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Review Article

Extended Subtotal Pancreatectomy (Near Total) For Adults With Diffuse Nesidioblastosis

Short Title: Extended subtotal pancreatectomy for nesidioblastosis

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Abstract

Objective: To present a case series of patients diagnosed with hypoglycemia syndrome caused by non-tumorous pancreatogenic hyperinsulinism who underwent extended subtotal pancreatectomy.

Methods: All patients admitted with a diagnosis of hypoglycemia syndrome due to endogenous hyperinsulinism underwent a comprehensive laboratory and meticulous laboratory evaluation protocol. This protocol included a fasting test and measurements of glucose, insulin, C-peptide, proinsulin, and counterregulatory hormone levels. The diagnosis was based on the Whipple triad, a stringent set of criteria that requires glucose levels to be less than 45 mg/dL, insulin levels greater than five µU/mL, C-peptide levels above 1.2 picograms/mL, and proinsulin levels exceeding 5.0 pmol/L. Clinical evaluations included conventional and interventional Radiology and Imaging Studies, ensuring a thorough and accurate diagnosis.

Results: 132 patients (89.7%) were identified as having insulinoma, while 15 patients (10.3%) had nesidioblastosis. Given the lack of response to medical treatment and the findings of diffuse nesidioblastosis, all patients underwent extended subtotal pancreatectomy using an open surgical technique. Histopathological studies confirmed the diagnosis. The mean follow-up duration was 40 months, during which there were no recurrences of hypoglycemia, malabsorption issues, or neurological complications.

Conclusion: Nesidioblastosis should be considered in cases of non-tumorous hypoglycemia syndrome caused by pancreatogenic hyperinsulinism. Extended subtotal pancreatectomy is a viable option for patients who do not respond to medical treatment and present with diffuse nesidioblastosis.

Keywords: Hypoglycemia; nesidioblastosis; extended subtotal pancreatectomy

Introduction:

The most common cause of hypoglycemia due to endogenous hyperinsulinism in adults is insulinoma, a neuroendocrine tumor. It is well-differentiated in most cases and, typically benign and unifocal, is cured with surgical resection. 1,2 Less common is beta-cell nesidioblastosis, a rare entity characterized by abnormal beta-cell hyperplasia and the architectural arrangement of the pancreatic islets. It consists of a functional defect in beta cells and is widely recognized as the primary cause of persistent hyperinsulinemic hypoglycemia in newborns, also called congenital hyperinsulinemic hypoglycemia. Several genetic abnormalities have been identified as its cause, the most important being mutations in two genes, ABCC8 (Sur1) and KCNII (Kir6.2), on the short arm of chromosome 11 that

encode subunits of the ATP-sensitive potassium channel in the beta-cell membrane. These mutations cause loss of gene function and lead to permanent insulin secretion. Other causes have been identified, such as loss of function due to mutations in glucokinase (GCK), glutamate dehydrogenase (GLUD1), hydroxyl coenzyme A dehydrogenase (HADHi), plasma membrane pyruvate transporter (SLC16A1), mitochondrial uncoupling protein (UCP2), and nuclear transcription factor (HNF4a), among others. [3,4,5,6] Some congenital and adult-onset hyperinsulinism forms have been associated with Beckwith-Wiedermann, Kabuki, and Turner syndromes. [7] An association between gestational diabetes and congenital and adult-onset hyperinsulinism has been reported in families with a mutation that inactivates the ACC8E1506K gene. In these cases, the net effect is failing to reduce pancreatic insulin secretion in the presence of hypoglycemia (serum glucose levels below 60 mg/dL) [8,9]. An atypical form of congenital hyperinsulinism characterized by morphological mosaicism has recently been described, referring to two types of islets: large islets with beta cells with enriched cytoplasm and large nuclei coexisting with small islets with beta cells showing small cytoplasm and nuclei.[10] In these cases, it has given pause to the possibility of removing symptoms after a partial pancreatectomy.[11] With the advent of surgical alternatives for the treatment of morbid obesity, a cause of acquired nesidioblastosis in adults, it occurs after Roux-en-Y gastric bypass. This type of surgery increases trophic polypeptides in beta cells, such as glucagon-like peptide 1, contributing to beta cell hypertrophy. The annual incidence is 0.09/100,000, with a mean patient age of 47.[12,13] The term nesidioblastosis was coined by Laidlaw[14] in 1938 to describe the neoformation of pancreatic islets from the ductal epithelium. In 1971, Yakovac et al.[15] used this same term to report findings in the pancreas of 12 children with intractable hypoglycemia. The first case in adults was reported in 1975[16]; since then, the term nesidioblastosis has been used collectively to designate pancreatic changes in all conditions of persistent nontumoral hyperinsulinism (insulinoma). Major and minor histologic criteria have been proposed to diagnose adult beta-cell nesidioblastosis. The major criteria include: 1) multiple atypical beta-cells with enlarged and hyperchromatic nuclei; 2) islets with a natural spatial distribution of endocrine cell types; and 3) absence of endocrine cell proliferative activity. The minor criteria include: 1) increased number and size of islets; 2) lobulated islet architecture; 3) irregular islet shape; and 4) beta-cell macronucleoli. Beta-cell nesidioblastosis may be focal or diffuse.[17,18,19] Because nesidioblastosis is a focal or diffuse disease, partial (30–80% of parenchyma) or near-total (90–95%) pancreatectomy has been proposed because these types of resections involve various types of morphologic changes, results vary widely. Some authors suggest performing conservative resections with possible reinterventions if adequate glucose control is not achieved.[20]

