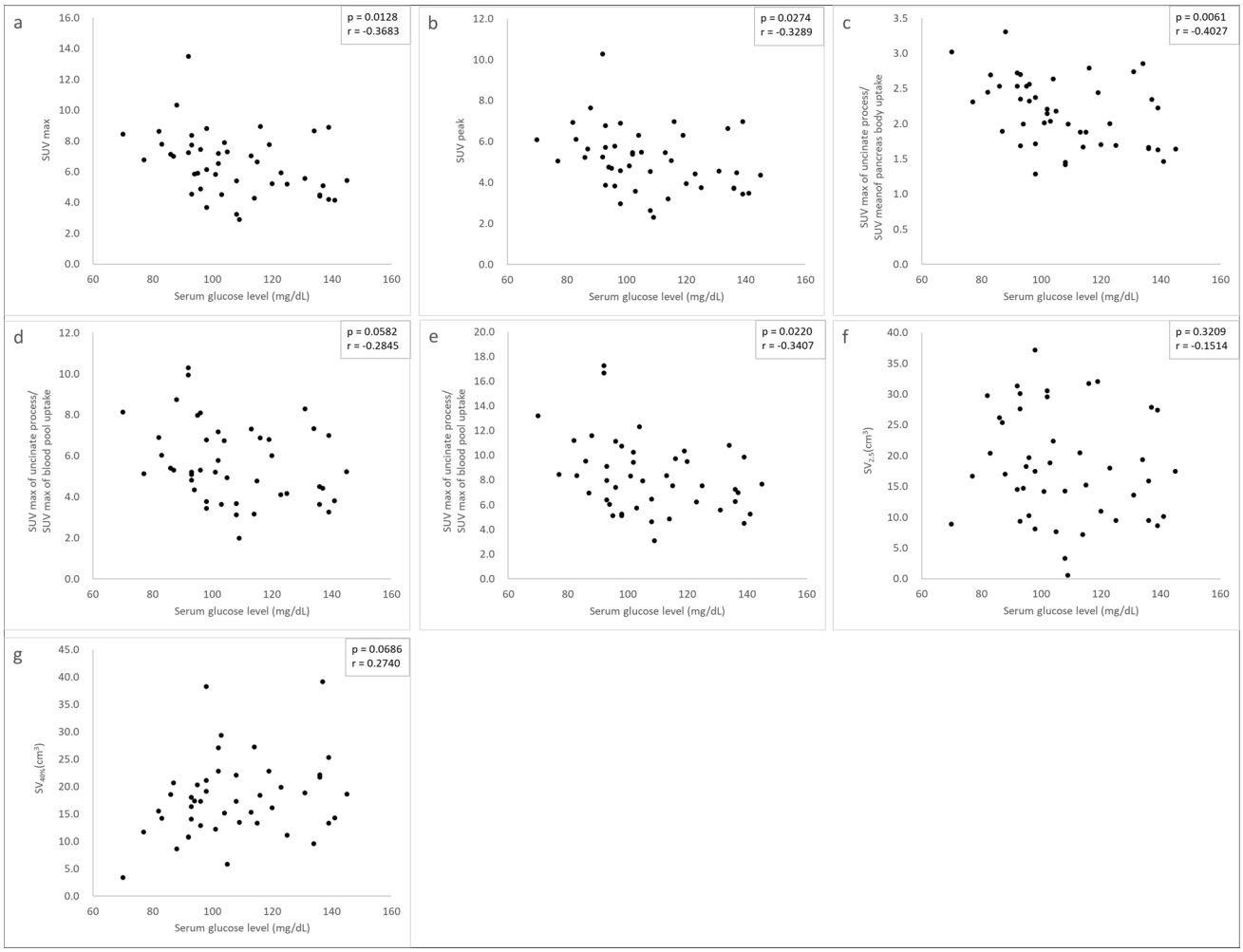

Fig. 4 Correlation between ^{68} Ga-DOTA-TOC PET parameters of physiologic uncinate process uptake. Significant negative correlation was found between serum glucose level and **a** SUVmax, **b** SUVpeak, **c** ratio of SUVmax in the pancreas uncinate process and the normal pancreas, and **e** ratio of SUVmax in the pancreas uncinate process and BP mean. The ratio between SUVmax of the pancreas uncinate process and **d** BP SUVmax showed a trend of negative correlation with serum glucose with a borderline significance (r=-0.28, p=0.06). **f** $SV_{2.5}$ (r=0.274, p=0.068) and **g** $SV_{40\%}$ (r=-0.151, p=0.321) did not show any significant correlation with serum glucose level

has negative correlation with metabolic activity could affect SSTR expression in PP cells in the pancreas uncinate which eventually affected ^{68} Ga-DOTA-TOC PET interpretation.

