Chapter 12
Management of Diabetes and Pancreatic Insufficiency After Pancreatectomy

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Introduction

Disruption of the endocrine and exocrine function of the pancreas may occur following surgery to treat hyperinsulinism. Clinicians have to evaluate and manage endocrine and exocrine insufficiency postoperatively, in the short and longer term. In this section, we will address pancreatic and hepatobiliary complications of pancreatic surgery and discuss management principles and practices.

Surgical Management of Hyperinsulinism

A large proportion of patients with K_{ATP} HI are diazoxide unresponsive and may require surgery to control hypoglycemia. Historically, near total pancreatectomy was performed for all those unresponsive to diazoxide; however, since the early descriptions of focal HI [1], discovery of the genetic mechanism causing it [2] and the development of surgical techniques to remove only that affected portion of the

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pancreas have dramatically changed outcomes for focal HI [3]. Together, preoperative genetic testing [4] and preoperative pancreatic imaging with 18F-DOPA PET may enable the clinician to identify those with focal HI and locate the lesion [5]. Cure rates following local resection of the lesion focal disease have been reported to be 85–95%.

For those with diffuse disease and failure of diazoxide therapy, the current approach is to attempt to maintain the glucose in the normal range with a complex feeding program typically consisting of continuous enteral feeds or intragastric glucose administration in combination with pharmacologic therapy (see Chap. 6 on medical management). However, in patients in whom the enteral glucose infusion rate (GIR) needed to maintain euglycemia is >10 mg/kg/min, surgery may be indicated. When contemplating 98% pancreatectomy for diffuse disease, the physicians and family must be familiar with the likely outcome post-surgery. This includes ongoing hypoglycemia, the short- and long-term risks of diabetes, and the occurrence of exocrine pancreatic insufficiency.

In patients with diffuse disease undergoing 98% pancreatectomy, immediate post-op outcomes include persistent hypoglycemia in about 60% of patients [6], persistent diabetes in 20%, and transient diabetes followed by hypoglycemia in the remainder. Beltrand et al. [7] found that 48% of patients had diabetes by 8 years and 91% by 14 years. Since the development of focal surgery, Beltrand reports no diabetes occurring in focal patients [7].

Management of Diabetes in the Immediate Postoperative Period

Transient diabetes progressing to hypoglycemia may be difficult to manage. The physiological stress of the surgery combined with transiently impaired blood flow to the remaining 2–3% of the pancreas often results in immediate hyperglycemia. Initially fluids should be adjusted to reduce the glucose infusion rate (GIR), and if glucose persists >250 mg/dL, then continuous insulin by infusion is recommended to prevent diabetic ketoacidosis (see Chap. 10). Alternatively, subcutaneous insulin bolus therapy may be started every 4–8 h if it is likely that enteral feeding may soon start. Starting with a low dose is recommended to prevent hypoglycemia. Resolution of transient diabetes may take 2–3 days or as much as 4–6 weeks. If patients need to go home on insulin, various approaches may be undertaken including continuous subcutaneous infusion (CSI) insulin with pump therapy using either U-100 or U-10 insulin.

Transient diabetes can also occur in patients with focal disease treated by diazoxide until the day of surgery. In this case, removal of the lesion results in cure, but due to the half-life of diazoxide in the system, complete inhibition of insulin secretion

can occur in the remaining normal tissue until 3–5 days post discontinuation of diazoxide. In these cases, lowering the GIR to 0–4 mg/kg/min and judicious use of subcutaneous rapid-acting insulin will usually suffice until the diazoxide has cleared the system in 3–5 days.

Persistent Diabetes in Infancy and Early Childhood

The management of insulin-dependent diabetes in infants presents a unique set of challenges. Infants require small, accurate doses of insulin which should be administered for all carbohydrates ingested. Insulin pump therapy is the best way to attempt to mimic physiologic insulin dosing for an infant. Dilute insulin in a subcutaneous insulin pump allows for small doses with appropriate timing based on the infant's schedule and feeding regimen [8, 9]. Dilute insulin by syringe also allows for precise dosing of subcutaneous insulin. Dilute insulin is diluted with normal saline [10] or manufacturer-provided diluent [11] to 1 unit of insulin in 10 units/cc (U-10) rather than the standard insulin which is 100 units/cc (U-100). U-10 insulin allows for doses as small as 0.1 units/dose with syringe and 0.01 units with pump therapy.

