

Hypoglycemia in Pancreatic Disease

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1. The Problem of Hypoglycemia

Plasma glucose is maintained in a narrow range (~60 to ~120 mg/dl or 3.3 to 6.7 mmol). Glucose that falls significantly below this concentration is a potentially life threatening medical emergency. Severe hypoglycemia is associated with increased mortality in diabetic patients (23). It has been said that, as a group, people with diabetes fear hypoglycemia more than they fear the long term complications of diabetes (2). In this review we consider both the severe forms of hypoglycemia that may occur in diabetic patients with an underlying disease of the pancreas (pancreatogenic diabetes) and uncommon forms of hyperglycemia that result from pancreatic disorders in the absence of diabetes

The Spectrum of Hypoglycemia Pathogenesis

Hypoglycemia is almost always the result of excess insulin and occurs most commonly in persons with diabetes. It is generally the result of an unintended overdose with exogenous insulin. It can also result from intentional overdoses and oral hypoglycemic drugs. As we will discuss below, it is a particularly vexatious problem in persons whose insulin-requiring diabetes is the consequence of pancreatic surgery. Other causes of hyperinsulinemic hyperglycemia that we consider here are insulinomas, congenital and adult-onset nesidioblastosis, and hypoglycemia as

a complication of Roux-en-Y and other upper gastrointestinal surgical procedures.

Rarely, the primary disorder leading to hypoglycemia is impaired glucose production. These causes of hypoglycemia include inborn errors of metabolism, certain medications, advanced hepatic and renal diseases, certain poisons, and alcoholic ketoacidosis. These topics are reviewed elsewhere (27) and will not be discussed further in this chapter.

Clinical Presentation of Hypoglycemia

The symptoms and signs of hypoglycemia are summarized in **Table 1**. Hypoglycemia needs to be considered in any individual presenting with a change in mental status. In the healthy individual, hypoglycemia causes an autonomic nervous system response which functions as an early warning signal. If hypoglycemia persists, neuroglycopenic symptoms develop. The presentation of hypoglycemia may vary depending on many factors including the interval since the last meal, exercise, and altered mental status from other causes.

- **Autonomic Symptoms.** Hypoglycemia activates the sympathetic nervous system, generating a sympathoadrenal response. Symptoms and signs include palpitations, tremor, anxiety, sweating, and increased hunger.

Table 1: Hypoglycemia: Symptoms & Signs

<i>Sympathetic Nervous System</i>	<i>Central Nervous System: Neuroglycopenia</i>
Sweating	Cognitive impairment, confusion
Palpitations	Behavioral changes
Tremor	Weakness
Hunger	Paresthesias
Arousal/Anxiety	Lack of motor coordination
Pallor	Slurred speech
	Visual disturbances
	Vertigo
	Focal neurological deficits
	Seizures
	Coma and Death

- **Neuroglycopenia.** With persistent hypoglycemia, the sympathetic response is followed by neuroglycopenic symptoms because brain metabolism is almost totally dependent on glucose. Symptoms and signs include fatigue, confusion, and bizarre and/or combative behavior. If untreated, neuroglycopenia can progress to loss of consciousness and seizures.
- **Hypoglycemia Unawareness.** Individuals with longstanding diabetes or frequent hypoglycemia may lose their protective autonomic response and develop neuroglycopenic symptoms without warning. Most typically associated with longstanding type 1 diabetes, hypoglycemia unawareness can also complicate the management of patients with insulinoma and the diabetes that follows pancreatectomy (1).

The Physiologic Response to Hypoglycemia

Normal Physiologic Response

The principal responses that prevent and reverse hypoglycemia are decreased secretion of insulin, increased secretion of glucagon, and increased release of epinephrine. The glycemic threshold for a decrease in insulin secretion is approximately 80 mg/dl (4.4 mmol/l). Hypoglycemia increases glucagon and sympathoadrenal responses at a threshold of approximately 65–70 mg/dl (3.6–3.9 mmol/l) (7).