We present our series of 15 adult patients with hypoglycemia due to non-tumorous pancreatogenic hyperinsulinism who underwent near-total pancreatectomy as an alternative due to a lack of response to medical treatment.

Patients and methods

Retrospective study of patients admitted to a university hospital's Endocrinology and Gastrointestinal Surgery Department, diagnosed with hypoglycemia, and enrolled in a protocol between 2002 and 2020. Upon admission to the Endocrinology Department, an endocrinologist established a diagnosis of hypoglycemia syndrome based on clinical signs and symptoms. Definitive diagnosis was made by fasting test (partial or complete), plasma determinations of glucose, insulin, circulating C-peptide, and counterinsular hormones (growth hormone and cortisol). During the study, non-caloric fluids were allowed; peripheral blood samples (glucose, insulin, and C-peptide) were obtained every 4-6 hours or when the patient was symptomatic, and the test was considered complete when the glucose level was below 45 mg/dL or in the presence of symptoms. The diagnosis of Endogenous Hyperinsulin Hypoglycemia Syndrome was established with symptoms and the following criteria: glucose <45 mg/dL; insulin >3 micro U/ml; C-peptide >1.2 microgram/ml; proinsulin >5.0 picomoles /L. Diagnostic imaging methods included conventional ultrasound, multidetector computed tomography scan, and angiography combined with selective calcium gluconate stimulation, magnetic resonance imaging, and endoscopic ultrasound in some cases. All patients underwent intraoperative ultrasound. A bilateral subcostal laparotomy was performed for complete exposure of the pancreas. The surgical technique included a bimanual exploration of the pancreas, and an ultrasound was performed along the entire length of the organ. Once the absence of solitary lesions (insulinomas) was confirmed, the pancreas was dissected, freeing adjacent structures. Based on the topographic relationship of the duodenum with the head of the pancreas, the organ resection was considered to begin at 2.0 cm, right at the level of the confluence of the superior mesenteric vein and splenic vein, as well as the portal vein, toward the distal part of the pancreas (approximately 95% of the total) with or without preservation of the spleen. The residual edge of the pancreas was invaginated with 2/0 silk in a continuous manner, and the pancreatic duct was closed with continuous 4/0 vascular prolene suture. The Clavien-Dindo classification was used to stratify complications and postoperative mortality within the first 30 days after surgery. [21] The presence of pancreatic fistula and its stratification were defined according to the International Pancreatic Fistula Study Group (2005) [22] criteria and redefined in 2016. [23] All specimens were analyzed, certifying the final histopathological diagnosis using immunohistochemical techniques (chromogranin, enolase, synaptophysin, and Ki67 proliferation index) and based on the major and minor criteria previously defined. [18,19] Follow-up included periodic medical checkups every 3 months in the Endocrinology and Gastrointestinal Surgery Department during the first year and every 6 months in subsequent years. A multidetector computed tomography or MRI scan was performed if symptoms recurred or laboratory abnormalities were detected.