Dilute insulin has been found to decrease the amount of hypoglycemia in young children as the ability to give minute doses allows dosing for what children eat rather than getting them to eat for the amount of insulin they need to receive [8]. It has also been noted that there are less pump alarm occlusions when dilute insulin is utilized compared to using very small doses of U-100 insulin [10]. Dilute insulin is not without challenges as it does need to be mixed every 7–14 days [8]; however, the benefits of accurate dosing outweigh the risks. Typical starting doses of insulin are 0.5 units/kg/day with 50% as basal and 50% as bolus with adjustments made from there.

While dilute insulin does allow for increased accuracy in dosing, it does present certain risks both while the patient is hospitalized and at home. Nurses are familiar with standard U-100 insulin. Extreme caution must be taken in order to prevent overdosing the infant. Orders must specify U-10 insulin, the dose to be drawn up, and the dose to be given. An example would be this: "please give 0.3 units (0.03 ml) of U-10 insulin and have a 2-nurse check." A "2-nurse check" must be mandated. Families tend to have fewer safety issues with dilute insulin as this is the only type of insulin they are familiar with, and parents/caregivers do not generally have prior knowledge of U-100 insulin. However, they do need to be told to tell everyone they meet in future medical settings that they are on "special" insulin and only their home insulin may be used. Families must be instructed to bring their home insulin to all medical appointments and emergency care visits.

Late-Onset Diabetes

Children with hyperinsulinism status post 98% pancreatectomy may require continued treatment for hypoglycemia until approximately the age of 3–8 years, and then they may have a period of relative euglycemia. The onset of diabetes often disrupts the first period of euglycemia that children and families have experienced. The idea of needing to give insulin, the hormone that was overproduced for so long, may be daunting for children and caregivers as also is the idea of restricting carbohydrates when they have been lifesaving thus far.

Management of the postoperative patient during childhood and early adolescence should focus on the early identification of a rising trend in blood glucose. Screening HbA1c should be done yearly until >6.2% and then every 6 months or if home glucose monitoring starts to show fasting glucose >100 mg/dL or random >200 mg/dL. Once this occurs, there should be a weaning of anti-hypoglycemic medications and a lowering of the carbohydrate supplementation.

One of the most difficult issues in the early development of diabetes is the time when the patient has what appears to be postprandial hyperglycemia (diabetes) and fasting hypoglycemia (hyperinsulinism). There are several approaches to solving this problem. One can wait and watch until the HbA1c rises >7.0% as one is unlikely to do better than that with insulin therapy. Another approach is to start with moderate carbohydrate restriction and correction factor during the day (but not at night). In some patients, using a basal insulin during the day that does not have such a large effect at night, such as low-dose insulin detemir given before breakfast, will prevent the daytime highs and minimize the nighttime lows. Once the A1C is >7.5%, a full-fledged MDI or CSI insulin program should be initiated.

Pancreatic Insufficiency and Biliary Complications of Surgery

Exocrine pancreatic insufficiency (EPI) may be a consequence of partial or subtotal pancreatectomy. EPI may be subtle and can be difficult to diagnose after subtotal pancreatic resection. In children, long-term data is limited by the infrequency of pancreatic resection and a paucity of studies examining long-term exocrine function outcomes, especially for children with resection due to hyperinsulinism. Most of the data discussed below regarding EPI diagnosis and management emanates from the literature regarding cystic fibrosis, the prototypical disorder associated with EPI in children.

Clinical Features

EPI after pancreatectomy is a result of reduced pancreatic secretion of digestive enzymes, hormones, and electrolytes (especially bicarbonate). The primary clinical features of EPI result from fat malabsorption, secondary to decreased lipase quantity and activity in the lumen of the small bowel. The consequences of fat malabsorption specifically include risk for essential fatty acid (EFA) deficiency and fat-soluble vitamin deficiency in addition to fecal energy loss. Loss of pancreatic bicarbonate secretion results in incomplete alkalization of the duodenal lumen, the consequences of which include impaired pancreatic enzyme activity, and potentially adverse effects on vitamin B_{12} digestion and absorption [12]. Other nutrients at risk for malabsorption related to impaired bicarbonate secretion and duodenal alkalinization may include calcium, magnesium, iron, zinc, and selenium. Zinc is a cofactor in EFA metabolism, and zinc and EFA deficiency may manifest similarly.

Steatorrhea and malnutrition are often the most striking symptoms of EPI, frequently accompanied by gas, bloating, or abdominal distension. Decline in growth trends, suboptimal weight gain, and weight loss can be observed [13]. Patients may have biochemical evidence of EPI prior to manifestation of clinical features [14]. Given the number of nutrients at risk for deficiency, the clinical consequences are numerous and can be subtle or profound, with the degree of malabsorption and duration of deficiency potential risk factors for deficiency states and presentation. The potential nutritional consequences of EPI are summarized in Table 12.1.

