Case Report

Brunner’s Gland Hyperplasia in a Patient after Roux-Y Gastric Bypass: An Important Pitfall in GLP-1 Receptor Imaging

Matthias Hepprich, Kwadwo Antwi, Beatrice Waser, Jean Claude Reubi, Damian Wild, and Emanuel R. Christ

1Division of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Petersgraben 4, 4053 Basel, Switzerland
2Clinic of Endocrinology, Cantonal Hospital Olten, Basler Strasse 150, 4600 Olten, Switzerland
3Division of Nuclear Medicine, University Hospital Basel, Petersgraben 4, 4053 Basel, Switzerland
4Institute of Pathology, University of Berne, Berne, Switzerland
5Center for Neuroendocrine and Endocrine Tumors, University Hospital Basel, Petersgraben 4, 4053 Basel, Switzerland

Correspondence should be addressed to Emanuel R. Christ; emanuel.christ@usb.ch

Received 2 December 2019; Revised 10 February 2020; Accepted 20 February 2020; Published 4 April 2020

Severe cases of postprandial hypoglycaemia after bariatric surgery can be a diagnostic and therapeutic challenge. The diagnostic role of 68Ga-DOTA-Exendin-4 PET/CT in postbariatric hypoglycaemia for further treatment decisions is unclear. We present a case of a 50-year-old woman with frequent and severe postprandial hypoglycaemic (≤2.5 mmol/L) episodes starting three years after Roux-Y gastric bypass. Despite strict dietary adherence and several medical therapies, the patient remained severely affected, and 68Ga-DOTA-Exendin-4 PET/CT was performed to exclude atypical presentation of an insulinoma or nesidioblastosis. No pancreatic abnormalities were found, but intensive tracer accumulation in the first and second part of the duodenum was detected, which proved to be hyperplastic Brunner’s glands on histology and were strongly positive for the glucagon-like peptide-1 receptor. This case provides histopathological verification that duodenal 68Ga-DOTA-Exendin-4 uptake is caused by uptake in Brunner’s glands and points to a potential relationship between bariatric surgery and Brunner’s glands.

1. Introduction

Postbariatric hypoglycaemia (PBH), formerly also described as late dumping, is a significant but under-recognized medical complication after bariatric surgery [1, 2]. Depending on the diagnostic test, recent data suggest higher incidence rates than previously thought, occurring in up to 48% of patients after Roux-Y gastric bypass and up to 25% of patients after sleeve gastrectomy [3–5]. The characteristic hallmark of PBH is a rapid increase in blood glucose shortly after ingestion of carbohydrates followed by increased insulin secretion, resulting in postprandial symptomatic hypoglycaemia [1]. The exact mechanisms of PBH have not been fully elucidated, and thus, no approved medical treatment exists so far. Patients, uncontrolled with dietary modifications, are often treated with off-label medications according to individual case-finding strategies [1, 6]. Based on controversial data suggesting an increase in β-cell mass or even development of nesidioblastosis, some severely affected patients were reported to be either anatomically reverted or (hemi)pancreatectomized with varying success rates [6].

For patients with other forms of endogenous hyperinsulinaemic hypoglycaemia, such as insulinoma or adult nesidioblastosis [7], glucagon-like peptide-1 receptor (GLP-1R) imaging using 68Ga-DOTA-Exendin-4 PET/CT has been reported to be very useful in localizing the insulinomas or focal nesidioblastosis [7, 8]. However, in vitro data using autoradiography in pancreatectomized patients with severe PBH indicate that the density of GLP-1R is not increased in islets compared to normal islets and is significantly lower than that in insulinomas [9]. GLP-1R imaging may, therefore, not be useful in patients with PBH to prove possible
nesidioblastosis in PBH. Nevertheless, GLP-1R imaging in vivo has not yet been reported in patients with PBH.

