

## CASE REPORT

# Embolization for Insulinoma in Complicated Severe Obesity: Description of an Inoperable Case and Review of the Literature

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### ABSTRACT

**Context** Insulinoma is a rare cause of obesity. In severely obese patients, high anesthesiological risk can prompt the use of local non-surgical ablative therapies. **Case report** A seventy-two-year old female patient was referred to our institution for morbid complicated obesity by insulinoma of the pancreas head, sized 1.5 × 1.7 cm as assessed by computed tomography scan. Because the patient was considered inoperable due to progressively worsening comorbidities and was poorly responsive to diazoxide and other medical treatments, she was subjected to selective trans-catheter embolization. Due to partial disease control, the procedure was repeated, and led to shrinkage and partial necrosis of the tumor; followed by recovery of hypoglycemia. As a result, the patient lost 28 kg in bodyweight with marked reduction of abdominal adiposity, and achieved a significant clinical improvement. Four years post-procedure, mild recurrence of insulinoma-related symptoms was documented and diazoxide was restarted with full symptom response. At present, after 10-year follow-up, the patient is stable and the residual disease remains well controlled. Analysis of Literature suggests that selective trans-catheter embolization is a feasible, safe and repeatable procedure in patients who are elderly or poor candidate to surgery or if they refuse surgery, when harbouring single, well-defined, localized insulinoma. **Conclusion** Considering its positive outcomes, non-surgical ablation of symptomatic insulinomas is a feasible, safe and beneficial alternative to surgery in selected patients.

### INTRODUCTION

Insulinomas are the most common functioning pancreatic neuroendocrine tumor (pNET) and account for 20-30% of cases [1]. Most insulinomas are sporadic and develop as benign, solitary intrapancreatic lesions, while ectopic and aggressive forms are extremely rare

[2, 3]. The overall clinical hallmark of insulinoma is the Whipple's triad, which typically includes glucose-responsive hypoglycaemia with neuroglycopenia [4]. Cognitive dysfunction can be as severe as to trigger seizures, unconsciousness, coma or even permanent brain damage, or simulate a cerebrovascular event [4]. Because snacking helps insulinoma-bearing patients to compensate for recurrent hypoglycaemia, a potential consequence of insulinoma is bodyweight accrual. This affects up to 40% of patients, and often mimics the clinical course of the metabolic syndrome [5, 6, 7].

Upon insulinoma localization, surgery by enucleation or distal pancreatectomy represents the therapeutic mainstay in nearly 98% of cases; yet postsurgical complications can occur in 16-43% of patients, particularly if abdominally obese [2, 8, 9]. Medical alternatives, such as diazoxide, calcium channel blockers, hydrochlorothiazide and somatostatin analogues, are available for those who are inoperable, show persistent postsurgical disease, or necessitate clinical improvement prior to undergoing surgery [10]. Unresponsiveness to medical therapies or

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**Abbreviations** BMI body mass index; COPD chronic obstructive pulmonary disease; CPAP continuous positive airway pressure; CT computed tomography; DXA dual-energy X-ray absorptiometry; EUS endoscopic ultrasonography; FM fat mass; MEN multiple endocrine neoplasia; OSAS obstructive sleep apnea syndrome; pNET pancreatic neuroendocrine tumor; PVA polyvinyl alcohol

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adverse events usually prompt to explore alternative therapies for insulinoma. However, evidence on feasibility and usefulness of non-surgical ablative interventions is sparse. This case report illustrates the multifold therapeutic approach for an elderly obese patient with insulinoma, in whom control of disease symptoms was achieved by selective embolization. In addition, we have summarized currently available literature on the safety and usefulness of non-surgical ablative approaches in insulinoma-bearing patients.

### CLINICAL PRESENTATION

In March 2007, a 72-year old woman was referred to Istituto Auxologico Italiano, Verbania, Italy, for complicated diet-resistant obesity. Her clinical record was noticeable for arterial hypertension, treated since 1997 with calcium channel blocker, obstructive sleep apnea syndrome (OSAS) treated since 2004 with continuous positive airway pressure (CPAP) ventilotherapy, mild depression well controlled with benzodiazepines. She reported two full-term pregnancies and physiological menopause at the age of 52 years. In 1996, she had started complaining of episodic dizziness and hyperhidrosis responsive to sugary snacks. In 1999, she was diagnosed with a transient ischemic attack. Narratively, in that occasion, her blood glucose on admission was 9 mg/dl. In 2005, the patient was referred to an endocrine centre to perform a diagnostic workup. She underwent a prolonged fasting test, which was stopped after 16 hours because of symptomatic hypoglycaemia accompanied by inappropriately high insulin and c-peptide levels. Sulfonylurea metabolites screening was negative. Abdominal CT scan visualized a single lesion located in the pancreas head, while radiolabelled octreotide scintigraphy showed no uptake. Consistent with the diagnosis of insulinoma and because of high anesthesiological risk, she was discharged on diazoxide therapy, progressively increased up to 800 mg daily.

