

Glucagon-like peptide-1 receptor PET/CT in patients with and without post gastric bypass hypoglycemia – a prospective, matched case-control study

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Abstract

Purpose

The aim of this pilot study is to prospectively compare *in vivo* glucagon-like peptide-1 (GLP-1) receptor expression in the duodenum and pancreas of patients with and without postprandial hypoglycemia after gastric bypass using GLP-1 receptor imaging with ⁶⁸Ga-DOTA-exendin-4 PET/CT.

Methods

Five patients after Roux-Y-gastric bypass (RYGB) surgery with postprandial hypoglycemia (PGBH) and five patients after RYGB without PGBH matched for sex, age, operative procedure and postoperative interval underwent ⁶⁸Ga-DOTA-exendin-4 PET/CT. Total ⁶⁸Ga-DOTA-exendin-4 uptake in the duodenum and pancreas, defined as the sum of the standard uptake value (SUV_{sum}) for each voxel in the volume of interest (VOI) was measured by two independent readers who were blinded for the clinical information. Additionally, three further patients with PGBH who received ⁶⁸Ga-DOTA-exendin-4 PET/CT at our center were added to the analysis. Clinical follow-up data was collected for all patients with PGBH.

Results

⁶⁸Ga-DOTA-exendin-4 PET/CT exhibited a greater range of total duodenal and pancreatic uptake (SUV_{sum}) for matched hypoglycemic patients (2144-7802, median 3022) than for matched normoglycemic patients (5104-7507, median 7072), with no statistical significant difference of total uptake = total *in vivo* GLP-1 receptor expression (p-value of 0.187). In one patient with PGBH a focal tracer uptake in the pancreatic tail was identified. Four patients with PGBH required ultimately a reversal of their gastric bypass surgery due to insufficient dietary and medical therapy of their hypoglycemic episodes.

Conclusion

⁶⁸Ga-DOTA-exendin-4 uptake appears not to be significantly different in patients with PGBH compared to matched normoglycemic patients but may reflect varying stages of the complex pathophysiology of postbariatric hypoglycemia.

Introduction

Postprandial hypoglycemia after bariatric surgery is an endogenous form of hyperinsulinemic hypoglycemia [1, 2]. It is a frequent, underdiagnosed, intricate medical complication [2], which impairs quality of life [3] and jeopardizes the beneficial effects of bariatric surgery [4]. Several factors are important for the development, intensity and frequency of postprandial hypoglycemia and the multifactorial etiology may partly explain the lack of an effective medical therapy [1, 5]. So far, no established diagnostic test for postprandial hypoglycemia after bariatric surgery exists, but the diagnosis is based on a typical clinical pattern and confirmatory postprandial glucose sampling in case of symptomatic hypoglycemia (often < 3.0 mmol/l) with improvement of symptoms after ingestion of carbohydrates leading to normal glucose levels (Whipple's triad) [2]. Whereas the majority of patients can be treated with dietary measures alone, some may require additional medical therapy, which is generally off-label and based on an individual case-finding strategy [1, 2].

In patients who cannot sufficiently be treated with dietary measures, further evaluation is recommended to distinguish postprandial hypoglycemia caused by non-insulinoma pancreatogenous hypoglycemia syndrome from various entities such as insulinoma or nesidioblastosis, which may be successfully treated surgically [6–8].

Herein, glucagon-like peptide-1 (GLP-1) receptor PET/CT has proved to facilitate the localization of insulinomas, which usually overexpress GLP-1 receptor in a high incidence and density [9–12]. Few studies have shown that GLP-1 receptor PET/CT can detect focal pancreatic islet cell hypertrophy/hyperplasia in neonates/children (congenital hyperinsulinism) and adults indicating an overexpression of GLP-1 receptors in pancreatic islet cell hypertrophy/hyperplasia [13, 14].

In the last decade, conflicting results on the expression of GLP-1 receptors of the pancreas in patients with postprandial hypoglycemia after bariatric surgery have been published. For example, Service et al. and Patti et al. suggested that postprandial hypoglycemia is caused by pancreatic β -cell hypertrophy and hyperplasia [16, 17]. In contrast, Meier et al. argued that it is not accompanied by an increased β -cell mass [18]. Using autoradiography, Reubi and colleagues also documented no increase in GLP-1 receptor expression in

surgically removed pancreatic tissue of patients with PGBH, indicating that *in vivo* imaging, using GLP1 receptor imaging may not be a suitable tool in this condition. Thus, it is of particular interest whether GLP-1 receptor PET/CT can also be used to quantitatively assess the GLP-1 receptor expression of the entire pancreas and/or duodenum in patients by measuring total ⁶⁸Ga-DOTA-exendin-4 uptake in a volume of interest.