2. Case Presentation

A 50-year-old woman was admitted to our outpatient clinic for medical workup of a severe form of postprandial hypoglycaemia. Seven years earlier, a Roux-Y gastric bypass was performed due to morbid obesity (preoperative BMI 44.7 kg/m² and weight 129 kg). Within two years, the patient lost 57 kg (BMI 25.5 kg/m²). A year later, the patient noticed, for the first time, hypoglycaemic episodes 1-2 hours after meal intake, which were mainly characterized by loss of concentration, severe fatigue, and auditory and visual impairment that quickly resolved after intake of carbohydrates. An oral glucose tolerance test, at that time, confirmed the presence of symptomatic postprandial hypoglycaemia (2.9 mmol/l). Symptoms persisted despite dietary modifications of up to twelve small meals, each containing a maximum of 20 g of carbohydrates. Off-label treatment with acarbose, saxagliptin, and metformin by her treating physician reduced the frequency and severity of hypoglycaemic episodes but did not significantly improve the situation. Eventually, the patient was referred to our hospital. Her remaining personal history included a mild form of orthostatic dysregulation, migraine, and a multilocular nodular hepatic hyperplasia that required a left-sided hemihepatectomy 17 years ago. The clinical examination was unremarkable apart from irritation-free scars after hemihepatectomy (height, 168 cm; weight, 72 kg; BMI, 25.5 kg/m²; blood pressure, 127/67 mmHg; regular heartbeat, 80 bpm). Laboratory analysis including blood smear; biochemistry comprising electrolytes and kidney and liver parameters; glycated haemoglobin; blood lipids; iron; vitamins B1, B6, B12, and D; and zinc were within reference ranges. A continuous glucose flash monitoring system confirmed a typical pattern of postbariatric hypoglycaemia without any signs of fasting or nocturnal hypoglycaemia. A mixed-meal test (300 ml Ensure plus®) containing 60 g of carbohydrates after a 10-hour fasting period confirmed symptomatic postprandial hypoglycaemia (sweating, drowsiness, odd behaviour, and incoordination) at a glucose level of 2.5 mmol/l, and intravenous glucose administration was required for immediate remission of symptoms (Figure 1(a)). Due to the severe symptomatic presentation of the patient, a ⁶⁸Ga-DOTA-Exendin-4 PET/CT was performed to exclude an atypical presentation of an insulinoma or focal nesidioblastosis, which might be a surgical target [10–12]. Therein, the pancreas showed a homogeneous signal distribution (SUV 5.7–8.3), but intensive uptake in the first and second part of the duodenum (SUVmax of 10.0) was observed (Figure 1(b)). To further differentiate this unexpectedly strong tracer accumulation, a double-balloon enteroscopy was performed, which revealed macroscopically unremarkable intraluminal structures in the duodenum. Histologically, there were no signs of malignancy or inflammation (Figure 1(c)). Representative biopsies of the pars 2 duodeni showed normal mucosa with hyperplastic Brunner’s glands, which were strongly positive for the GLP-1 receptor on immunohistochemistry but negative for insulin (Figures 1(d) and 1(e)).

3. Discussion

This is the first case of PBH with a histologically proven GLP-1R-mediated increase in ⁶⁸Ga-DOTA-Exendin-4 uptake in hyperplastic Brunner’s glands of the duodenum.

A complex interplay of several factors is important for the development of PBH rather than a dominant single factor [1]. One pivotal factor is the glucagon-like peptide-1 (GLP-1) concentration, which is significantly increased in patients after bariatric surgery and specifically in those patients with PBH [2, 13, 14]. Antagonizing its effect by using exendin 9–39 lowers the rate of PBH [15]. However, there are also reports of successful treatment with GLP-1 agonists [16], but data on its mechanisms still need to be unravelled [17]. There is currently no commercially and medically approved compound available for the treatment of PBH [1]. On the other hand, GLP-1R imaging is a new molecular imaging method that is useful for the localization of insulinomas and eventually adult nesidioblastosis in patients with endogenous hyperinsulinaemic hypoglycaemia (EHH) [7, 8]. The physiological background relies on high expression levels of GLP-1 in benign insulinomas and adult nesidioblastosis. Studies using autoradiography indicate that normal pancreatic islets express approximately six times less GLP-1R than insulinomas [9, 18, 19].