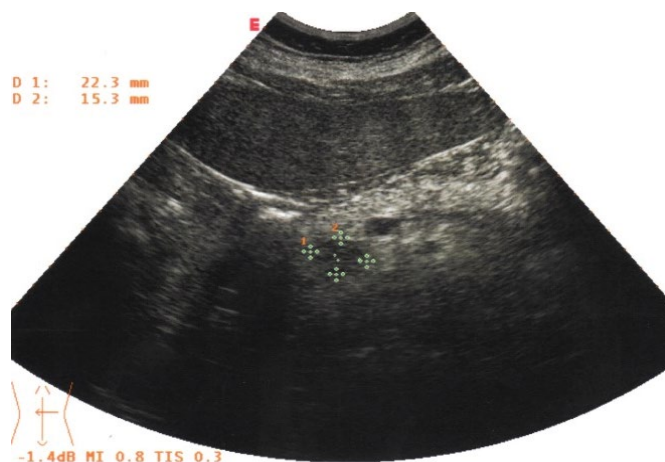
On admission to our clinic, the patient referred that she had withdrawn diazoxide therapy because of lack of efficacy. She appeared fatigued and suffered from oxygen desaturation. BMI was 50.3 kg/m<sup>2</sup> with abdominal obesity, and trunk fat mass (FM) by dual-energy X-ray absorptiometry (DXA) was 46.7% of total trunk. A fasting test was interrupted after 6 hours for hypoglycemia. There was no report of other endocrine disorders. A summary of clinical data is shown in **Table 1**. Echocardiography showed left ventricular hypertrophy with abnormal diastolic filling, left atrial enlargement, pulmonary hypertension (45 mmHg), mild mitral and aortic regurgitation. Pulmonary function tests indicated chronic obstructive pulmonary disease (COPD). Ultrasonography (**Figure 1**) and CT scan (**Figure 2a**) showed a solitary hypervascularized, well-defined, homogenous 1.5 by 1.7 cm large lesion with arterial enhancement located in the head of the pancreas, close to the medial wall of the duodenum and the main pancreatic duct. No nodal involvement was visible (**Figure 2b**).

Because of her overall poor medical conditions and unresponsiveness to short-term s.c. octreotide treatment, the patient was referred to the Istituto Nazionale Tumori in Milan for trans-catheter arterial embolization of the pancreatic tumor in May 2007. During the procedure, performed by experienced dedicated radiologists (BD and VT), arteriography via right femoral approach of the celiac trunk and the gastroduodenal artery showed in the late arterial phase a hypervascular mass in the pancreas head (**Figure 3a**). After selective microcatheterization of the gastroduodenal artery, tumor embolization was performed using blood flow exclusively to direct 2 ml of tris-acryl gelatine-coated 40 µm microspheres diluted with contrast material and saline solution, which were slowly injected in portions until stasis of blood flow in the tumor was obtained (**Figure 3b**). The procedure was well tolerated with the exception of transient pain and abdominal discomfort associated with hyperamylasaemia and a mild increase in lipase levels, which subsided spontaneously within two weeks. CT scan at 6 months post-embolization showed a partly necrotic tumor, and the patient remained

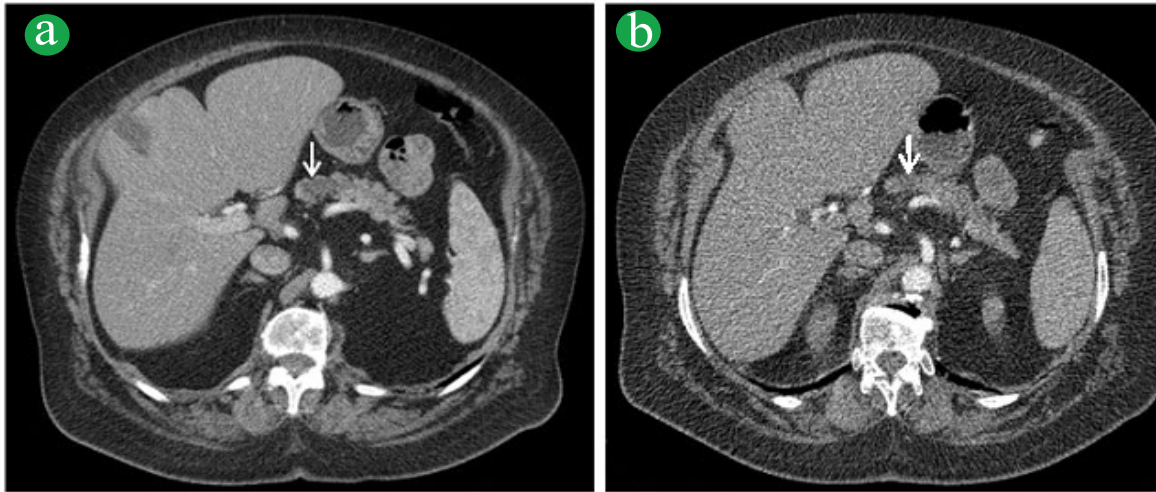
**Table 1.** Summary of anthropometric and biochemical data relating to pre-treatment and post-treatment period and during the last follow up evaluation.