Results

One hundred and forty-seven patients diagnosed with Endogenous Hyperinsulinism Hypoglycemia Syndrome were admitted and documented. One hundred and thirty-two (89.7%) were diagnosed with insulinomas and 15 (10.3%) with nesidioblastosis during the indicated period. Table 1 summarizes the demographic characteristics of the patients and the presenting symptoms of patients with nesidioblastosis.

Table I. Demographic Aspects.

Patient No. (age/gender).	Whipple´s. Triad.	Symptoms	Duration	Physical Exam (BMI) Kg/m^2
1 (27yr/F)	yes	Syncope. Diaphoresis, confusion	6m	26
2 (31yr/M).	yes	Seizures, confusion, headache	2m	30
3 (58yr/F).	yes	Irritability, headache	7m	25.5
4 (22yr/F).	yes	Diaphoresis, confusion, Somnolence	2yr	26
5 (18yr/F).	yes	Irritability, seizures	4wk	27
6 (25yr/F).	yes	Diaphoresis, confusion, headache.	3m	31
7 (27yr/F).	yes	Syncope, somnolence, headache	4m	28
8 (60yr/F).	yes	Seizures, somnolence	1m	27
9 (18yr/F).	yes	Irritability, diaphoresis, headache	6wk	26
10 (30yr/F).	yes	Seizures, somnolence	1m	30
11 (38yr/M).	yes	Headache, confusion, irritability	7m	32
12 (40yr/F)	yes	Seizures, somnolence	2yr	27.5
13 (22yr/M).	yes	Confusion, somnolence, Diaphoresis	1yr	28
14 (42yr/F).	yes	Headache, confusion, Somnolence	3yr	26
15 (34yr/F)	yes	Seizures, headache, diaphoresis	8m	25.8

F, female. M, male; m: months; yr: years; wk: weeks; BMI: body mass index

Two patients had a history of hypertension under medical supervision, and one had a benign thyroid nodule removed 8 years earlier. No patients had a history of surgery for morbid obesity. The mean age was 32.8 years (18–60), with 12 women (80%), and three men (20%). Follow-up ranged from 1 to 16 years (mean 5.2 years). All patients had weight gain since the onset of the condition. Patients were considered overweight when their Body Mass Index was 25 or greater and obesity was 30 or greater.

Table II: Fasting laboratory tests of patients with diffuse nesidioblastosis

Patient No.	Plasma Glycemia Levels	Plasma Insulin levels	Plasma C peptide levels	Plasma pro-Insulin levels
1	40	5.1	1.5	5.0
2	40	7.3	1.3	5.1
3	44	3.6	1.7	8.0
4	41	6.2	1.7	8.0
5	42	8.1	1.4	6.0
6	45	10.0	1.7	7.0
7	45	6.2	1.4	7.0
8	40	6.3	1.4	6.1
9	35	5.4	1.3	7.2
10	40	3.2	1.5	6.2
11	45	7.1	1.7	8.0
12	42	6.1	1.7	7.1
13	41	10.2	1.4	6.3
14	42	8.1	1.4	6.1
15	42	4.6	1.3	7.1

Diagnostic values: glucose < 45 mg/dL; insulin >3 microU/ml; C péptide > 1.2 microgm/ml; proinsulin >5.0picomoles /l.

