

Pancreas

The pancreas is an organ of the digestive system. It is located in the abdomen behind the stomach and functions as a gland.

The pancreas is a mixed or heterocrine gland, i.e. it has both an endocrine and a digestive exocrine function. 99% of the pancreas is exocrine and 1% is endocrine.

- As an endocrine gland, it functions mostly to regulate blood sugar levels, secreting the hormones insulin, glucagon, somatostatin, and pancreatic polypeptide.
- As a part of the digestive system, it functions as an exocrine gland secreting pancreatic juice into the duodenum through the pancreatic duct. This juice contains bicarbonate, which neutralizes acid entering the duodenum from the stomach; and digestive enzymes, which break down carbohydrates, proteins, and fats in food entering the duodenum from the stomach.



Figure 1: Location of the pancreas inside the human body...behind all of the other organs.

Inflammation of the pancreas is known as pancreatitis, with common causes including chronic alcohol use and gallstones. Because of its role in the regulation of blood sugar, the pancreas is also a key organ in diabetes mellitus. Pancreatic cancer can arise following chronic pancreatitis or due to other reasons, and carries a very poor prognosis, as it is often identified when it has spread to other areas of the body.

1. Functions

The pancreas is involved in blood sugar control and metabolism within the body, and also in the secretion of substances (collectively pancreatic juice) that help digestion. These are divided into an "endocrine" role, relating to the secretion of insulin and other substances within pancreatic islets that help control blood sugar levels and metabolism within the body, and an "exocrine" role, relating to the secretion of enzymes involved in digesting substances in the digestive tract.

Blood Glucose Regulation

The pancreas maintains constant blood glucose levels (shown as the red wavy line). When the blood glucose level is too high, the pancreas secretes insulin (blue line) and when the level is too low, the pancreas secretes glucagon (green line).

Cells within the pancreas help to maintain blood glucose levels (homeostasis). The cells that do this are located within the pancreatic islets that are present throughout the pancreas. When blood glucose levels are low, alpha cells secrete glucagon, which increases blood glucose levels. When blood glucose levels are high beta cells secrete insulin to decrease glucose in blood. Delta cells in the islet also secrete somatostatin which decreases the release of insulin and glucagon.

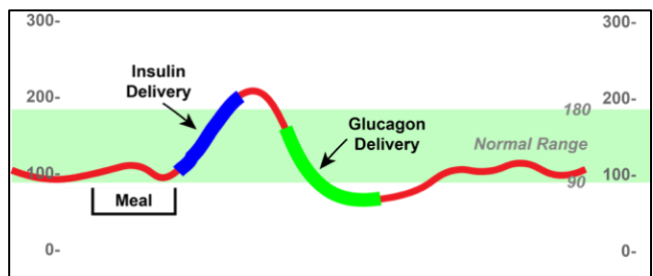


Figure 2: Illustration of fluctuating blood glucose (red line) after a meal. Blue line indicates insulin release to lower glucose, and green line indicates glucagon release to raise glucose.

Glucagon acts to increase glucose levels by promoting the creation of glucose and the breakdown of glycogen to glucose in the liver. It also decreases the uptake of glucose in fat and muscle. Glucagon release is stimulated by low blood glucose or insulin levels, and during exercise. Insulin acts to decrease blood glucose levels by facilitating uptake by cells (particularly skeletal muscle), and promoting its use in the creation of proteins, fats and carbohydrates. Insulin is initially created as a precursor form called preproinsulin. This is converted to proinsulin and cleaved by C-peptide to insulin which is then stored in granules in beta cells. Glucose is taken into the beta cells and degraded. The end effect of this is to cause depolarisation of the cell membrane which stimulates the release of the insulin.

The main factor influencing the secretion of insulin and glucagon are the levels of glucose in blood plasma. Low blood sugar stimulates glucagon release, and high blood sugar stimulates insulin release. Other factors also influence the secretion of these hormones. Some amino acids, that are byproducts of the digestion of protein, stimulate insulin and glucagon release. Somatostatin acts as an inhibitor of both insulin and glucagon. The autonomic nervous system also plays a role. Activation of Beta-2 receptors of the sympathetic nervous system by catecholamines secreted from sympathetic nerves stimulates secretion of insulin and glucagon, whereas activation of Alpha-1 receptors inhibits secretion. M3 receptors of the parasympathetic nervous system act when stimulated by the right vagus nerve to stimulate release of insulin from beta cells.