Parameters	Before embolization - 2007	After embolization - 2009	Last follow up - 2017
Weight (kg)	119.4	82.5	104
Height (cm)	154	154	154
BMI (kg/m <sup>2</sup> )	50.3	34.8	43.8
Waist (cm)	138	116	123
Hip (cm)	125	120	123
WHR	1.1	0.96	1
FM (%)	52.3	47.4	48.2
FFM (kg)	57.1	46.5	53.9
REE (kcal/24 hour)	1575	1428	na
Fasting Glucose (mg/dL)	49	67	78
Fasting Insulin (mU/L)	40.5	6.7	18.1

BMI body mass index; FFM free fat mass; FM fat mass; REE resting energy expenditure; WHR Waist-to-hip ratio



**Figure 1.** Insulinoma on pre-treatment abdomen ultrasonography: the pancreatic lesion appeared as a hypochoic circular lesion.



**Figure 2.** Abdominal CT. **(a).** Insulinoma on pre-treatment CT (arrow): the pancreatic lesion was 1.5 cm × 1.7 cm large. **(b).** Insulinoma on post-treatment CT: the pancreatic lesion appeared markedly reduced in size with necrotic behaviour.



**Figure 3.** Angiogram of gastroduodenal artery. **(a).** In the late arterial phase the insulinoma appears as hypervascularized mass. **(b).** Angiogram 5 min after embolization demonstrates the insulinoma completely devascularized.

free of endocrine symptoms for 8 month. Due to residual tumor activity with mild symptom recurrence, she underwent repeat embolization in June 2008 without complications, which led to full biochemical and clinical control of the disease (**Table 1**). As a result, she lost a significant 28 kg in bodyweight with marked reduction of abdominal adiposity (trunk FM, 36.5%), and achieved significant improvements in echocardiography, oxygen saturation and pulmonary function tests. CT at 6 months post-embolization documented a marked reduction of the insulinoma size, which appeared as a hypovascular partly necrotic mass (**Figure 2b**) and remained unaltered for the following years. In 2012, however, recurrence of mild insulinoma-related symptoms led us to restart diazoxide therapy (up to 200 mg/die) with complete symptom control. Despite the lack of biochemical or clinical signs of multiple endocrine neoplasia (MEN), in 2014, due to the detection of isolated hypogonadotropinemia, the patient

underwent pituitary MRI, which revealed the presence of a microadenoma. No abnormalities in the secretion of the other anterior pituitary hormones were disclosed. Genetic analysis performed on MEN1 and CDKN1B genes encoding menin and p-27(Kip1) respectively, ruled out mutations linked to MEN 1. Up to now, the patient undergoes regular yearly follow-ups at our centre, and residual disease remains biochemically well controlled on diazoxide therapy.

### DISCUSSION

This case describes an inoperable insulinoma-bearing elderly patient with multiple comorbidities from severe obesity, who could achieve control of her life-threatening disease by undergoing selective trans-catheter embolization of the lesion.

Despite the predominant benign nature of insulinomas in >90% of cases, uncontrolled insulin hypersecretion causes



hypoglycaemia and leads to compensatory carbohydrate-rich overfeeding. Diagnostic delay may trigger obesity [6] and thus prompt severe complications, which significantly increase cardiometabolic risk [11, 12]. In the case herein reported, abdominal obesity and progressive onset of arterial hypertension, hypertrophic cardiomyopathy with valve disease, pulmonary hypertension, and ventilatory disorders with OSAS were leading features, suggestive of an unfavorable clinical outcome and high anesthesiological risk [12].