The aim of this study was to quantitatively investigate the *in vivo* GLP-1 receptor expression of the duodenum and pancreas in RYGB patients with and without PGBH using ⁶⁸Ga-DOTA-exendin-4 PET/CT and retrospectively collect data on all patients with PGBH who underwent ⁶⁸Ga-DOTA-exendin-4 PET/CT at our center.

Material And Methods

Participants

Five consecutive patients with confirmed postprandial hypoglycemia (PGBH) after gastric bypass surgery received ⁶⁸Ga-DOTA-exendin-4 PET/CT and five patients without postprandial hypoglycemia matched for sex, age, operative procedure and postoperative interval were prospectively included. Nineteen potential patients serving as controls and matched for age, gender, operative procedure, and postoperative interval, were screened in the outpatient clinic at the Division of Endocrinology, Diabetes and Metabolism at the University Hospital Basel (see study flow chart in Fig. 1). All potential controls underwent a standardized liquid mixed-meal-test (300 ml Ensure plus®, 60 g carbohydrates, 450 kcal). 14/19 patients showed symptomatic hypoglycemia and were, therefore, not considered as control patients. 5/19 patients remained asymptomatic and euglycemic during mixed-meal testing and were, therefore, included in the study as matched controls and also received a ⁶⁸Ga-DOTA-exendin-4 PET/CT using the same protocol as in the five patients with PGBH. Exclusion criteria were pregnancy, allergy to exendin-4, renal (creatinine concentrations > 140 µmol/L) and hepatic insufficiency (> 3x increased levels of transaminases). All patients gave written informed consent. The study was approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz) and amended for five matched normoglycemic control patients (EKBB 163/12).

Furthermore, three additional patients with PGBH and ⁶⁸Ga-DOTA-exendin-4 PET/CT could be added from clinical routine. For all patients, clinical follow-up data were retrospectively collected.

Imaging

piCHEM (Graz Austria), synthesized DOTA-exendin-4 ([Nle¹⁴,Lys⁴⁰(Ahx-DOTA)NH₂]-exendin-4, where Ahx = aminohexanoic acid and DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) according to good manufacturing practice. Eckert and Ziegler (Berlin, Germany) supplied the ⁶⁸Ge/⁶⁸Ga generator (IGG100 or GalliaPharm™). The synthesis of ⁶⁸Ga-DOTA-exendin-4 is performed at the University Hospital of Basel. ⁶⁸Ga-DOTA-exendin-4 was prepared on an automated synthesis unit (PharmTracer, Eckert & Ziegler, Berlin, Germany) by loading the eluate of the ⁶⁸Ge/⁶⁸Ga-generator onto a cation exchange column (Strata-XC, Phenomenex). ⁶⁸Ga was eluted with a mixture of acetone/HCl (97.6%/0.02 N) directly into the reaction vial containing DOTA-exendin-4 in sodium acetate buffer (0.2 M, pH 4.0). DOTA-exendin-4 was labeled with ⁶⁸Ga at 85°C within 300 sec. The product was purified by C8 solid-phase extraction using 50% ethanol in water, followed by dilution with isotonic NaCl 0.9% and filtration using Millex-GV 0.22 µm sterile filters (Millipore). ⁶⁸Ga-DOTA-exendin-4 was synthesized with a labeling yield of > 95% and radiochemical purity > 93%.

PET/CT was performed on two different scanners in supine position: PET/64-detector CT scanner (Discovery ST; GE Healthcare) and PET/128-detector CT scanner (Biograph mCT-X (128); Siemens Healthineers). Calibration of PET scanners and their cross-calibration was performed. One bed position of the upper abdomen was acquired during 8 min, 2.5 h after slow (5 min) intravenous injection of 88.7 ± 1.5 MBq (range 60–90 MBq) for hypoglycemic patients and 88.5 ± 35.6 MBq (range 38–114 MBq) for normoglycemic matches. PET images were reconstructed using an ordered-subsets expectation maximization (OSEM) algorithm with 3 iterations and 25 subsets. An unenhanced low-dose CT (120 kVp, 30–100 mAs) for attenuation correction and anatomic guidance was performed in all patients.