Increased cortisol and growth hormone secretion are primarily involved in defense against more prolonged hypoglycemia and are clinically less important. For this reason, adrenocortical failure and hypopituitarism are not common causes of hypoglycemia in adults.

Impaired Physiologic Response to Hypoglycemia

Glucagon deficiency due to defective or absent alpha cells may contribute significantly to the risk of hypoglycemia. This is frequently encountered in persons with post-pancreatectomy diabetes. Glucagon release may also be impaired during hyperinsulinemic hypoglycemia because insulin directly inhibits release of glucagon. Abrupt cessation of insulin secretion from beta cells during hypoglycemia appears to be a necessary signal for the glucagon release from downstream alpha cells (44).

In both longstanding type 1 or 2 diabetes and post-pancreatectomy diabetes, the adrenergic responses to hypoglycemia may also be reduced. The precise mechanisms of this attenuated sympathoadrenal response are not known. Hypoglycemia-associated autonomic failure (HAAF) has been induced by experimental hypoglycemia in non-diabetic persons (8). The resulting impairment in response to hypoglycemia contributes to hypoglycemia unawareness, which frequently complicates the management of patients with pancreatic diseases. The severity of HAAF increases with increasing frequency of hypoglycemic episodes. It is important to note that HAAF can be observed relatively soon after post-pancreatectomy diabetes.

It should also be borne in mind that both adrenergic and neuroglycopenic symptoms of hypoglycemia may be blunted in patients with cognitive impairment. These include severely ill individuals and many elderly persons. In these settings caregivers need to be particularly alert for the possible development of hypoglycemia. The symptoms and signs of hypoglycemia may also be inapparent in persons treated with beta adrenergic blockers, narcotics, sedatives, and other medications that blunt physiological responses.

Diagnosis of Hypoglycemia

No single plasma glucose concentration categorically defines hypoglycemia. Similarly, no one specific set of symptoms define it, in part because relative tolerance to hypoglycemia may develop in patients with recurrent hypoglycemia due both to loss of the counter-regulatory responses and enhanced neuronal extraction of available glucose. Hypoglycemia can be classified as “asymptomatic” vs. “symptomatic”, depending on the presence or absence of symptoms, and additionally as “severe” when it requires the assistance of another individual (9).

- **Asymptomatic Hypoglycemia** is a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/l) without typical symptoms of hypoglycemia. As discussed below, some cases are associated with documented pathology, but the clinical significance of asymptomatic hypoglycemia is questionable in many cases.
- **Classical Symptomatic Hypoglycemia** should fulfill Whipple’s triad: (1) symptoms, signs, or both consistent with hypoglycemia, (2) low plasma glucose concentration (at least ≤ 70 mg/dl or 3.9 mmol/l, but usually lower), and (3) resolution of symptoms after administration of carbohydrate. Whipple, a surgeon, developed these criteria in the 1930s to guide the pre-operative diagnosis of insulinoma (42). As noted above, initial symptoms are sympathoadrenal; neuroglycopenic symptoms subsequently occur at approximately 50–55 mg/dl (2.8–3.0 mmol/l) (7).
- **Severe Hypoglycemia** is defined by the American Diabetes Association as a hypoglycemic event requiring assistance from another person for treatment. Plasma glucose measurements may not be available during the event, but neurological recovery attributable to the restoration of plasma glucose provides

sufficient evidence to diagnose hypoglycemia.