According to the European Neuroendocrine Tumor Society guidelines [13], the use of ablative therapy (ethanol injection or radiofrequency) can be successfully used in patients with localized insulinoma who are not candidate to surgery. These procedures can use endoscopic or percutaneous approach, and be assisted by endoscopic ultrasonography (EUS) or CT guidance. Trans-catheter embolization is an alternative approach which has been reportedly used so far in 5 cases. A summary of available literature on these ablative approaches is provided in **Table 2**. In 1982, Moore et al. described the case of a young patient who underwent surgical resection of an insulinoma with a recurrence one year later, treated with embolization using microfibrillar collagen [14]. Ten years later, Uflacker et al. reported embolization with small polyvinyl alcohol (PVA) particles in 2 cases of insulinoma patients [15]. In 2008, Rott et al. described the case of an elderly woman with a symptomatic insulinoma who refused surgery and was treated using trisacryl gelatin microspheres as a definitive treatment [16]. The last case was reported by Peppia et al., who described a young patient with

MEN 1 and recurrent insulinoma, considered inoperable due to tumor adhesions to large blood vessels and prior repeated surgeries. The patient was treated by repeated embolization using spherical polyvinyl alcohol particles, resulting in shrinkage of the tumor and improvement in the frequency and severity of the hypoglycaemic episodes [17]. Compared to these previous reports, our case patient is characterized by high degree of adiposity, increasing severity of systemic complications, and long follow-up duration.

The lack of comparative data among the different ablative techniques reviewed herein (**Table 2**) does not allow to discriminate which procedure achieves the best outcome for this rare disease. Indeed, our choice of trans-arterial embolization depended on the extensive operators' experience and the high degree of abdominal adiposity of our patient. In fact, alternative methods such as EUS-guided ethanol injection, could have been difficult to perform with precision in this case and ethanol injection is not free of complications due to the scarce control of its diffusion. Because islet cells are surrounded by a rich blood supply and receive about 10-15% of the pancreatic blood flow, this case seems to confirm that insulinoma is a suitable target for transcatheter embolization, alternative to surgical treatment in insulinoma-bearing patients with advanced age, severe obesity, comorbidities and with increased risk for postoperative complications. High-quality microcatheters and precisely applicable embolization materials minimize the risk of severe or long-term complication [16]. Transcatheter embolization for insulinomas is also favoured by minimal invasiveness,

**Table 2.** Summary of the main case reports related to minimally invasive therapeutic procedures of benign insulinomas.

Therapeutic Procedure	Author	N° of cases	Age	Gender	Tumor Size (mm)	Location of Tumor	Rationale for foregoing resection	Comorbidities	N° of treatments	Post-procedure complications	Follow up (months)	Recurrence	Time of Recurrence (months)
<b>Embolization</b>	Moore [14]	1	38	F	20	Head	Surgical failure	None	1	- Low-back pain - Nausea - ↑ in liver enzyme values	11	No	-
	Uflacker [15]	2	56	M	18	Head	Refusal of surgery	Obesity	2	- Abdominal pain - Hyperamylasaemia	18	No	-
			49	M	20	Body	Emergency	Not specified	1	None	40	No	-
	Rott [16]	1	84	F	14	Head	Refusal of surgery	Not specified	1	- Abdominal pain - Mild pancreatitis	12	No	-
	Peppia [17]	1	30	M	30	Peripancreatic	Recurrence after total pancreatectomy	MEN 1	1	Abdominal pain	12	Yes	12
Our case	1	72	F	17	Head	Presence of significant comorbidities	- Morbid abdominal obesity - Cardiopulmonary problems (hypertensive cardiomyopathy, OSAs, COPD, pulmonary hypertension)	2	- Abdominal pain - Mild pancreatitis	108	Yes	48	