The hyperplasia of Brunner’s glands and high accumulation of ⁶⁸Ga-DOTA-Exendin-4 in those Brunner’s glands resulting in a positive GLP-1R PET/CT scan (Figure 1(b)) is a surprising finding. The underlying pathophysiological mechanism is unclear. Brunner’s glands are mucinous glands that are primarily located in the proximal duodenum, where their glycoprotein-rich mucus serves as a protective barrier for underlying structures against acidic and pepsin-containing agents from the stomach. Incretins (glucagon, GLP-1, vasoactive intestinal peptide, secretin, and cholecystokinin) and neuronal factors (acetylcholine) stimulate mucus and bicarbonate secretion from the glands [20]. These glands have been convincingly shown in vitro to express GLP-1R in high density and with a strong membranous pattern via immunohistochemistry staining, reflecting the localization of this G-protein coupled receptor, as depicted in Figure 1(d) [19, 21]. Duodenal GLP-1R appears to be important for neuro-glucoregulation and gut-lipid-sensing [22]. Recent data also suggest a role for pathogen defence, mucosal layer protection, and mucosal healing by targeting GLP-1R in Brunner’s glands [23]. Whether these murine data translate to humans and whether ligands other than GLP-1 play a role remain uncertain [24]. It is conceivable that in patients with PBH, increased GLP-1 levels but also other incretins such as GLP-2 with trophic effects may also lead to hyperplasia of Brunner’s glands, as observed in this patient [25, 26]. However, the distinct pathophysiological role and the interrelationship between GLP1, GLP-1 receptors, and hyperplasia of Brunner’s glands remain to be determined.

Christ et al. speculated in 2009 that Brunner’s glands may explain the false-positive result in GLP-1 receptor imaging due to the close location of a lesion to the pancreatic head [27]. To the best of our knowledge, this is the first
histologically proven GLP-1R-mediated uptake of $^{68}$Ga-DOTA-Exendin-4 in duodenal Brunner’s gland hyperplasia detected with PET/CT (Figure 1). More importantly, immunohistochemistry of Brunner’s glands was negative for insulin (Figure 1(e)), suggesting that hyperplasia of Brunner’s glands is not related to autonomous insulin secretion in this patient. However, the relatively high GLP-1 levels observed in this patient compared to other published data [14] may be related to the clinical presentation and/or the hyperplasia of Brunner’s glands. Generally, hyperplasia of Brunner’s glands is reported to occur in response to an acidic environment or Helicobacter pylori infection and can even be obstructive [28]. However, in this patient, the remainder of the histological examination did not find any signs of inflammation or H. pylori colonization. The exact factor leading to Brunner’s gland hyperplasia remains to be determined. In addition, whether these changes are critical for the occurrence of postprandial hypoglycaemia after bypass surgery needs to be evaluated.

4. Conclusions

This case indicates a potential relationship between gastric bypass surgery, PBH, GLP-1, GLP-1R, and Brunner’s glands. Further investigation is warranted to identify the role of GLP-1 receptors in Brunner’s glands in patients after bariatric surgery and specifically in those affected by post-bariatric hypoglycaemia.

GLP-1 receptor-positive Brunner’s glands are an important differential diagnosis of positive $^{68}$Ga-DOTA-Exendin-4 PET/CT and a possible pitfall for the location of insulinomas.

Disclosure

Grant institutions had no influence on clinical management of the patient nor the writing process of this manuscript.

Conflicts of Interest

All authors report no competing interests with regard to this case report.