Total uptake measurements of pancreas and duodenum

The total uptake of the pancreas and duodenum, defined as the sum of the standard uptake value (SUV_{sum}) for each voxel in the volume of interest (VOI), was measured to compare the ⁶⁸Ga-DOTA-exendin-4 uptake in both patient groups. The VOI was defined as the total volume of ⁶⁸Ga-DOTA-exendin-4 uptake in the pancreas and duodenum (see Fig. 3). The upper SUV threshold was set at 10. Two independent readers (Reader 1 KA, board-certified nuclear medicine physician with three years of experience after certification and

Reader 2 PW, resident) who were blinded to patients' identity, clinical and laboratory information, carried out the uptake measurements with MIM Software, Version 7.0.1 using the universal PET/CT workflow. On consecutive, axial fused PET/CT images, a region of interest (ROI) was marked, including the entire duodenal and pancreatic tissue. After the ROIs were plotted, the VOI was calculated automatically. Due to the acquisition of an unenhanced low-dose CT for anatomical correlation, differentiation between duodenum and pancreatic head was not possible in all patients. In patients where differentiation of the uptake in the pancreatic head and the duodenum was clearly possible, an additional VOI with the pancreatic uptake only was created and the duodenal uptake was excluded.

Statistical analysis

To compare the uptake of the two paired matched groups, Wilcoxon signed-rank test and for comparison of unpaired groups, Mann-Whitney U test was performed. Due to the small sample size, tests for non-normally distributed data were used. An alpha level of 0.05 was regarded as statistically significant.

Results

Clinical characteristics of patients

Characteristics of hypoglycemic patients are summarized in Supplementary table 1 and of normoglycemic matched patients in Supplementary table 2. All participants were female. The median age was 37 years (range 28–51) for the hypoglycemic and 35 years (range 28–46) for the normoglycemic group. The median interval between surgery and PET-CT was 84 months (range 30–103 months) for the hypoglycemic and 74 months (range 29–102 months) for the normoglycemic group. Whipple triad was positive in all five hypoglycemic patients and negative in all five matched normoglycemic patients. Median preoperative body mass index (BMI) was 44.7 kg/m² (36–51.1 kg/m²) for the hypoglycemic group and 38.3 kg/m² (34.8–51.7 kg/m²) for the normoglycemic group. Median postoperative BMI at the time of imaging was 25.5 kg/m² (20.5–29.4 kg/m²) for the hypoglycemic group and 25.6 kg/m² (24.9–39.7 kg/m²) for the normoglycemic group. Median age and range for the hypoglycemic patients including the three additional patients was 36 years (range 27–53), median interval between surgery and PET-CT 72 months (range 30–103).

Total uptake measurements of pancreas and duodenum

The median of the total uptake was 3022 (range 2144–7802) for matched hypoglycemic patients and 7072 (range 5104–7507) for matched control patients, respectively. The uptake of ⁶⁸Ga-DOTA-exendin-4 in the pancreas and duodenum in patients with PGBH was not statistically different compared to the matched normoglycemic participants (p-value 0.187).

The total uptake in the pancreatic tissue and the duodenum by the two readers are shown in Table 1 for hypoglycemic and Table 2 for the normoglycemic patients and in Fig. 2A. Representative axial views of a patient from the hypoglycemic group (patient 3) and of the normoglycemic control group (match 3) are shown in Fig. 3. For hypoglycemic patient 5 and normoglycemic matched patients 1, 2, and 5, it was possible to clearly differentiate the uptake of the duodenum from the pancreas and a separate VOI was drawn on the pancreatic uptake only.

Table 1
Uptake measurements of the hypoglycemic patients (reader 1 = KA, reader 2 = PW, N/A = not applicable)

Pancreas and Duodenum									
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Uptake	Reader 1	2780	1948	1874	3364	8259	2701	6743	8530
Uptake	Reader 2	3264	2454	2414	3713	7345	2887	6145	8197
Uptake	Mean	3022	2201	2144	3539	7802	2794	6444	8363
Pancreas only									
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Uptake	Reader 1	N/A	N/A	N/A	N/A	6427	N/A	N/A	N/A
Uptake	Reader 2	N/A	N/A	N/A	N/A	5045	N/A	N/A	N/A
Uptake	Mean	N/A	N/A	N/A	N/A	5736	N/A	N/A	N/A

Table 2
Uptake measurements of the normoglycemic matched patients (reader 1 = KA, reader 2 = PW, N/A = not applicable)

Pancreas and Duodenum						
		Match 1	Match 2	Match 3	Match 4	Match 5
Uptake	Reader 1	4483	7352	7266	7786	6056
Uptake	Reader 2	5725	7455	6878	7227	5025
Uptake	Mean	5104	7404	7072	7507	5540
Pancreas only						
		Match 1	Match 2	Match 3	Match 4	Match 5
Uptake	Reader 1	2706	5392	N/A	N/A	5311
Uptake	Reader 2	2992	6184	N/A	N/A	4034
Uptake	Mean	2849	5788	N/A	N/A	4672

Whereas in the matched cohort ⁶⁸Ga-DOTA-exendin-4 PET/CT did not show an increased focal or diffuse uptake in the pancreas, consistent with an insulinoma or nesidioblastosis (Fig. 2A), in one patient (#6) with PGBH a focal tracer uptake in the pancreas (Fig. 4) was observed.