- **Fasting vs Post-prandial Hypoglycemia** is a distinction useful for evaluating a person suspected of having hypoglycemia. This is simply a determination whether symptoms occur in a fasting state (e.g., overnight or early morning) or post-prandially (e.g., 2-5 hours following a meal). Insulinoma typically causes fasting hypoglycemia whereas hypoglycemia as a late complication of upper gastrointestinal surgery is usually post-prandial. The distinction is clinically very useful and should always be part of an evaluation.
- **Diagnostic strategies.** Hypoglycemia often occurs in a setting where diagnostic testing cannot be easily be performed. In such cases an effort can be made to replicate the circumstances in which suspected hypoglycemia happened. For fasting hypoglycemia, this is traditionally accomplished with a monitored fast of up to 72 hours. For postprandial hypoglycemia, an attempt can be made to induce a hypoglycemic episode after a mixed meal or 100 gm glucose challenge (26). Baseline studies should include, at minimum, glucose, insulin, proinsulin, and c-peptide. If symptoms of hypoglycemia are induced, confirmatory diagnostic testing should include a laboratory-determined (not fingerstick) plasma glucose <55 mg/dl (3.0 mmol/liter). An insulin level ≥ 3.0 μ U/ml (18 pmol/liter) confirms hyperinsulinemia. A c-peptide ≥ 0.6 ng/ml (0.2 nmol/liter), and proinsulin of ≥ 5.0 pmol/liter suggest that hypoglycemia is mediated by endogenous hyperinsulinemia (9).
- **Pitfalls in the diagnosis of hypoglycemia.** Symptoms and signs of hypoglycemia generally develop at a plasma glucose concentration of approximately 55 mg/dl (3.0 mmol/liter) (9), but healthy individuals may be

asymptomatic at significantly lower levels; this is particularly true in women and children and during periods of fasting. Because fingerstick blood glucose determinations can be less accurate at the lower end of their scale, they may require confirmation by a clinical laboratory. *Pseudohypoglycemia* may result from ongoing glycolysis in blood samples left at room temperature or due to the presence of large numbers of leukemic white cells. This can be prevented by immediate centrifugation to separate the plasma (or serum) from red cells or by addition of an inhibitor of glycolysis to the sample. Factitious hypoglycemia may also occur with venous or fingerstick blood glucose testing during states of decreased perfusion as the result of increased extraction of glucose.

Treatment of Hypoglycemia

Treatment of hypoglycemia has two components, short-term and long-term management. Treatment of hypoglycemia in alert, cooperative patients should be oral ingestion of rapidly absorbed carbohydrates such as juice, candy, glucose tablets, or oral glucose gel. Treatment with 15-20 grams of oral carbohydrate is often sufficient to resolve mild symptomatic hypoglycemia; it should be repeated after 15 minutes if the blood glucose level remains low. For the patient unable to ingest oral carbohydrate due to any cause, glucose may be given intravenously as a 25 gram bolus of a 50% glucose solution (50 ml). Care should be taken to avoid extravasation as the solution can cause tissue damage. A 1 mg glucagon intramuscular bolus injection is an alternative in situations where intravenous access is not available, but this treatment may fail to resolve the hypoglycemia if the person has not eaten and liver glycogen stores are depleted. If hypoglycemia recurs after these interventions, additional diagnostic evaluation in an emergency department is indicated.

Long-term management often involves intensive adjustment of diet and diabetes therapy. In addition, strategies to detect and abort impending hypoglycemia are becoming increasingly important, especially when hypoglycemia unawareness or HAAF or abrupt falls in glucose occur, as in post-pancreatectomy diabetes. In these contexts, continuous glucose monitoring (CGM) devices can lead to dramatic reductions in the frequency and severity of hypoglycemia (20). Additional treatment strategies unique to specific hypoglycemic conditions are described below.

2. Hypoglycemia as a Complication of Diabetes Treatment in Patients with Pancreatic Disease

Many pancreatic diseases can lead to diabetes ("pancreatogenic" or type 3c diabetes (10)), among them pancreatitis, trauma, cystic fibrosis, hemochromatosis, and (rarely in tropical countries only) fibrocalculous pancreatopathy (1). Treatment of these disorders with insulin or other drugs can lead to hypoglycemia, but in general its frequency and severity are comparable to what is observed in the more common forms of diabetes unless associated with pancreatectomy.

Pancreatitis

In a notable prospective study, 500 patients with chronic pancreatitis were followed for an average of 7 years. The cumulative rate of diabetes was 83% 25 years after disease onset and half of the diabetic patients required insulin therapy. About half of the subjects underwent pancreatic surgery for pain relief. Interestingly, the prevalence of diabetes did not increase in the surgical group overall, though it was higher after distal pancreatectomy than after pancreaticoduodenectomy (22). Only in the surgical group was severe hypoglycemia observed (see below).