Diagnosis

Testing for EPI may be performed through direct or indirect methods. Currently, direct measures of exocrine pancreatic function are either invasive or lack standardization; thus, indirect methods are more commonly used for practical diagnosis. Direct pancreatic stimulation testing can measure bicarbonate output, pancreatic enzyme output, or both and has been standardized by the Dreiling tube method [15, 16]. Endoscopic pancreatic stimulation testing has been standardized in adults but not in pediatrics.

The gold standard for indirect measurement of pancreatic function is the coefficient of fat absorption (CFA), obtained by a 72-h fecal fat collection concurrent to a 3-day dietary intake record, with recommended amounts of dietary fat intake for the study and analyzed by the gravimetric method. The more commonly utilized indirect method of screening for EPI is the fecal elastase monoclonal assay[17]. Elastase is secreted by the pancreas, binds to bile acids, and is not degraded in the digestive tract. This test was validated in patients with cystic fibrosis. While there is universal agreement that >500 ug/g stool is normal and that <15 ug/g stool is abnormal, dif-

Table 12.1 Exocrine pancreatic insufficiency: indirect surrogate nutritional markers

Nutrient	Functions	How/what to measure clinically	Deficiency	Toxicity[a]
Vitamin A and the carotenoids	Vision, gene expression, reproduction, growth, immune function, bone health	Serum retinol [μmol/L], expressed in relationship to retinol binding protein and to transthyretin (normal ratio 1:1:1) Should also measure retinyl esters [% of total retinol] Esters in fasting state are concerning for potential toxicity	Vision, impaired dark adaptation, xerophthalmia, Bitot's spots, corneal xerosis	Birth defects (1st trimester supplementation)
			Hematological: anemia	Risk for hepatitis, hepatic fibrosis
			Immune: increased susceptibility to measles and risk for diarrheal diseases, infant mortality	Bone mineral loss and increased risk for fracture
				Headaches; increased intracranial pressure
Vitamin D	Intestinal absorption of calcium and phosphorous, cellular function, immune function	Serum 25 [OH] vitamin D Measured in ng/mL and nmol/L. Serum levels may relate to clinically important outcomes Deficiency <20 ng/mL (<50 nmol/L) Insufficiency: <21–29 ng/mL (52.5–72.5 nmol/L) Optimal range: > 30–99 ng/mL (75–247.5 nmol/L) Risk for toxicity: >100 ng/mL (>250 nmol/L)	Bone health	Polyuria, polydipsia; hypercalciuria; tissue calcification; nephrolithiasis; impaired renal function
			Immune function	
			Increased risk for certain cancers	
Vitamin E	Antioxidant, CNS functions	Serum alpha tocopherol and gamma tocopherol serum Recommended to obtain fasting labs and to express as a function of total cholesterol or to total lipids (functional compartment)[b]	Peripheral neuropathy; spinocerebellar ataxia; myopathy; retinopathy; RBC fragility	Potentially hemorrhagic toxicity and diminished blood coagulation and also vitamin K deficiency

Vitamin K	Coenzyme for blood coagulation and bone metabolism	Serum PIVKA-II (*p*rotein expressed *i*n the absence of *v*itamin *K*), *currently unavailable*	Easy bruising; prolonged bleeding. Decreased bone mineralization	No known toxicity
		Percent undercarboxylated osteocalcin, bone marker; research tool		
		Prothrombin time (PT)/INR: currently the most commonly used tool. Liver disease may complicate interpretation. Factor V is not related to vitamin K status		
Vitamin B_{12}	Coenzyme for 1-methyl metabolism, essential for normal hematological and neurological function	Serum vitamin B_{12} and methylmalonic acid; high MMA is suggestive of B_{12} deficiency Deficiency can be masked with folate supplementation Elevated serum levels of B_{12} can be observed with: Increased intake/supplementation Renal disease Liver disease Bone marrow disease Cancer	Glossitis	No known toxicity
			Megaloblastic anemia	
			Atrophic gastritis	
			Myelopathy and neuropathy; dementia can be irreversible	
Essential fatty acids	2 essential fatty acids: linoleic acid (LA; omega or n6) Alpha linolenic acid (ALA; omega or n3)	Fatty acid profile Levels of LA, ALA expressed as mol% or μmol/L; triene/tetraene Zinc is a cofactor in the metabolic pathway	Alopecia	Not known; balance of dietary fats may influence inflammation
			Bruising	
			Gingival bleeds	
			Seborrhea	
			Impaired growth, short stature	

Otten et al. [23]
Ross et al. [24]
Rifai et al. [25]
[a]Primarily from supplementation
[b]Huang et al. [26]

ferent labs cite different cutoff points of 100 and 200 ug/g stool. The test is highly sensitive and specific (98% and 80%, respectively), though its sensitivity is lower in patients with mild EPI. Fecal elastase testing can detect decline in exocrine pancreatic function prior to the appearance of steatorrhea [18]. The monoclonal antibody test is preferred, as the monoclonal antibodies do not react with bacterial antigens or porcine-derived pancreatic enzyme supplements to yield false positives, as is the case with the polyclonal assay [19]. Fecal elastase testing may also be falsely positive due to dilution when stool is watery, so a formed sample is required for an accurate test.