When comparing total pancreatic and duodenal uptake of all eight patients with PGBH (median 3281, range 2144–8363) to the non-hypoglycemic group (median 7072, range 5104–7507, Fig. 2B) no statistical significant difference was found (p-value 0.284) but a much greater range of tracer uptake was observed in patients with PGBH.

Clinical follow-up of patients with PGBH

Data on clinical follow-up of all patients with PGBH is depicted in supplementary table 1. In four of eight patients (# 1, 2, 7 and 8) with PGBH who were insufficiently controlled with dietary and off-label medications, a reversal operation of their gastric bypass and in patient 4 an extension of the common channel was performed which led to an improvement of the intensity and frequency of all their hypoglycemic episodes. Patient 6 with a possible focal nesidioblastosis refused to undergo hemipancreatectomy and could be treated successfully with a minimizer ring after several unsuccessful off-label trials with sandostatin and diazoxide.

Discussion

To the best of our knowledge, this is the first article in which *in vivo* pancreatic and duodenal GLP-1R expression is compared in patients with and without PGBH using ^{68}Ga -DOTA-exendin-4 PET/CT.

Postprandial hypoglycemia gained significant attention as an important medical complication after bariatric surgery. Especially for patients who are symptomatic despite intensified dietary and/or off-label medical therapeutic measures, exclusion of surgically curable causes such as insulinoma or focal nesidioblastosis-like lesions should be considered [6]. Thus, GLP-1 receptor imaging may be a valuable tool for the identification of such alterations guiding therapeutic decisions [9, 13].

In our study, one patients with PGBH showed a focal nesidioblastosis-like pattern. However, there were no significant differences in the GLP-1 receptor expression in patients with and without PGBH, but patients with PGBH showed a much greater range of tracer uptake compared to normoglycemic patients after RYGB. This is an intriguing finding and the pathophysiological background is ill-defined. It may be that patients with PGBH have a downregulation or internalization of GLP-1 receptors due to high postprandial peak glucose and/or GLP-1 levels, thereby explaining the lower pancreatic/duodenal ^{68}Ga -DOTA-exendin-4 accumulation in some of our hypoglycemic patients compared to controls [21–24]. However, three patients with PGBH (# 5, 7, and 8) had a pancreatic and duodenal ^{68}Ga -DOTA-exendin-4 uptake comparable to normoglycemic counterparts. This may indicate that the disease is per se heterogeneous and/or may change during the course of the disease.

Additionally, there may be alternative explanations for this observation. In this study, imaging was performed in a non-fasted state due to the initial suspicion of an insulinoma in the hypoglycemic population and subsequently in the normoglycemic group. Postprandially, high endogenous GLP-1 levels may compete with ^{68}Ga -DOTA-exendin-4 and thereby lead to GLP-1 receptor saturation and consequently low ^{68}Ga -DOTA-exendin-4 accumulation in the pancreas and duodenum.

Interestingly, Boss et al. described in a poster presentation a higher beta-cell mass using ^{68}Ga -DOTA-exendin-4 PET/CT in patients with PGBH compared to patients with incomplete remission of their diabetes after gastric bypass surgery but did not find a correlation of beta-cell activity and beta-cell mass [25]. We would, therefore, argue that our data represent more likely snapshots of ^{68}Ga -DOTA-exendin-4 uptake in patients with PGBH within a heterogeneous morphologic spectrum of GLP-1 receptor distribution in the pancreas and eventually duodenum reflected by the greater range of receptor distribution compared to normoglycemic patients after RYGB. This would add more conflicting data on hypertrophic beta-cells [16, 26, 27] as a reason for PGBH and other studies where these changes were not detected [18, 26]. Post-bariatric hypoglycemia emerges over time after the bariatric procedure and its severity as well as the factors resulting in this disorder are multifaceted. Since we did not further characterize our patients immunometabolically, it remains elusive whether the patients differed substantially therein. Even though for five of our patients a well-controlled matching for sex, age, postoperative interval, and operative procedure, was performed, differences in limb length as well as other potentially contributing factors (incretins, inflammatory parameters, etc.) may explain our observations [5, 28, 29].