Cystic Fibrosis and Hemochromatosis

Treatment of cystic fibrosis related diabetes can also be associated with hypoglycemia but its severity appears not to be increased when

compared to treatment of other forms of diabetes (32). Diabetes associated with hemochromatosis affecting the pancreatic islets is not associated with severe hypoglycemia, probably because of preservation of alpha cells and glucagon secretion (29, 33).

Pancreatic Surgical Resection

In contrast, hypoglycemia associated with diabetes due to loss of pancreatic parenchyma is different. In one study of pancreatectomized patients, episodic hypoglycemia was experienced by 79%, and 41% experienced severe hypoglycemia despite using complex insulin treatment programs (30). This form of diabetes is characterized by (1) loss of some or all of both of the pancreatic glucoregulatory hormones, insulin and glucagon, (2) consequent glycemic lability, and (3) frequent hypoglycemia ("brittle" diabetes). The severity of post-pancreatectomy diabetes is directly proportional to the extent of the resection, the more extensive the surgery the more difficult-to-manage the diabetes. When individuals with post-pancreatectomy diabetes require exogenous insulin therapy, as explained above, the absence of glucagon renders them very vulnerable to severe hypoglycemia. In addition, they also have increased risk of hypoglycemia unawareness due to HAAF despite plasma glucose levels less than 30 mg/dl.

In post-pancreatectomy, diabetes hypoglycemia is not easily avoided because without glucagon, it is a daunting task to precisely mimic physiologic insulin secretion, which varies widely throughout the course of a day as a function of carbohydrate ingestion, physical activity, stress and underlying circadian rhythms. In addition to losses of hormones, post-operative alterations in GI transit time and malabsorption due to exocrine pancreatic insufficiency complicate management.

In some cases, post-pancreatectomy diabetes can be prevented or at least ameliorated by auto-transplantation of pancreatic islets from the surgical specimen (36). The strategy preserves at

least some insulin and glucagon functionality and is suitable when the underlying disease is not a malignancy. The isolation procedure is not easy or always successful. However, given the difficulty in managing post-pancreatectomy diabetes, we suggest that auto-transplantation be considered whenever possible.

3. Hypoglycemia without Diabetes in Patients with an Underlying Pancreatic Disorder

Compared to the common problem of hypoglycemia occurring during insulin therapy, primary hypoglycemic disorders resulting from insulin overproduction in the absence of diabetes are rare. Essentially all are disorders of the pancreas.

Hypoglycemia Due to Insulinoma

The classic example of hypoglycemia due to a pancreatic disorder is insulinoma; its management is discussed at length in another Pancreapedia entry (14). Here we focus on issues relevant to hypoglycemia *per se*. Individuals with an insulinoma typically have fasting hypoglycemia but may occasionally also experience postprandial hypoglycemia. Diagnosis requires documentation of hyperinsulinemia during a hypoglycemic episode. It is usually not possible to obtain laboratory data during a spontaneous event, and for that reason a 72-hour monitored fast is often required to make the diagnosis. Most, but not all, patients with the disease experience hypoglycemia within 72 hours. Hypoglycemia occurs in less than 24 hours in about two thirds of cases, and in less than 48 hours of fasting in the great majority of affected patients (9).

By the time an insulinoma comes to clinical attention, hypoglycemic events are typically characterized by episodes of neuroglycopenia. This may be due to HAAF since diagnosis is typically delayed. In one series reporting 58 cases, the interval between onset of symptoms and diagnosis of insulinoma ranged from 1 month

to 30 years, with a median of 24 months; only 28% were diagnosed within 1 year of symptom onset and the diagnosis was delayed beyond 5 years in 19% (13).

Often patients are given other diagnoses such as seizure disorder, before hypoglycemia due to an insulinoma is considered. Common neuroglycopenic symptoms include confusion and personality changes or bizarre behavior that may not be recognized as metabolic in origin. Patients may have amnesia for the hypoglycemic events.