Digestion

The pancreas has a role in digestion, highlighted here.

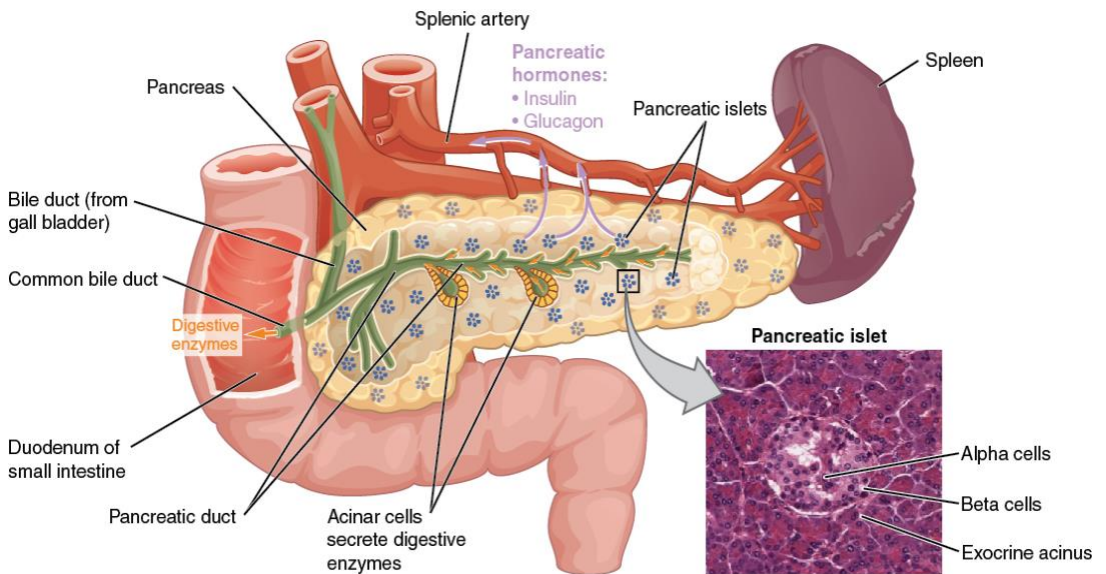


Figure 3: Diagram showing the pancreatic ducts (green) and the pancreatic islets (blue). Also shows the bile duct and where it attaches to the pancreatic duct (before the Whipple surgery).

Ducts in the pancreas (green) conduct digestive enzymes into the duodenum. This image also shows a pancreatic islet, part of the endocrine pancreas, which contains cells responsible for secretion of insulin and glucagon.

The pancreas plays a vital role in the digestive system. It does this by secreting a fluid that contains digestive enzymes into the duodenum, the first part of the small intestine that receives food from the stomach. These enzymes help to break down carbohydrates, proteins and lipids (fats). This role is called the "exocrine" role of the pancreas. The cells that do this are arranged in clusters called acini. Secretions into the middle of the acinus accumulate in intralobular ducts, which drain to the main pancreatic duct, which drains directly into the duodenum. About 1.5 - 3 liters of fluid are secreted in this manner every day.

The cells in each acinus are filled with granules containing the digestive enzymes. These are secreted in an inactive form termed zymogens or proenzymes. When released into the duodenum, they are activated by the enzyme enterokinase present in the lining of the duodenum. The proenzymes are cleaved, creating a cascade of activating enzymes.

Enzymes that break down proteins begin with activation of trypsinogen to trypsin. The free trypsin then cleaves the rest of the trypsinogen, as well as chymotrypsinogen to its active form chymotrypsin.

Enzymes secreted involved in the digestion of fats include lipase, phospholipase A2, lysophospholipase, and cholesterol esterase.

Enzymes that break down starch and other carbohydrates include amylase.