Our study also has limitations. It is a single-center study with a small sample size and only female patients with postprandial hypoglycemia after gastric bypass surgery. However, among all bariatric procedures, this is the intervention with the highest rate of post-bariatric hypoglycemia and there is a female preponderance [1, 30]. In addition, our hypoglycemic patients were strongly affected by post-bariatric hypoglycemia with frequent and severe hypoglycemic episodes and may, therefore, not reflect the majority of patients suffering from less severe symptoms.

In addition, a clear separation of pancreatic and duodenal parts was only possible in three of the non-hypoglycemic and in one hypoglycemic patient, limiting assertions on differences in pancreatic and duodenal GLP-1 receptor distribution. Furthermore, since none of the patients underwent a pancreatectomy, no histological data on β -cell morphology is available.

Ongoing studies in patients undergoing bariatric surgery with diabetes or confirmed post-bariatric hypoglycemia (NCT03182192, NCT02542059) may shed further light on our first observations.

However, we would raise a word of caution when performing studies with GLP-1 receptor imaging in patients undergoing bariatric surgery in general or specifically in those with post-bariatric hypoglycemia. Patients should be very well metabolically characterized, including fasting and postprandial glucose, insulin and incretin levels as well as inflammatory parameters [5, 31]. In addition, GLP-1 receptor imaging should be performed in a standardized way after a fasting period to avoid potential postprandial competition of endogenous GLP-1 levels which are high after bariatric surgery and may be high enough to explain different tracer distribution in those

with postprandial hypoglycemia. Longitudinal follow-up may be of particular importance to better characterize and differentiate GLP-1 receptor distribution after bariatric surgery to allow reliable assumptions about GLP-1 receptor imaging and its role in postprandial hypoglycemia, but must be balanced against radiation exposure.

Conclusion

GLP-1 receptor imaging with ⁶⁸Ga-DOTA-exendin-4 PET/CT in patients with post gastric-bypass hypoglycemia was not significantly different from matched normoglycemic controls but revealed a greater variety of uptake compared to matched non-hypoglycemic patients. This may reflect a varying spectrum of GLP-1 receptor distribution in patients with PGBH and suggests a heterogeneous disease.

Declarations

Funding: The study was funded intramurally.

Competing Interests: All authors declare no competing interests.

Author Contributions: All authors planned the study. MH screened control patients and performed mixed-meal-testing. KA and PW did PET/CT readings. MH, KA, and PW did the analysis and wrote the first draft of the manuscript. All authors critically proved data, edited and approved the manuscript.

Data Availability: All data is available from the corresponding author on request.

Ethics approval: The study was approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, Basel, Switzerland, EKBB 163/12).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: All authors approved the manuscript for submission.