Author Contribution The study was designed by Dongkyu Oh and Hongyoon Choi. Material preparation and data collection and analysis were performed by Dongkyu Oh, Hongyoon Choi, and Jin Chul Paeng. The first draft of the manuscript was written by Dongkyu Oh. Review, editing and supervision were performed by Keon Wook Kang and Gi Jeong Cheon. All authors read and approved the final manuscript.

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Data Availability Please contact author for data requests.

Declarations

Competing Interests Dongkyu Oh, Hongyoon Choi, Jin Chul Paeng, Keon Wook Kang, and Gi Jeong Cheon declare no conflict of interest.

Ethics Approval and Consent to Participate The study design of the retrospective analysis and exemption of informed consent were approved by the Institutional Review Board of the Seoul National University Hospital (2108–072-1244). All procedures followed were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The institutional review board waived the need to obtain informed consent.

Consent for Publication The institutional review board waived the need to obtain informed consent because of the anonymity and the retrospective nature of the study.

References

1. Zhang H, Moroz MA, Serganova I, Ku T, Huang R, Vider J, et al. Imaging expression of the human somatostatin receptor subtype-2 reporter gene with ^{68}Ga-DOTA-TOC. J Nucl Med. 2011;52:123–31.
2. Hennrich U, Benešová M. [^{68}Ga]Ga-DOTA-TOC: the first FDA-approved ^{68}Ga-radiopharmaceutical for PET imaging. Pharmaceuticals (Basel). 2020;13:38.
3. Jacobsson H, Larsson P, Jonsson C, Jussing E, Grybäck P. Normal uptake of ^{68}Ga-DOTA-TOC by the pancreas uncinate process mimicking malignancy at somatostatin receptor PET. Clin Nucl Med. 2012;37:362–5.
4. Imperiale A, Meuter L, Pacak K, Taïeb D. Variants and pitfalls of PET/CT in neuroendocrine tumors. Semin Nucl Med. 2021;51:519–28.
5. Wang X, Zielinski MC, Misawa R, Wen P, Wang TY, Wang CZ, et al. Quantitative analysis of pancreatic polypeptide cell distribution in the human pancreas. PLoS One. 2013;8:e55501.
6. Rizza R, Go V, Cryer P, Verdonk C, Gerich J. Stimulation of human pancreatic polypeptide secretion by hypoglycemia is independent of adrenergic mechanisms. J Clin Endocrinol Metab. 1982;55:1234–6.
7. Veedfald S, Plamboeck A, Hartmann B, Svendsen LB, Vilsbøll T, Knop FK, et al. Pancreatic polypeptide responses to isoglycemic oral and intravenous glucose in humans with and without intact vagal innervation. Peptides. 2015;71:229–31.
8. Kim W, Fiori JL, Shin YK, Okun E, Kim JS, Rapp PR, et al. Pancreatic polypeptide inhibits somatostatin secretion. FEBS Lett. 2014;588:3233–9.
9. Portela-Gomes GM, Stridsberg M, Grimelius L, Oberg K, Janson ET. Expression of the five different somatostatin receptor subtypes in endocrine cells of the pancreas. Appl Immunohistochem Mol Morphol. 2000;8:126–32.
10. Ludvigsen E, Olsson R, Stridsberg M, Janson ET, Sandler S. Expression and distribution of somatostatin receptor subtypes in the pancreatic islets of mice and rats. J Histochem Cytochem. 2004;52:391–400.
11. Csaba Z, Peineau S, Dournaud P. Molecular mechanisms of somatostatin receptor trafficking. J Mol Endocrinol. 2012;48:R1-12.
12. Olsen C, Memarzadeh K, Ulu A, Carr HS, Bean AJ, Frost JA. Regulation of somatostatin receptor 2 trafficking by C-tail motifs and the retromer. Endocrinology. 2019;160:1031–43.