These enzymes are secreted in a fluid rich in bicarbonate. Bicarbonate helps maintain an alkaline pH for the fluid, a pH in which most of the enzymes act most efficiently, and also helps to neutralise the stomach acids that enter the duodenum. Secretion is influenced by hormones including secretin, cholecystokinin, and VIP, as well as acetylcholine stimulation from the vagus nerve. Secretin is released from the S cells which form part of the lining of the duodenum in response to stimulation by gastric acid. Along with VIP, it increases the secretion of enzymes and bicarbonate. Cholecystokinin is released from Ito cells of the lining of the duodenum and jejunum mostly in response to long chain fatty acids and increases the effects of secretin. At a cellular level, bicarbonate is secreted from centroacinar and ductal cells through a sodium and bicarbonate cotransporter that acts because of membrane depolarisation caused by the cystic fibrosis transmembrane conductance regulator. Secretin and VIP act to increase the opening of the cystic fibrosis transmembrane conductance regulator, which leads to more membrane depolarisation and more secretion of bicarbonate.

A variety of mechanisms act to ensure that the digestive action of the pancreas does not act to digest pancreatic tissue itself. These include the secretion of inactive enzymes (zymogens), the secretion of the protective enzyme trypsin inhibitor, which inactivates trypsin, the changes in pH that occur with bicarbonate secretion that stimulate digestion only when the pancreas is stimulated, and the fact that the low calcium within cells causes inactivation of trypsin.

Additional functions

The pancreas also secretes vasoactive intestinal peptide and pancreatic polypeptide. Enterochromaffin cells of the pancreas secrete the hormones motilin, serotonin, and substance P, as it is often identified when it has spread to other areas of the body.

About Cancer of the Pancreas

Pancreatic cancer, shown here, most commonly occurs as an adenocarcinoma in the head of the pancreas. Because symptoms (such as skin yellowing, pain, or itch) do not occur until later in the disease, it often presents at a later stage and has limited treatment options.

Pancreatic cancers, particularly the most common type, pancreatic adenocarcinoma, remain very difficult to treat, and are mostly diagnosed only at a stage that is



Figure 4: Example of adenocarcinoma on the head of the pancreas.

too late for surgery, which is the only curative treatment. Pancreatic cancer is rare in people younger than 40 and the median age of diagnosis is 71. Risk factors include chronic pancreatitis, older age, smoking, obesity, diabetes, and certain rare genetic conditions including multiple endocrine neoplasia Type-1, hereditary nonpolyposis colon cancer and dysplastic nevus syndrome among others. About 25% of cases are attributable to tobacco smoking, while 5–10% of cases are linked to inherited genes.

Pancreatic adenocarcinoma is the most common form of pancreatic cancer and is cancer arising from the exocrine digestive part of the pancreas. Most occur in the head of the pancreas. Symptoms tend to arise late in the course of the cancer, when it causes abdominal pain, weight loss, or yellowing of the skin (jaundice). Jaundice occurs when the outflow of bile is blocked by the cancer. Other less common symptoms include nausea, vomiting, pancreatitis, diabetes or recurrent venous thrombosis. Pancreatic cancer is usually diagnosed by medical imaging in the form of an ultrasound or CT scan with contrast enhancement. An endoscopic ultrasound may be used if a tumor is being considered for surgical removal, and biopsy guided by ERCP or ultrasound can be used to confirm an uncertain diagnosis.

Because of the late development of symptoms, most cancer presents at an advanced stage. Only 10 to 15% of tumors are suitable for surgical resection. As of 2018, when chemotherapy is given the FOLFIRINOX regimen containing fluorouracil, irinotecan, oxaliplatin and leucovorin has been shown to extend survival beyond traditional gemcitabine regimens. For the most part, treatment is palliative, focus on the management of symptoms that develop. This may include management of itch, a choledochojejunostomy or the insertion of stents with ERCP to facilitate the drainage of bile, and medications to help control pain. In the United States pancreatic cancer is the fourth most common cause of deaths due to cancer. The disease occurs more often in the developed world, which had 68% of new cases in 2012. Pancreatic adenocarcinoma typically has poor outcomes with the average percentage alive for at least one and five years after diagnosis being 25% and 5% respectively. In localized disease where the cancer is small (< 2 cm) the number alive at five years is approximately 20%.