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Figures

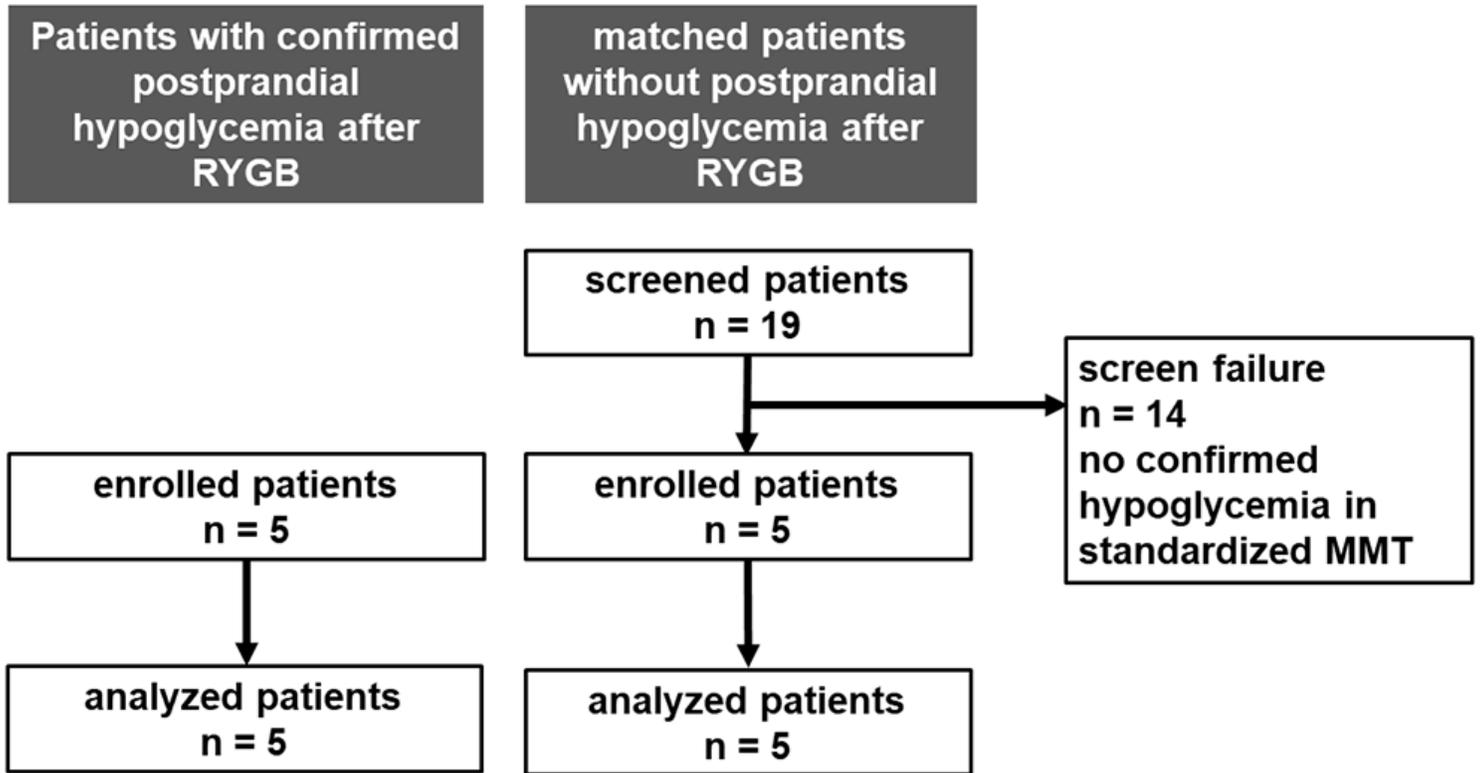


Figure 1

Study flow chart of recruiting of hypoglycemic patients and matched normoglycemic patients (PGBH = post gastric bypass hypoglycemia, MMT = mixed meal test).