Hypoglycemia due to Congenital Nesidioblastosis

This is a rare condition of diffuse hyperplasia of pancreatic islet beta cells leading to hyperinsulinemia and hypoglycemia. It presents in infants and young children as lethargy, irritability, or difficulty feeding. There is potential for serious complications, including seizures and permanent brain damage, when diagnosis is delayed. It is relatively rare, affecting approximately 1 in 50,000 newborns. Multiple genetic defects have been found to cause congenital hyperinsulinemia. Mutation in the *ABCC8* gene, which encodes the sulfonylurea receptor 1 (SUR1) protein, is the most common gene defect occurring in approximately 40% of cases. Second most common are mutations that occur in *KCNJ11*, which encodes the ATP-dependent potassium (K-ATP) channel involved in insulin secretion. In up to 50% of cases the cause remains unknown.

The classical treatment for this cause of hypoglycemia has been subtotal pancreatectomy, typically on the order of 95% (21); some of these cases subsequently develop diabetes. There have, however, been reports of successful medical treatment of the condition with calcium channel blockade (3, 19) and octreotide (15) both as monotherapy and in conjunction with surgery. We suggest that a trial of these medications may be warranted before surgery.

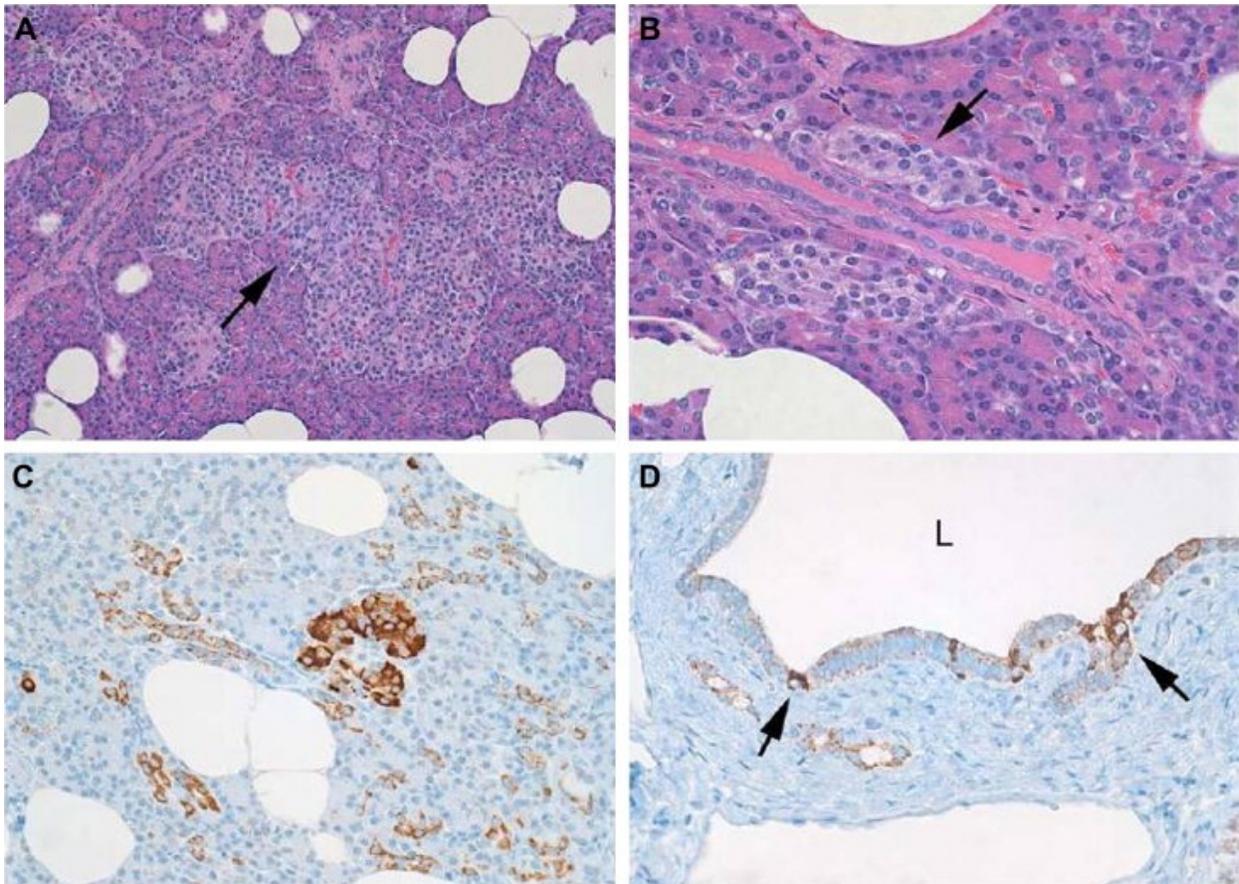


Figure 1. Characteristic histologic and immunocytochemical features of nesidioblastosis in a patient with neuroglycopenia after Roux-en-Y gastric bypass. A Extreme variation in islet size and the presence of large lobulated islets (center of panel). B Ductulo-insular complexes. Endocrine cell clusters are intimately connected with a small pancreatic duct. C Insulin positive endocrine cell clusters are scattered throughout the acinar parenchyma. D Insulin positive cells are seen scattered amongst the pancreatic duct epithelium. From Rabiee et al. (ref. 33) with permission.

Hypoglycemia Following Roux-en-Y Gastric Bypass Surgery

Roux-en-Y gastric bypass (RYGB) is a common bariatric procedure for the treatment of obesity and type 2 diabetes. Hyperinsulinemic hypoglycemia not attributable to dumping is a rare complication of the procedure and typically begins to occur 2 to 4 years after surgery (26, 37). Most cases are characterized by post-prandial symptoms. The underlying mechanism responsible for hyperinsulinemia is not fully characterized. It has been attributed to the induction of nesidioblastosis (11, 34, 37) (**Figure 1**), but this pathological diagnosis has been called into question (18, 25) and has not always been