There are several types of pancreatic cancer, involving both the endocrine and exocrine tissue. The many types of pancreatic endocrine tumors are all uncommon or rare and have varied outlooks. However, the incidence of these cancers has been rising sharply; it is not clear to what extent this reflects increased detection, especially through medical imaging, of tumors that would be very slow to develop. Insulinomas (largely benign) and gastrinomas are the most common types. For those with neuroendocrine cancers the number alive after five years is much better at 65%, varying considerably with type.

A solid pseudopapillary tumor is a low-grade malignant tumor of the pancreas of papillary architecture that typically afflicts young women.

2. Problems Caused by Removal: Diabetes Mellitus

Type-1 Diabetes

Diabetes mellitus Type-1 is a chronic autoimmune disease in which the immune system attacks the insulin-secreting beta cells of the pancreas. Insulin is needed to keep blood sugar levels within optimal ranges, and its lack can lead to high blood sugar. As an untreated chronic condition, complications including accelerated vascular disease, diabetic retinopathy, kidney disease and neuropathy can result. In addition, if there is not enough insulin for glucose to be used within cells, the medical emergency diabetic ketoacidosis, which is often the first symptom that a person with Type-1 diabetes may have, can result. Type-1 diabetes can develop at any age but is most often diagnosed before age 40. For people living with Type-1 diabetes, insulin injections are critical for survival. An experimental procedure to treat Type-1 diabetes is pancreas transplantation or isolated transplantation of islet cells to supply a person with functioning beta cells.

Type-2 Diabetes

Diabetes mellitus Type-2 is the most common form of diabetes. The causes for high blood sugar in this form of diabetes usually are a combination of insulin resistance and impaired insulin secretion, with both genetic and environmental factors playing a role in the development of the disease. Over time, pancreatic beta cells may become "exhausted" and less functional. The management of Type-2 diabetes involves a combination of lifestyle measures, medications if required and potentially insulin. With relevance to the pancreas, several medications act to enhance the secretion of insulin from beta cells, particularly sulphonylureas, which act directly on beta cells; incretins which replicate the action of the hormone's glucagon-like peptide 1, increasing the secretion of insulin from beta cells after meals, and are more resistant to breakdown; and DPP-4 inhibitors, which slow the breakdown of incretins.

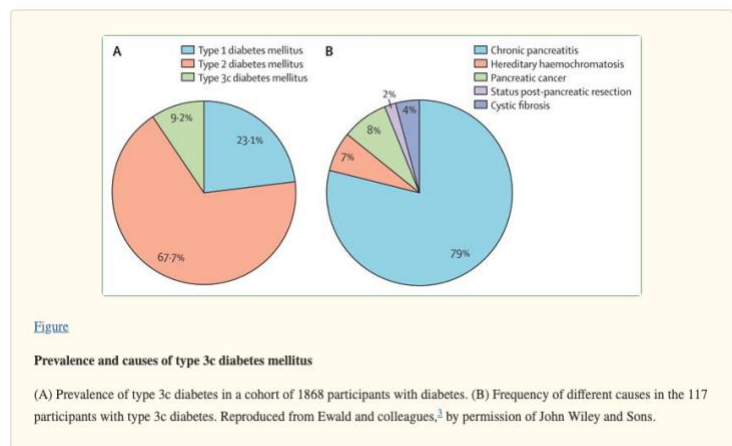
Type-3c Diabetes

Type-3c Diabetes (or Pancreatogenic Diabetes) can develop when the pancreas stops producing enough of the hormone called insulin. This can happen due to an illness or condition that affects or damages the pancreas. It can also occur if you have had surgery on your pancreas or if it is removed. When there isn't enough insulin in the body, the blood glucose levels begin to rise above the average level, and if left untreated, this can lead to complications.

Approximately 9% of all diabetes cases are Type-3c, but the condition is underdiagnosed. There is a lack of awareness amongst the general public and some health care professionals.

The leading causes of Type-3c diabetes are shown in Figure 6. It is important to remember that not everyone with chronic pancreatitis or the

other conditions here will develop Type-3c diabetes. The severity of the condition will depend on the damage caused to the pancreas, the amount of the pancreas removed during surgery and the health of any remaining organ.