Cortisol and growth hormone tests were negative in all patients. Preoperative imaging studies were invasive and noninvasive; all patients underwent conventional abdominal ultrasound (US), multidetector contrast-enhanced abdominal computed tomography (CT), and magnetic resonance imaging (MRI). The findings were nonspecific (e.g., a slight increase in local or total pancreatic size, irregularities in its contour), and the presence of one or multiple tumors that would raise suspicion of insulinoma was ruled out. For this reason, selective catheterization with intra-arterial calcium injection was performed in 15 patients (100%) with increased insulin in the hepatic vein after calcium injection in two or more arterial territories, but no insulinoma-type lesion was detected. An endoscopic ultrasound (EU) was also performed, confirming that no insulinoma-like tumor lesion was present. Nine patients (60%) underwent octreotide scintigraphy (octreoscan) and body scanning with octreotide, with diffuse uptake in 5 (60%) and body scanning in the remaining 4 (40%). Upon admission and during the hypoglycemia workup phase, patients were prescribed a low-carbohydrate, low-glycemic index diet to prevent elevations in insulin response. Once the biochemical parameters supporting hypoglycemia were obtained, all patients were administered oral acarbose (50-150 mg, once daily); in 8 patients (53%), diazoxide (1-3 mg/kg/day) was used; in 7 (47%), amlodipine (5 mg/day). Due to lack of response and/or side effects of the medications, all 15 patients were administered subcutaneously somatostatin analogs - octreotide - 50 mcg-150 mcg, twice a day. Due to a lack of clinical and biochemical improvement, all patients underwent surgery. Initially, all patients underwent intraoperative ultrasound to rule out the presence of solitary lesions (insulinoma). Operative findings were macroscopically normal pancreatic gland in size and consistency. Extended open subtotal pancreatectomy was performed (conventional surgery) with splenectomy in all patients. The average blood loss was 100 ml; the average operative time was 170 minutes (120-240 minutes). All patients had a closed drain placed in the surgical bed, which was removed before discharge. The average hospital stay was 6.7 days (5-14 days), and no perioperative mortality was recorded. All patients had resolution of hypoglycemic symptoms. Postoperative complications are described in Table III.

Table III: Postoperative Complications

Patient No.	Fistula	Transient hyperglycemia or insulin-dependent Diabetes (treatment)	Pancreatic exocrine failure (bloating, flatulence, Diarrhea, steatorrhea)
1		8 units/day PNHI*	mild
2		14 units/day PNHI	moderate
3		18 units/day PNHI	moderate
4**	+		
13**	+		mild

*PNHI (protamine neutral Hagedorn insulin). Patient 1 required insulin use during six months; patients 2 and 3 for 1 year.
**were considered biochemical leak (no clinical impact).

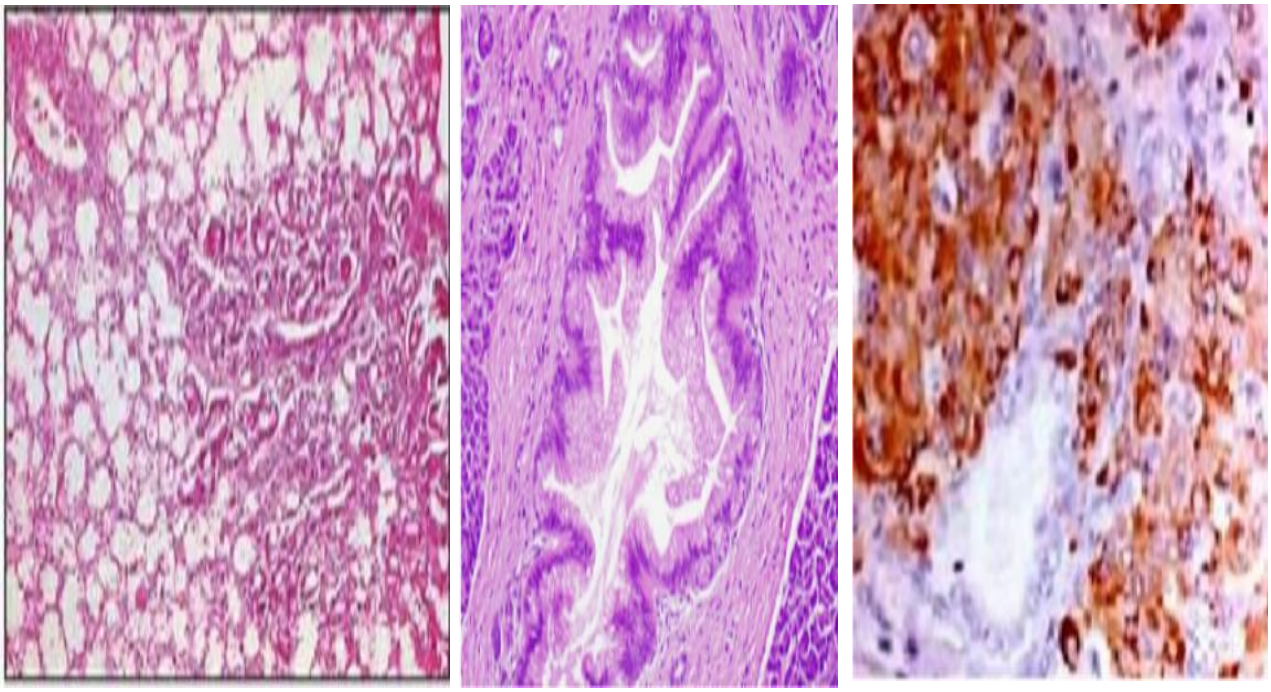
The follow-up was 40 months (12-120 months). No patient experienced a recurrence of hypoglycemia, malabsorption syndrome, or neurological sequelae during follow-up. Patients with symptoms of exocrine insufficiency were treated with pharmacotherapy, pancreatic enzymes, and 1-2 tablets before each meal, with clinical improvement after 6 months of treatment and subsequent use only before the main meal, with the help of dietary guidance. Histopathological findings are described in Table IV.