Outside of the United States, the ^{13}C-mixed triglyceride breath test may be used to diagnose EPI. This test measures exhaled $^{13}CO_2$ as dietary triglycerides are hydrolyzed by pancreatic lipase. The accuracy of this test may be affected by the rate of gastric emptying, mucosal absorption of CO_2, and other factors [17].

Recommended Screening for EPI

The incidence and prevalence of EPI after pancreatectomy in patients with hyperinsulinism are not well defined. As such, screening for any patients who have had pancreatic resections may be reasonable. The frequency of surveillance labs has not been determined for this population of patients. Assessment of surrogate markers of nutritional status susceptible to EPI and fecal elastase screening may be reasonable approaches. We suggest screening if there are clinical symptoms, and in the asymptomatic patient who is at risk based on surgical intervention, with baseline screening prior to discharge and every 6–12 months thereafter.

Treatment

The main principle underlying treatment of EPI is to minimize energy and micronutrient losses in stool and to also prevent overcorrection/potential toxicity. At this time, there is insufficient data to support firm recommendations supporting biochemical evidence over clinical evidence when deciding to initiate therapy for EPI [6]. Pancreatic enzyme replacement therapy (PERT) is the mainstay of this approach. PERT is available in multiple forms, including delayed-release capsules, tablets, and as an in-line cartridge for tube feedings. PERT is generally dosed based on lipase units per kilogram of body weight per meal, with a maximum of 10,000 lipase units/kg of body weight per day. See Table 12.2 below for more general principles of PERT dosing. Despite taking PERT, fat-soluble vitamin supplementation may be necessary [20]. There is an upper limit to PERT dosage, above which the risk of fibrosing colonopathy increases [21]. Adding an acid blocker may enhance PERT efficacy [22]. The principle underlining PERT and vitamin supplementation is to prevent deficiency and avoid toxicity/adverse effects.

Table 12.2 Management of exocrine pancreatic insufficiency

Product	Details and dosing	Use/monitoring	Cautions/troubleshooting
Pancreatic enzyme replacement therapy (PERT)	Dosing is based on lipase units Two dosing modalities: 1. By grams of fat in the meal/formula feed (For infants and young children; also can be used for overnight supplemental enteral tube feeding) 2000–4000 lipase units/120 ml breastmilk/standard formula Increase as needed to 4000 lipase units/g fat ingested 2. By weight (in kg) a. Per meal; usually half as much with snacks b. By weight per day c. Age considerations <4 years of age: 1000 units lipase/kg/meal ≥4 years of age: 500 units lipase/kg/meal Dose adjustments: Increase up to 2000–2500 lipase units per kg per meal and not to exceed 10,000 lipase units per kg per day	Start at the lower end of the dose range and follow clinical signs and symptoms as well as indirect/nutritional surrogate markers; adjust accordingly For formula-fed infants and children as well as patients treated with supplemental enteral tube feeding, non-enteric-coated products may be preferable and can be added to feeds. Clogging of feeding tubes can occur. Alternatively, PERT can be given at the beginning and toward the end of tube feeding Timing enzymes at the beginning of a meal is generally recommended. Doses can be divided for meals lasting >20 min	PERT does not improve malabsorption of carbohydrates PERT has a shelf life and may be temperature sensitive PERT should not be chewed, as oral ulcers may occur Exceeding the maximal dose (2500 lipase units/kg/meal or 10,000 lipase units/kg/d) may increase risk for fibrosing colonopathy Other variables involved in fat absorption may include GI motility, pH, and enzyme efficacy; small bowel bacterial overgrowth Acid blockers may enhance efficacy of PERT
Enteral in-line feeding cartridge (EFIC)	Intended for liquid nutrition primarily as a continuous feed Contains bacteriophage-derived liprotamase adhered to inert beads Triglycerides are lysed to 2 free fatty acids and a monoglyceride	Each EFIC device can process 500 ml of fluid EFIC can be connected in serial to proceed 1000 ml of formula	EFIC filters could clog with high fiber formulas

Sinaasappel et al. [27]
Cystic Fibrosis Foundation et al. [28]
Sermet-Gaudelus et al. [29]

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