Figure

Prevalence and causes of type 3c diabetes mellitus

(A) Prevalence of type 3c diabetes in a cohort of 1868 participants with diabetes. (B) Frequency of different causes in the 117 participants with type 3c diabetes. Reproduced from Ewald and colleagues,³ by permission of John Wiley and Sons.

Figure 5: Types and causes of Diabetes Mellitus.

Diagnosing Type-3c Diabetes

Diagnosis and management of Type-3c diabetes can be challenging, partly due to a lack of awareness. But remember, we know that Type-3c is linked to problems with the pancreas. So, you can ask your doctor to check for Type-3c if you've had pancreatic issues and you can explain your reasons why.

Researchers have identified criteria for diagnosing Type-3c diabetes, including the poor function of the pancreas, damage that is visible on imaging scans (such as CT) or removal of the pancreas. Diagnosis also requires the ruling out of other types of diabetes, so doctors may look for autoimmune markers for Type-1 Diabetes using a blood test. Giving doctors a thorough medical history may help them to diagnose the condition. We know that Type-3c diabetes is linked to problems with the pancreas, so you can ask your doctor to check for this if you have had pancreatic issues.

People with Type-3c diabetes often require insulin therapy with regular monitoring.

Symptoms of Type-3 Diabetes

If you have Type-3c diabetes, then your pancreas may not be able to give you what you need to digest your food. This is called pancreatic exocrine insufficiency (PEI) and means that your pancreas isn't working correctly.

The signs to look out for can include:

- Losing weight without trying to
- Stomach pain
- Feeling more tired than usual
- Frequently passing wind
- Diarrhea or fatty or oily stools.

There are also common signs and symptoms of diabetes to look out for as well:

- Feeling thirsty
- Going to the toilet more often (urine)
- Genital thrush or itching
- Blurred vision.

3. Strategies for Mitigating Problems

Treatment and Management—With Some Pancreatic Function

Management of Type-3c diabetes partly depends on the level of damage to the pancreas and the cause of the damage. Type-3c diabetes can be managed with insulin injections or sometimes oral medications/tablets. If you require insulin injections, your diabetes team will go through all the relevant information with you, and you will receive regular check-ups.

It is likely that your healthcare team will also discuss any dietary or lifestyle changes you might need to make; this may include treatment to help with digesting food.

Diabetes can be complicated and can cause different problems in the short term and the longer term, but these are not inevitable. Diabetes-related complications can include nerve, eye, foot, and kidney damage. However, keeping blood glucose levels, blood pressure, and blood fat (lipids) levels under control will help to reduce the risk of developing complications. It is vital to attend your diabetes health checks and that you know how to look after yourself between appointments.

Management of Type-3c diabetes also requires effectively treating the underlying pancreatic disease. In general, giving up smoking is essential to prevent further damage to the pancreas. Cutting out alcohol also helps maintain the health of the remaining pancreas and prevents alcohol-induced hypoglycemia (low blood sugar).

Treatment and Management—With No Pancreatic Function

For patients with no pancreatic function, (such as patients with a total pancreateoduodenectomy) all of the pancreatic functions will have to be managed manually.

1. Insulin will need to be delivered either via insulin pens or through an insulin delivery system like the Tandem t-Slim, Medtronic, or Omnipod insulin delivery pumps. These new insulin delivery pumps make glucose management much easier than it was in the past. However, they are primarily programmed for Type-1 and Type-2 diabetics, not Type-3c. So, you will still need to manually control rapidly occurring highs or lows.
2. Glucose will also need to be managed through food and physical/mental activity. Food helps bring the blood glucose (BG) up, and mental/physical

activity brings it down. For many pancreatic cancer survivors, it is surprising to learn how much glucose the body can burn from just doing difficult mental tasks...since the eyes and brain can burn up to 50% of all of the body's energy-producing glucose. Also, be aware of events that cause stress and/or anxiety. These events can trigger very rapid spikes or drops in BG...by as much as 30 points every 5 minutes, or a total spike or plunge of up to 240 points. Understanding how your individual body burns glucose can be a very powerful tool in managing your BG and insulin needs.