Table IV: Histopathological criteria for the diagnosis of diffuse nesidioblastosis

- Macroscopic, normal
- Multiple atypical b cells with enlarged and hyperchromatic nuclei
- Absence of endocrine cell proliferative activity
- Increased number and size of islets
- Lobulated islet architecture and irregular shape
- Increased and transparent cytoplasm
- Immunohistochemistry analysis: hypertrophic b cells and no proliferative activity of the Ki-67 antigen

Discussion

In our series of 147 patients diagnosed with hypoglycemia due to hyperinsulinism, 15 of them were diagnosed with nesidioblastosis. The definitive diagnosis was established postoperatively through histological examination, as the preoperative-only exclusion of a tumor as the cause of the hypoglycemia (insulinoma) was possible. Symptoms are similar in both conditions. The clinical and biochemical findings are often described as non-tumorous pancreatogenic hypoglycemia syndrome; the adult-onset form is considerably less common than the findings associated with congenital hyperinsulinism (CHI) or persistent hyperinsulinemic hypoglycemia of infancy. The latter condition is usually caused by mutations in several genes associated with insulin secretion, and clinical symptoms appear within the first weeks or months after birth; an example is the mutation in the ABCC8 gene, which causes familial hyperinsulinemic hypoglycemia. In 2005, Anlauf et al. [17] defined major and minor criteria for its diagnosis to establish a histological distinction. In the present series, all patients presented Whipple's triad (symptoms of hypoglycemia, serum glucose level less than 45 mg, and resolution of symptoms with glucose administration), overweight, or morbid obesity due to excessive intake of carbohydrate-rich foods to compensate for neuroglycopenic symptoms. Different synonyms have been used for this pathology: nesidioblastosis, endocrine cell dysplasia, nesidiodysplasia, multifocal ductulosis, islet cell adenomatosis, islet hyperplasia, or islet cell hypertrophy. Based on the histological diagnostic criteria (enlarged beta cells with nuclei hyperchromatic and abundant cytoplasm, to mention a few), it seems that the terms nesidiodysplasia, insular dysplasia, or islet cell atypia would be the most pertinent due to the alterations in their histological architecture. However, the term nesidioblastosis is used in cases of hypoglycemia due to hyperinsulinism with histological disorders[25]. The definitive diagnosis in the cases presented was made based on the histological findings. (Figure 1.)



A B C

Figure 1: A Hematoxylin-eosin staining showed increase in islet density with cell nuclear pleomorphism. B, Ductuinsular complex. C, beta-cell hyperplasia demonstrated by immunohistochemistry.