Acknowledgments

The authors are grateful to Prof. Lukas Degen, MD, Clinic of Gastroenterology, University Hospital Basel, for performing double-balloon enteroscopy and Prof. Luigi Terracciano,
MD, Institute of Pathology, University Hospital Basel, Basel, Switzerland, for providing H&E staining. Furthermore, they thank Hélène Mérreau and Marianne Böni-Schnetzler, PhD, for GLP-1 assay analysis. The development and implementation of GLP-1R imaging in endogenous hyperinsulinemic hypoglycaemia was supported by the Swiss National Science Foundation (grant no. 320030-152938) and the Desireé and Niels Yde’s Foundation (grant no. 389-12).

References

[1] M. Salehi, A. Vella, T. McLaughlin, and M.-E. Patti, “Hyperglycemia after gastric bypass surgery: current concepts and controversies,” The Journal of Clinical Endocrinology & Metabolism, vol. 103, no. 8, pp. 2815–2826, 2018.

[2] J. J. Holst and S. Madsbad, “Mechanisms of surgical control of type 2 diabetes: GLP-1 is key factor,” Surgery for Obesity and Related Diseases, vol. 12, no. 6, pp. 1236–1242, 2016.

[3] M. Emous, M. van den Broek, R. Wijma et al., “Prevalence of hypoglycaemia in a random population after Roux-en-Y gastric bypass after a meal test,” Endocrine Connections, vol. 8, no. 7, pp. 969–978, 2019.

[4] E. Capristo, S. Panunzi, A. De Gaetano et al., “Incidence of hypoglycemia after gastric bypass vs sleeve gastrectomy: a randomized trial,” The Journal of Clinical Endocrinology & Metabolism, vol. 103, no. 6, pp. 2136–2146, 2018.

[5] C. J. Lee, J. M. Clark, M. Schweitzer et al., “Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy,” Obesity (Silver Spring), vol. 23, no. 5, pp. 1079–1084, 2015.

[6] D. Eisenberg, D. E. Azagury, S. Ghiassi, B. T. Grover, and J. J. Kim, “ASMBS position statement on postprandial hyperinsulinemic hypoglycaemia after bariatric surgery,” Surgery for Obesity and Related Diseases, vol. 13, no. 3, pp. 371–378, 2017.

[7] E. Christ, D. Wild, K. Antwi et al., “Preoperative localization of adult nesidioblastosis using 68Ga-DOTA-exendin-4-PET/CT,” Endocrine, vol. 50, no. 3, pp. 821–823, 2015.

[8] K. Reubi, M. Fani, T. Heye et al., “Comparison of glucagon-like peptide-1 receptor (GLP-1R) PET/CT, SPECT/CT and 3T MRI for the localisation of occult insulinomas: evaluation of diagnostic accuracy in a prospective crossover imaging study,” European Journal of Nuclear Medicine and Molecular Imaging, vol. 45, no. 13, pp. 2318–2327, 2018.

[9] J. C. Gloor, A. Perren, R. Rehmann et al., “Glucagon-like peptide-1 (GLP-1) receptors are not overexpressed in pancreatic islets from patients with severe hyperinsulinemic hypoglycaemia following gastric bypass,” Diabetologia, vol. 53, no. 12, pp. 2641–2645, 2010.

[10] N. Dadheech, D. Garrel, and J. Buteau, “Evidence of unrestrained beta-cell proliferation and neogenesis in a patient with hyperinsulinemic hypoglycaemia after gastric bypass surgery,” Islets, vol. 10, no. 6, pp. 213–220, 2018.

[11] A. L. d. V. Macedo, J. T. Hidal, W. Marcondes, and F. C. Mauro, “Robotic near-total pancreatectomy for nesidioblastosis after bariatric surgery,” Obesity Surgery, vol. 26, no. 12, pp. 3082–3083, 2016.