3. Digestive enzyme supplements containing amylase, protease, and lipase must be taken with every meal and snack (for digesting carbohydrates, proteins and fats, respectively). Popular enzyme tablets include CREON, Pancreaze, Zenpep, Ultresa, Voikace, Pertzye, & others. Work with your doctors and insurance providers to find an enzyme product you can get and afford.

Treating Conditions That Cause Type-3c Diabetes

Many conditions affecting the pancreas can result in digestion issues and put people at risk of malnutrition and raised blood glucose levels after eating (meal-induced hyperglycemia). If the pancreas is damaged or not functioning correctly, pancreatic enzyme replacement therapy (PERT) will be required to aid digestion. Taking digestive enzymes with food (CREON, Pancreaze, Zenpep, Ultresa, Voikace, Pertzye, & others) is critical. Your body will not be able to digest food nor absorb necessary nutrients without it. Good nutrition is needed to help gain or maintain weight and to help keep blood sugars stable.

People with pancreatic cancer can find it challenging to eat, digest their food, and maintain their weight. This may make managing blood sugars more difficult. The goal of treating Type-3c diabetes in someone with pancreatic cancer is to prevent very high and very low blood glucose levels, stop further weight loss and avoid longer-term complications of diabetes.

Advice for Patients With Type-3c Diabetes

- Eat smaller meals often, and in a regular pattern (at similar times every day) and include starchy carbohydrates such as potatoes, bread, rice, or pasta.
- Try not to skip meals.
- You may be advised to test blood glucose levels. Your healthcare team will show you how to do this and inform you when to test.
- Consider a diary to record insulin, pancreatic enzymes, exercise, and food intake...and pay attention to the unique patterns your body goes through as you learn how it responds to different food types, at different times of the day, and how fast it responds to insulin deliveries.
- Ask for a dietitian referral—preferably one familiar with Type-3c diabetes.

Symptoms To Be Concerned About

People with Type-3c diabetes may experience high and/or low blood glucose levels. Low blood glucose is known as hypoglycemia, or “hypo”.

A hypo is when the blood glucose level drops below 55mg/dl, this can happen if you take insulin or certain tablets for diabetes. It is essential to avoid hypos as damage to the pancreas can reduce the typical response to low blood glucose levels. Many Type-3c diabetics begin to feel the symptoms of a hypo when blood glucose levels drop below 90mg/dl. If one does occur, treatment must be given immediately.

Common Symptoms of Hypoglycemia Include:

- Trembling and feeling shaky
- Sweating
- Being anxious or irritable
- Becoming pale
- Palpitations and a fast pulse
- Lips feeling tingly
- Blurred sight
- Being hungry
- Feeling tearful
- Sudden tiredness
- Having a headache
- Lack of concentration.

A hypo requires immediate treatment with one of the following 15-20g fast-acting carbohydrates:

- 5-6 dextrose tablets
- 150ml sugary drink (non-diet) drink (fruit juice or pop/soda)
- 200ml pure fruit juice
- Five jelly babies
- 60ml GlucoJuice.

To stop your sugar levels from going down again, eating a snack or meal containing slower-acting carbohydrates is essential—preferably with a little fat and protein.

This could be a:

- A sandwich
- A piece of fruit
- A bowl of cereal
- A glass of milk
- Or it could be your next meal if it's due.

Hypos that are not resolving after treatment require urgent medical attention. If you test your blood glucose levels, you should test your blood glucose more frequently after a hypo. Let your health professional team know that it has occurred as you may need a treatment change.

Note: Of the 20 chemicals¹ secreted by the pancreas and/or duodenum mentioned in this section, only 4 can be replaced after surgery. These are:

- Insulin — Either replaced by injection pens or insulin pumps.
- Glucagon — Replaced by consuming carbohydrates.

¹ Somatostatin, intestinal peptide, pancreatic polypeptide, secretin, cholecystokinin, VIP, acetylcholine, zymogens, trypsin inhibitor, motilin, serotonin, bicarbonate, phospholipase A2, lysophospholipase, and cholesterol esterase.

- Digestive enzymes Lipase, Amylase, and Protease — Replaced by supplements like Creon.

What is amazing is that the human body is capable of adapting to the loss of these chemicals, and the functions they once performed, well enough for patients to live a successful life post Whipple!