The results of the preoperative studies (abdominal ultrasound, computed tomography, magnetic resonance imaging) were negative in all patients. Given this situation of clinical and biochemical manifestations of hyperinsulinemic hypoglycemia with negative conventional studies, the intra-arterial calcium stimulation test is a procedure that allows identifying a response with elevated insulin, which in turn allows differentiating between a disease of local beta-cell hyperactivity and diffuse disease, confirming the nontumoral pancreatogenic hypoglycemia syndrome and thus planning the surgical procedure. Furthermore, this test would avoid the need for staged pancreatic resections (blind resections and/or those based on clinical and biochemical evolution and those susceptible to further surgical interventions). In the cases presented, this calcium stimulation test was not routinely used; it was performed if previous studies were negative. Figure 2 shows the diagnostic and therapeutic algorithm for patients with hypoglycemia due to hyperinsulinism.

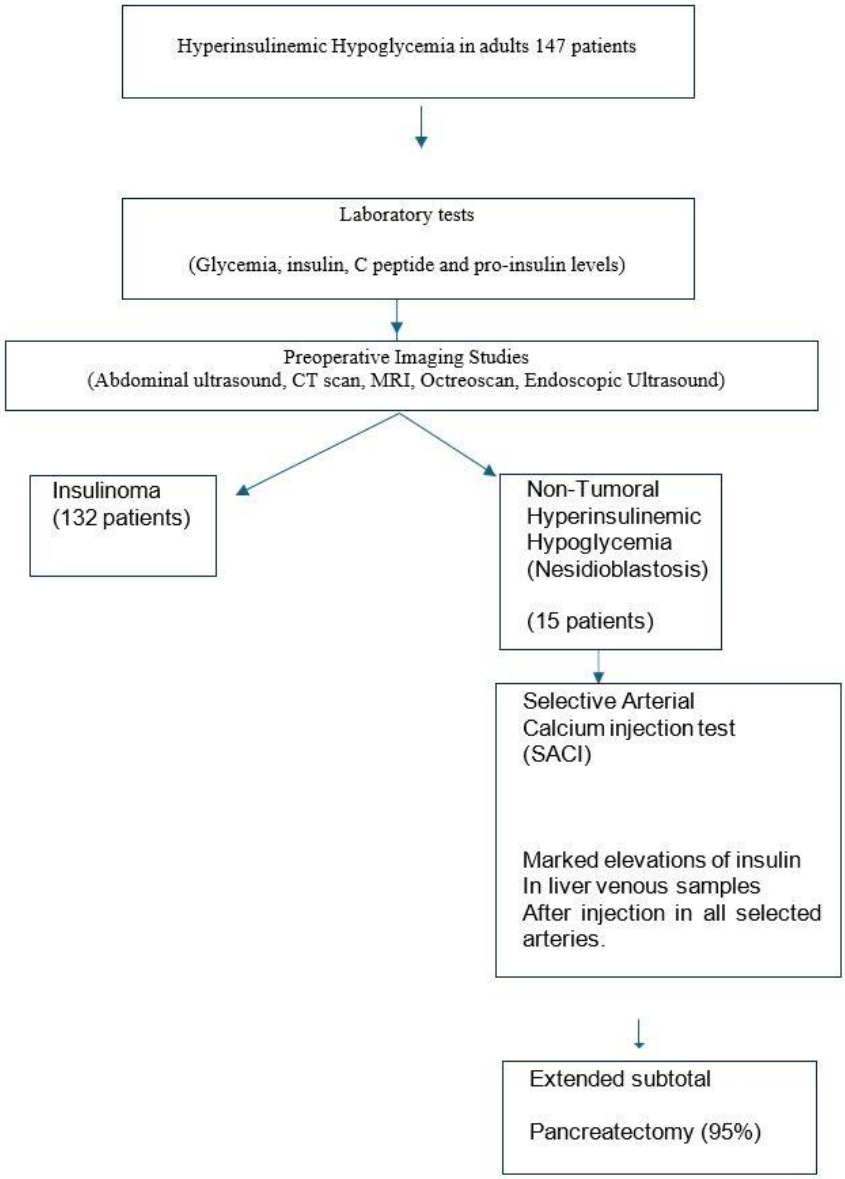


Figure 2: Flow chart of the Study Population.