[12] J. M. Duff, H. K. Ghayee, M. Weber, and R. M. Thomas, “Delayed imaging presentation of a symptomatic insulinoma after bariatric surgery,” Journal of Gastrointestinal Surgery, vol. 21, no. 2, pp. 412–414, 2017.

[13] A. B. Goldfine, E. C. Mun, E. Devine et al., “Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal,” The Journal of Clinical Endocrinology & Metabolism, vol. 92, no. 12, pp. 4678–4685, 2007.

[14] M. Salehi, R. L. Prigeon, and D. A. D’Alessio, “Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans,” Diabetes, vol. 60, no. 9, pp. 2308–2314, 2011.

[15] C. M. Craig, L.-F. Liu, C. F. Deacon, J. J. Holst, and T. L. McLaughlin, “Critical role for GLP-1 in symptomatic post-bariatric hypoglycaemia,” Diabetologia, vol. 60, no. 3, pp. 531–540, 2017.

[16] N. Abrahamsson, B. E. Enگstrøm, M. Sundbom, and F. A. Karlsson, “GLP1 analogs as treatment of postprandial hypoglycemia following gastric bypass surgery: a potential new indication?” European Journal of Endocrinology, vol. 169, no. 6, pp. 885–889, 2013.

[17] K. E. Almby, N. Abrahamsson, M. H. Lundqvist et al., “Effects of GLP-1 on counter-regulatory responses during hypoglycemia after GBP surgery,” European Journal of Endocrinology, vol. 181, no. 2, pp. 161–171, 2019.

[18] M. Korner, M. Stockli, B. Waser, and J. C. Reubi, “GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting,” Journal of Nuclear Medicine, vol. 48, no. 5, pp. 736–743, 2007.

[19] B. Waser, A. Blank, E. Karamitopoulou, A. Perren, and J. C. Reubi, “Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas,” Modern Pathology, vol. 28, no. 3, pp. 391–402, 2015.

[20] W. J. Krause, “Brunner’s glands: a structural, histochemical and pathological profile,” Progress in Histochemistry and Cytochemistry, vol. 35, no. 4, pp. 259–367, 2000.

[21] C. Pyke, R. S. Heller, R. K. Kirk et al., “GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody,” Endocrinology, vol. 155, no. 4, pp. 1280–1290, 2014.

[22] M. Yang, J. Wang, S. Wu et al., “Duodenal GLP-1 signaling regulates hepatic glucose production through a PKC-δ-dependent neurocircuitry,” Cell Death & Disease, vol. 8, no. 2, Article ID e2609, 2017.

[23] C. H. Bang-Berthelsen, T. L. Holm, C. Pyke et al., “GLP-1 induces barrier protective expression in Brunner’s glands and regulates colonic inflammation,” Inflammatory Bowel Diseases, vol. 22, no. 9, pp. 2078–2097, 2016.

[24] L. L. Fleckner, Q. Huang, T. J. Brown, and D. J. Drucker, “Oxysterol modulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure,” Gastroenterology, vol. 127, no. 2, pp. 546–558, 2004.

[25] J. A. Koehler, L. L. Baggio, B. Yusta et al., “GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7,” Cell Metabolism, vol. 21, no. 3, pp. 379–391, 2015.

[26] J. Debédat, C. Amouyal, J. Aron-Wisniewsky, and K. Clément, “Impact of bariatric surgery on type 2 diabetes: contribution of inflammation and gut microbiome?” Seminars in Immunopathology, vol. 41, no. 4, pp. 461–475, 2019.

[27] E. Christ, D. Wild, F. Forrer et al., “Glucagon-like peptide-1 receptor imaging for localization of insulinomas,” The Journal of Clinical Endocrinology & Metabolism, vol. 94, no. 6, pp. 4398–4405, 2009.

[28] S. H. Park, K.-M. Park, and J. S. Kim, “18F-FDG-avid Brunner gland hyperplasia,” Clinical Nuclear Medicine, vol. 39, no. 8, pp. 728–730, 2014.