Author	Year	Age	Sex	Height	Weight	Site	Reason	Comorbidities	Number	Complications	Survival (%)	Quality of Life	Notes
Jürgensen [18]	1	78	F	13		Body	Refusal of surgery	Not specified	1	- Abdominal pain - Mild acute pancreatitis	34	No	-
Deprez [19]	1	78	F	20		Head	Presence of significant comorbidities	- Arterial hypertension - Severe aortic stenosis - Overweight	1	- Mild pancreatitis - Ulcer of the duodenal wall	24	No	-
Vleggaar [20]	1	82	F	9.5		Body	High risk of complication	Heart failure	1	None	6	No	-
		67	M	11		Head	Refusal of surgery	Not specified	1	None	16	No	-
		72	F	17		Head	Refusal of surgery	- Thyroid cancer - COPD	3	None	13	Yes	13
		60	M	14		Head	Refusal of surgery	Not specified	1	- Fluid collection - Pseudocyst	35	No	-
		82	M	23		Tail	Presence of significant comorbidities	Not specified	2	None	13	Yes	13
Levy [21]	8	80	F	21		Body	Presence of significant comorbidities	Not specified	2	None	12	No	-
		57	F	9		Head	Refusal of surgery	Not specified	2	None	38	Yes	38
		34	M	16		Head	Multiple previous abdominal operations	MEN 1	2	None	5	No	-
		79	F	15		Head	Intraoperative bleeding during attempted resection	Not specified	1	- Pancreatitis - Pseudocyst	7	No	-
Lee [22]	1	26	F	17 (multiple lesions)		Head, body, tail	Elective	MEN 1	1	None	12	No	-
		48	F	10		Head	Elective	Not specified	1	None	6	No	-
		56	F	5.4		Head	Elective	Not specified	1	None	4	No	-
Qin [23]	4	56	M	11.8		Junction of head and body	Elective	Not specified	1	None	5	No	-
		66	F	10		Body	Elective	Not specified	1	None	2	No	-
		59 (mean age)	N/A	N/A	N/A		Presence of significant comorbidities		2 (n=1)	N/A	17.3 (mean)		
Yang [24]	4						Surgical failure	N/A	1 (n=3)		(range, 2-30)	1	N/A
							Refusal of surgery						
		99	M	9		Head	Age	Not specified	1	None	Not specified	No	-
Paik [25]	3	20	M	11		Head	Not specified	Not specified	1	None	Not specified	No	-
		32	M	14		Head	Surgical failure	Not specified	2	Abdominal pain	6	No	-
							Presence of significant comorbidities	- Decompensated heart failure - Atrial fibrillation - Asthma and COPD - Post-traumatic stress disorder	1	None	1.5	No	-
Trikudanathan [26]	1	66	M	14		Head							

									- Obesity	None		
									- Arterial hypertension			
									- Ischemic cardiomyopathy			
	Limmer [27]	1	80	F	15	Tail	High surgical risk	1		7	No	-
									- Cholecystolithiasis			
									- Epilepsy and meningeoma			
									- Breast cancer			
									- Obesity	Transitory diabetes		
									- Arterial hypertension			
<b>Radiofrequency Ablation</b>	Procházka [28]	1	75	F	17	Body	Presence of significant comorbidities	1		3	No	-
									- Chronic ischemic heart disease			
									- Liver steatosis			
									- Anxiodepressive syndrome			
									- Atrial fibrillation	None		
	Waung [29]	1	70	F	18	Uncinate	Presence of significant comorbidities	3		10	No	-
									- COPD			
			42	M	14	Body	Risk associated with poor cardiac status	1		12	No	-
									- Chronic pancreatitis	None		
									- Cardiomyopathy			
									- Morbid obesity			
	Lakhtakia [30]	3	41	M	17	Genu	Risk associated with obesity	1		12	No	-
									- Not specified			
			52	M	22 (multiple lesions)	Head, body, tail	Concern over major surgery	1		12	No	-
									- Non-small cell lung cancer	None		
									- Atrial fibrillation			
<b>Percutaneous Microwave Ablation</b>	Chen [31]	1	60	M	32	Neck	Presence of significant comorbidities and limited life expectancy	1		3	No	-
									- COPD and OSA			
									- Morbid obesity			
									- Prior pulmonary embolism			

COPD chronic obstructive pulmonary disease; MEN 1 multiple endocrine neoplasia type 1; OSA obstructive sleep apnea

repeatability, limited hospital stay, and lower risk of post-procedural complications as compared to surgical treatment, including abdominal pain, mild pancreatitis and transitory mild diabetes [14, 15, 16, 17]. Although transcatheter embolization carries the risk of conventional angiography plus the complication of inadvertent embolization of non-targeted structures, these adverse effects can be avoided by obtaining a super selective arterial approach to the tumor area and performing embolization with permanent particles under fluoroscopic and angiographic control. In our patient, only a mild transiently elevation of amylase and lipase was observed, which subsided spontaneously within 2 weeks.

Our 10-yr experience with this patient suggests that trans-catheter embolization was able to induce partial tumor necrosis, contributing to control hypoglycaemic symptoms and consequently improved intractable obesity and its comorbidities.

Considering such positive outcomes and based on literature data [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33], we are inclined to suggest that non-

surgical ablation of symptomatic insulinomas is a feasible, safe and repeatable procedure in patients who are elderly or poor candidate to surgery or if they refuse surgery, when harbouring single, well-defined, localized insulinoma.

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### Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

### Conflict of Interest

The authors have declared that no competing interests exist.

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