Despite receiving medical treatment with a low-carbohydrate diet, alpha-glucosidase inhibitors (Acarbose), calcium channel agonists (Diazoxide), calcium channel antagonists (Nifedipine), and/or somatostatin analogs (octreotide or lanreotide), the patients underwent surgery due to side effects or lack of response. The definitive treatment for late-onset nesidioblastosis (adults) is surgical resection. Previous knowledge of pancreatic resections is available in neonatal and pediatric patients, where diffuse disease is usually resistant to medical management, and extended subtotal or near-total pancreatectomy (95%) is recommended.[26,27]. In many patients, partial or subtotal pancreatectomy, or even total pancreatectomy, remains the only option. The extent of resection is still debatable; while some surgeons prefer limited pancreatic resections (50-60%), others suggest subtotal or extended resections (80-95%), usually performed in pediatric patients. In a subset of patients, symptoms recur after partial or distal resections, necessitating repeat surgery with total resections.[28,29,30] In the present series, the decision to perform near-total pancreatectomy was based on the severity of symptoms, the poor response to medical management, and the results of the intra-arterial calcium stimulation test, which demonstrated diffuse involvement (Figures 3, 4,5, and 6).

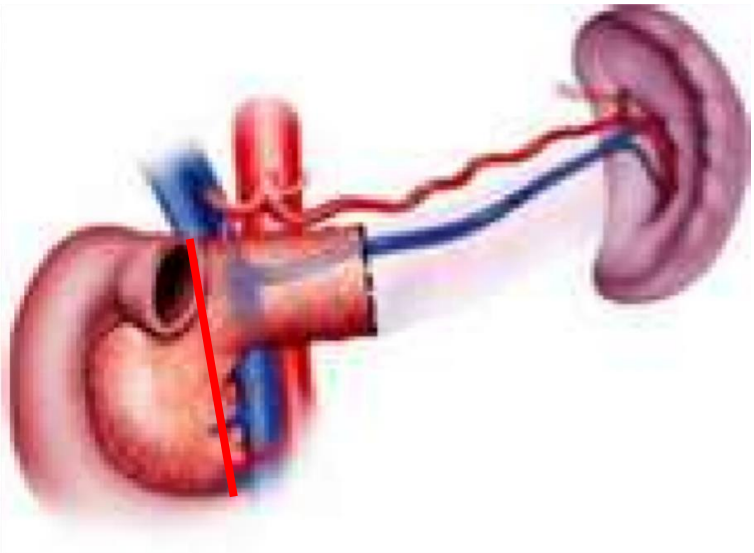


Figure 3: Illustration of anatomical boundaries for extended sub-total pancreatectomy. (Drawing was done for Dr. Patricio Sanchez Fernandez).

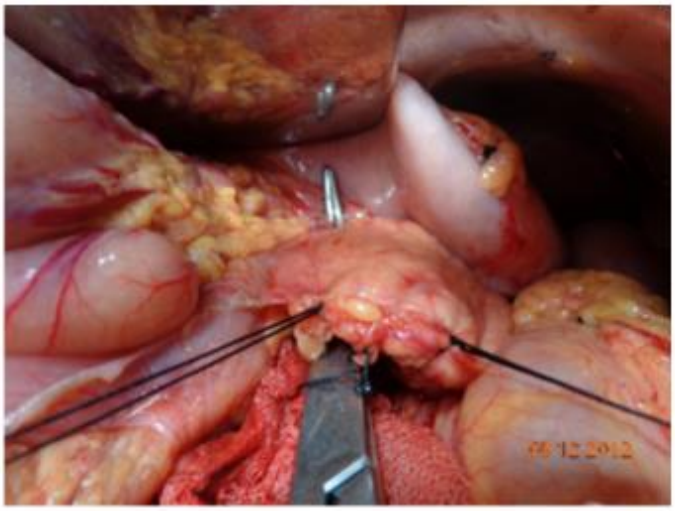


Figure 4: Transoperative image of pancreatic resection at 2.0 cm from duodenum. (The photography is the property of Dr. Patricio Sanchez Fernandez).