observed in pancreatectomy or pancreatic biopsy specimens (43). Another mechanism may involve rapid transit of nutrients into the upper small bowel and the enhanced secretion of incretin hormones, including gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1) (16).

This concept is supported by the observation that feeding via percutaneous gastrostomy tube placed in the bypassed stomach reduces hypoglycemia (24). Many cases of post-RYGB hypoglycemia occur with dumping syndrome and can be managed with modification of diet to include frequent high protein, low carbohydrate feedings (39). Some cases, however, are severe,

intractable, and refractory to dietary management (6, 31, 37, 43).

Surgical approaches to the problem have included gastric banding, based on the hypothesis that some cases are due “late severe dumping syndrome” (43). Others, including some that did not respond to banding (43), have been treated successfully with partial or near-total pancreatectomy (6; 31, 37, 43), but many of these have developed diabetes (37). Most recently, laparoscopic reversal of the bypass with resolution of hypoglycemia has been reported (5; 41).

Successful medical treatment of post-RYGB hypoglycemia has also been reported using acarbose (26), calcium channel blockade (26), diazoxide (38), and combined therapies (28). We suggest that a trial of medical management is indicated in cases of severe post-RYGB hypoglycemia, not only because it can be efficacious and obviate the need for surgery, but also because some cases managed in this way may undergo spontaneous remission (26).

Hypoglycemia Associated with Other Upper Gastrointestinal Surgical Procedures

Symptomatic hyperinsulinemic hypoglycemia can be a complication of procedures other than Roux-en-Y gastric bypass surgery. These include subtotal esophagectomy, subtotal gastrectomy, Billroth I partial gastrectomy, and Billroth II surgeries (4). Until the advent of histamine H2 receptor blockers and proton pump inhibitors, hypoglycemia was a commonly described complication of surgery performed for peptic ulcer disease. As early as 1965 it was recognized that post-prandial hypoglycemia in gastrectomized subjects was due to hyperinsulinemia attributable to incretin hormone secretion (17). Historically, most of these patients with hypoglycemia were treated with diet or distal pancreatectomy. Today, such cases would also be candidates for the

medical therapies described above with the addition of octreotide (4).