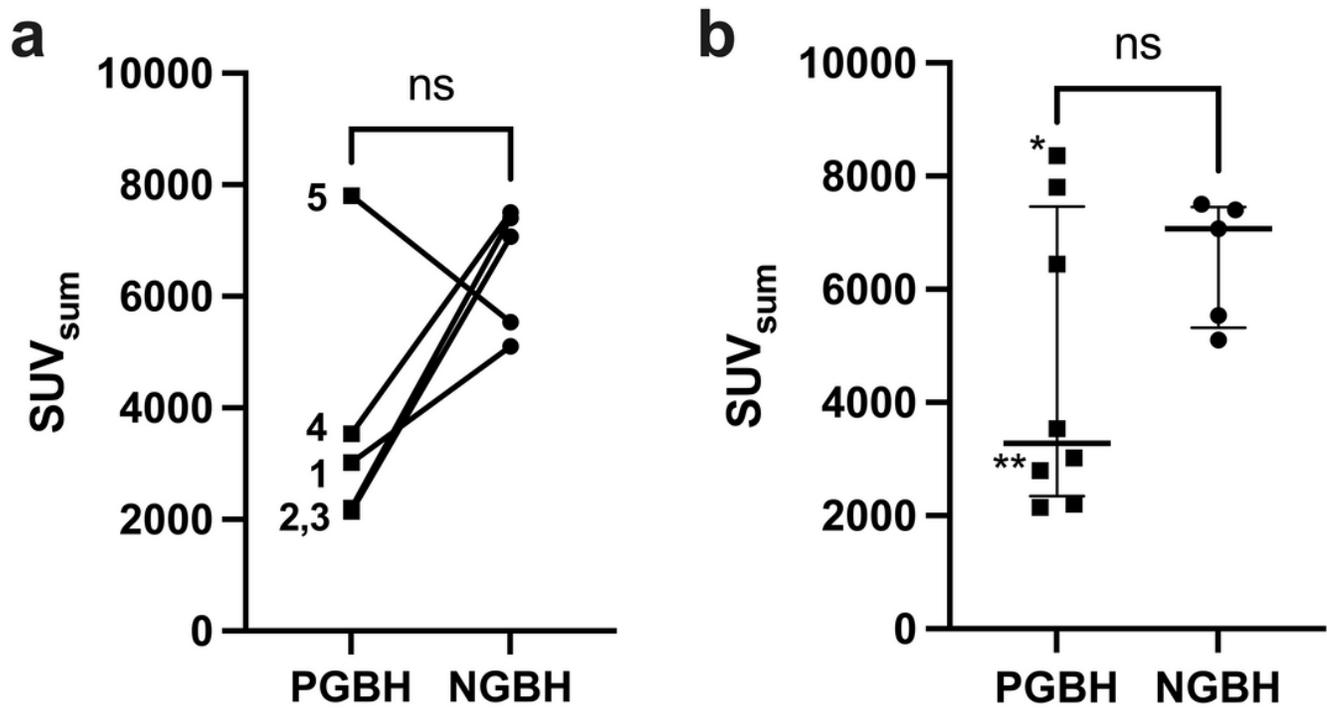


Figure 2

(a) SUV_{sum} of pancreas and duodenum in patients (1-5) with post gastric bypass hypoglycemia (PGBH, rectangles) and their respective normoglycemic matches (NGBH, dots) as well as (b) with additional PGBH patients of clinical routine examinations of which patient 8 with diffuse pancreatic enhancement is indicated with one asterisk (*) and patient 6 with focal enhancement in pancreatic tail with two asterisks (**).

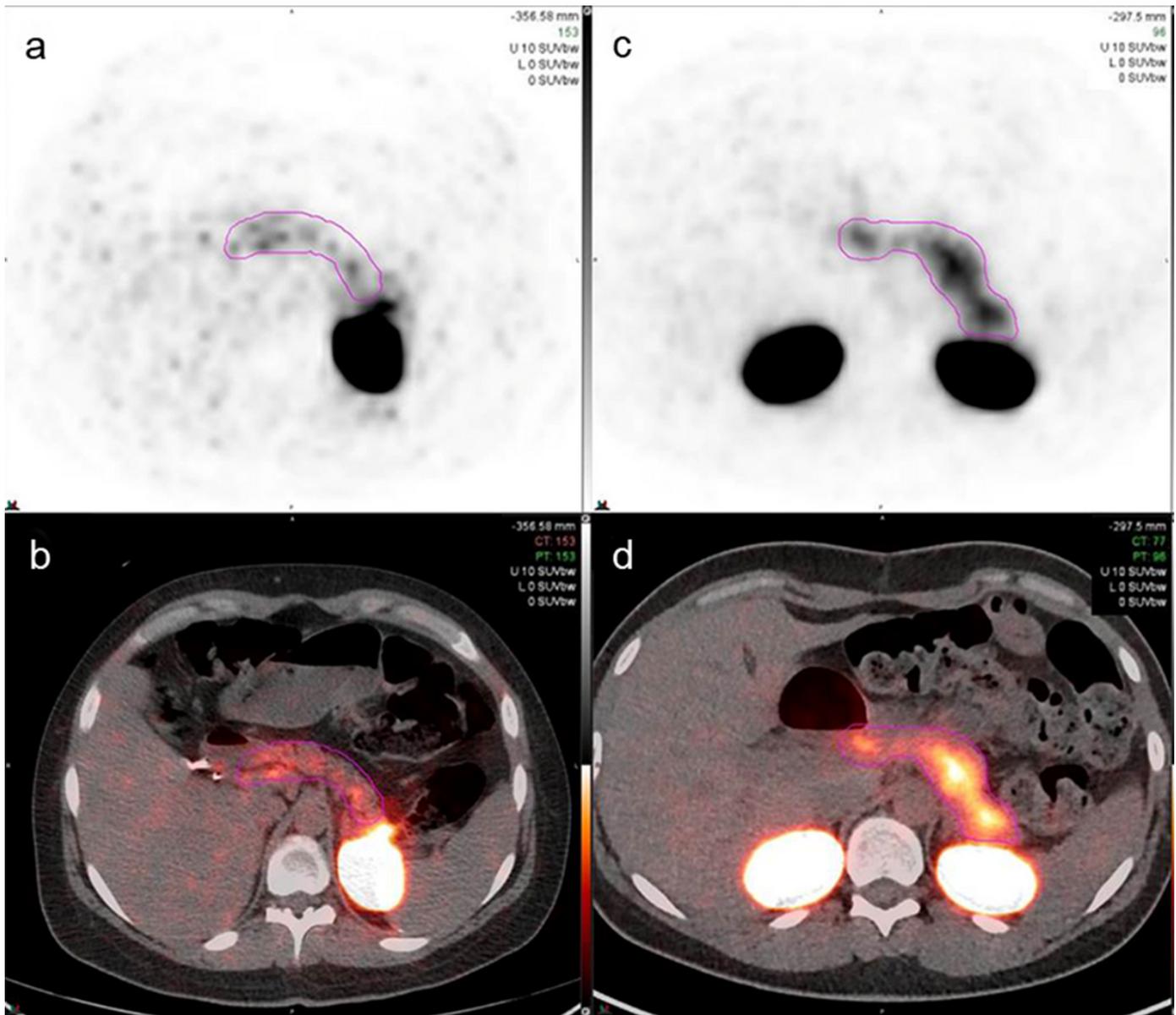


Figure 3

Axial view of the VOI on MIM software of hypoglycemic participant 3 (a+b) and normoglycemic match 3 (c+d)