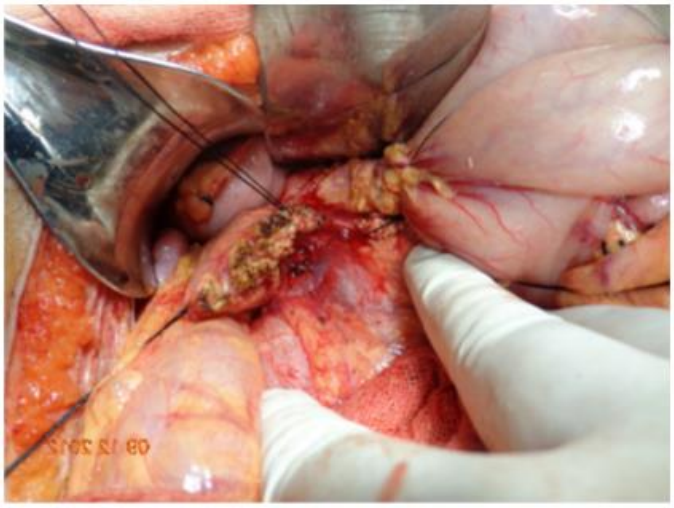


Figure 5: Residual pancreatic tissue (approximately 2.0 cm) fixed to duodenum. (The photography is the property of Dr. Patricio Sanchez Fernandez).

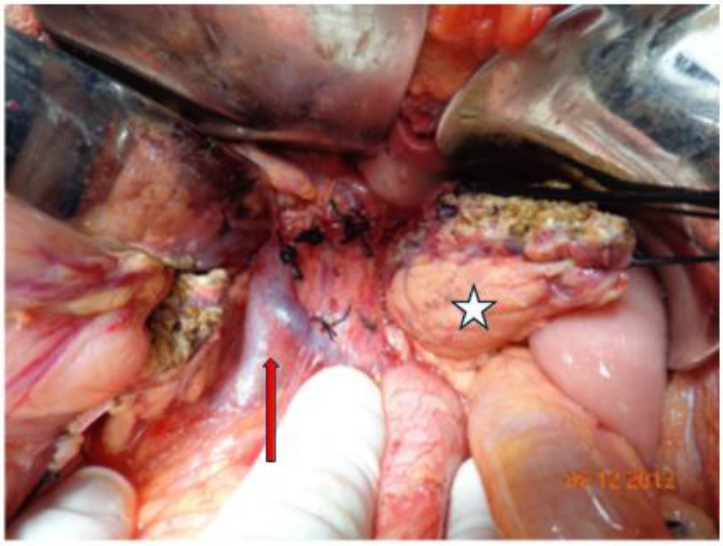


Figure 6: Transoperative image of Portal venous at the center (red arrow) and resected pancreas at the left of portal venous (white star). (The photograph is the property of Dr. Patricio Sanchez Fernandez).

Surgical intervention can be associated with postoperative morbidities such as diabetes mellitus, pancreatic insufficiency, or pancreatic fistulas. All patients were normoglycemic after pancreatic resection. Three of them (20%) presented hyperglycemia starting on the 5th postoperative day and were treated with rapid-acting insulin while hospitalized. Patient 1 required eight units of intermediate-acting insulin for 2 months; patients 2 and 3 had diabetes mellitus as a sequelae, requiring 14 units and 18 units of NPH insulin, respectively, for at least the first year of follow-up. Only two patients presented biochemical leak with symptoms of exocrine pancreatic insufficiency, which improved and disappeared 6 months postoperatively. It is suggested that this type of surgery be performed in hospitals with a high volume of patients and by specialists in the area of hepatobiliary-pancreatic surgery.[31]

Conclusions

Nesidioblastosis should be considered in the differential diagnosis of patients with hypoglycemia and endogenous hyperinsulinism, especially in cases where insulinoma has been ruled out. Surgery, either partial or subtotal pancreatectomy, helps control and cure the symptoms of hypoglycemia, and a definitive diagnosis is made by histological examination. Early diagnosis and timely treatment are vitally important in adults, as they promote an adequate response to the disease. Although the ideal surgical extension has not been defined, we propose extended subtotal pancreatectomy in cases where preoperative studies suggest diffuse disease.

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