Hypoglycemia due to Primary Adult Onset Nesidioblastosis

In adults, nesidioblastosis (also termed noninsulinoma pancreatogenous hypoglycemia syndrome, NIPHS), is a rare cause of hypoglycemia in adults who have not undergone gastrointestinal surgery. Fewer than 100 cases have been described. NIPHS is usually, but not always, distinguished from insulinoma by predominance of post-prandial rather than fasting hypoglycemia. More common in men than in women, it is characterized by diffuse beta cell hyperplasia and abnormal islet architecture (18). To date the mutations in *ABCC8* or *KCNJ11* found in congenital nesidioblastosis have not been described in NIPHS.

Among cases of persistent hyperinsulinemic hyperglycemia in adults, more than 95% are ultimately found at surgery to harbor an insulinoma (35). In one series of 75 patients treated by partial pancreatectomy for hypoglycemia attributed to diffuse islet cell disease, 80% had prior history of upper GI surgery (40). Very rarely, NIPHS and an insulinoma may coexist in the same patient (12). There are no reports of successful medical therapy of NIPHS. Distal pancreatectomy is often but not always successful in reversing hypoglycemia, and second surgeries may be required.

4. Summary

Hypoglycemia is a common and important problem in both patients who are diabetic due to an underlying pancreatic disorder and in non-diabetic patients with a hyperinsulinemic hypoglycemia due to a primary pancreatic disorder. In healthy individuals, hypoglycemia activates both hormonal and autonomic nervous system responses that prevent and reverse hypoglycemia. Patients with diabetes due to

pancreatectomy lose both insulin and glucagon responses and are uniquely susceptible to severe, recurrent hypoglycemia. In contrast, patients with other forms of pancreatogenic diabetes, e.g. cystic fibrosis and hemochromatosis, have preservation of glucagon, and they are less susceptible to hypoglycemia. All patients with hyperinsulinemic hypoglycemia are potentially at risk of losing their protective autonomic response and can develop neuroglycopenic symptoms without warning. This is particularly true for hypoglycemia due to insulinoma and hypoglycemia due to treatment of post-pancreatectomy diabetes. The underlying physiologic mechanisms are becoming better understood, and the number of therapeutic

options available for these patients is increasing as summarized in **Table 2**.

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Table 2: Causes and Treatment of Hyperinsulinemic Hypoglycemia

<i>Disorders</i>	<i>Clinical</i>	<i>Mechanisms</i>	<i>Therapeutics</i>
Hypoglycemia in diabetic patients with underlying pancreatic disease (pancreatogenic diabetes)			
Post –pancreatectomy brittle diabetes	Brittle diabetes	Loss of glucagon Altered GI transit	Intensive insulin therapy Continuous glucose monitor Islet auto-transplantation
Pancreatitis, hemochromatosis, cystic fibrosis	Ordinary risk of hypoglycemia	Preservation of glucagon	Intensive insulin therapy
Hypoglycemia in non-diabetic patients due to underlying pancreatic conditions			
Insulinoma	Fasting hypoglycemia	Unregulated insulin secretion	Surgery
Congenital nesidioblastosis	Fasting and post-prandial hypoglycemia	Unregulated insulin secretion Altered GI transit Altered incretin responses	Surgery Calcium channel blockade Calcium channel blockade, acarbose, diazoxide
Roux-en-Y gastric bypass surgery	Post-prandial hypoglycemia	Possible beta cell proliferation Altered GI transit	Laparoscopic banding Laparoscopic reversal Partial pancreatectomy
Other upper gastrointestinal surgery	Post-prandial hypoglycemia	Altered incretin responses	Calcium channel blockade, acarbose, diazoxide
Adult nesidioblastosis	Post-prandial hypoglycemia	Unregulated insulin secretion	Partial pancreatectomy

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