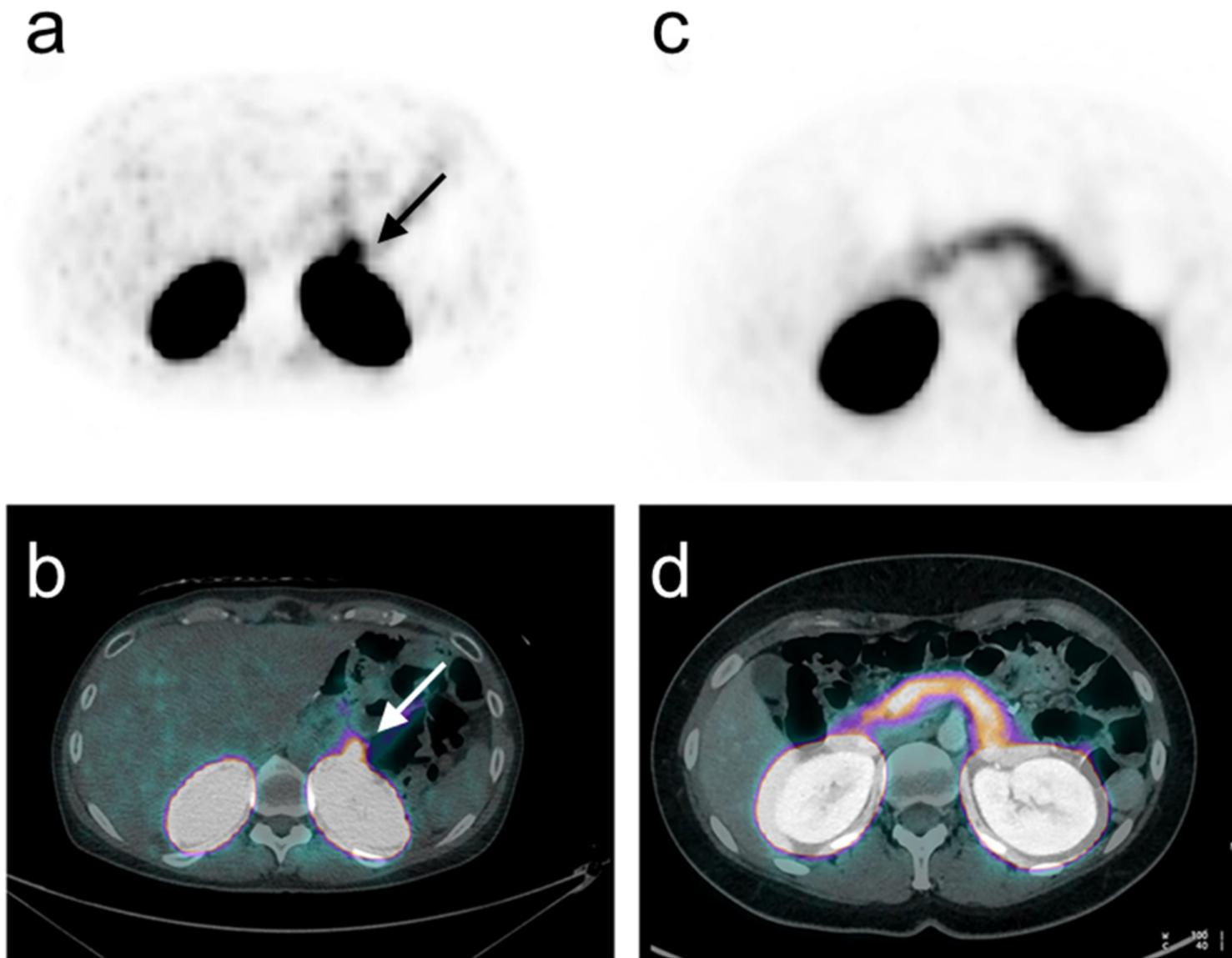


Figure 4

Axial view of the VOI on MIM software of patient 6 with focal uptake in pancreatic tail (a+b, arrow) and patient 8 without focal pancreatic uptake (c+d).

Supplementary Files

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- [GLP1RPETCTwithandwithoutPGBHsupplementarymaterial.docx](#)