Gastrointestinal tract 3: the duodenum, liver and pancreas

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In this article...

- Role of hormones and enzymes within the duodenum
- Role of liver and pancreas as accessory organs of the digestive system
- Common conditions affecting the duodenum, liver and pancreas

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Abstract  After its passage through the stomach, ingested food turned into acidic chyme arrives in the first segment of the small intestine, a U-shaped tube called the duodenum. The duodenum produces hormones and receives secretions from the liver (bile) and pancreas (pancreatic juice containing digestive enzymes). These various hormones, fluids and enzymes facilitate chemical digestion in the duodenum while also ensuring the acidity of chyme coming from the stomach is neutralised. This is crucial to avoid autodigestion and corrosive damage to the lining of the gut. This article, the third in a six-part series exploring the gastrointestinal tract, describes the anatomy, functions and common pathologies of the duodenum, liver and pancreas.


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Part 1 and part 2 in our series about the gastrointestinal (GI) tract looked at the role of the mouth, oesophagus and stomach in mechanical and chemical digestion. This third part of the series covers the anatomy and function of the duodenum – the first segment of the small intestine – and the role of the two major accessory organs of digestion, the liver and the pancreas. It also describes common pathologies that affect these parts of the GI tract.

Anatomy of the duodenum

The duodenum (Fig 1) is U-shaped and approximately 25-38cm long (Lopez and Khorasani-Zadeh, 2019). It consists of four regions:

- Superior region: an enlarged upper area of around 2cm called the duodenal bulb, which continues the pyloric sphincter and is connected to the liver by the hepatoduodenal ligament;
- Descending region: this extends downwards into the abdominal cavity from the superior duodenal flexure; approximately halfway down is the major duodenal papilla, the entry point of the common bile duct and pancreatic duct, which fuse before entering the duodenum. The entry of bile and pancreatic juice into the duodenum is regulated by a small ring of muscle, the sphincter of Oddi;
- Horizontal or transverse region: the largest section of the duodenum (10-12cm long) and the main area of mineral absorption;
- Ascending region: this passes slightly upwards into the abdominal cavity before connecting to the jejunum at the duodenojejunal flexure.

The duodenum is primarily a region of chemical digestion. It receives secretions from the liver and pancreas, and its mucosa contains large numbers of mucus-producing (goblet) cells and Brunner’s glands, which secrete a watery fluid that is rich in mucus and bicarbonate ions. As in the stomach (see part 2), mucus acts as a
protective barrier against autodigestion and lubricates the passage of chyme.

The mucosal lining of the duodenum also contains tall columnar epithelial cells and extends into circular folds and finger-like projections (villi), which increase the surface area for nutrient absorption. However, nutrient absorption is not the duodenum's primary function and occurs mainly further down the small intestine in the jejunum and ileum, where the villi are longer, more numerous and found at greater density.

Hormone production in the duodenum
The pyloric sphincter, which separates the stomach and duodenum, periodically opens to release small portions of acidic chyme (see part 2). This sudden increase in acidity stimulates the release of several hormones including:

- Secretin;
- Cholecystokinin;
- Gastric inhibitory polypeptide (GIP);
- Vasoactive intestinal peptide (VIP).

Secretin
Secretin, a peptide hormone comprising 27 amino acids, is secreted by the enteroendocrine S-cells of the duodenum and jejunum. It stimulates the production and release of bicarbonate ions by the pancreas; these accumulate in the pancreatic juice, giving it an alkaline pH of around 8.4. Neutralising the acidity of chyme prevents damage to the mucosa in subsequent sections of the GI tract and provides a pH favourable to the activity of pancreatic enzymes (Jun et al, 2016).

Cholecystokinin
Cholecystokinin (CCK) exists in several forms with numbers of amino acids ranging from four to 83. It is released by the enteroendocrine L-cells of the duodenum and jejunum. As Rehfeld (2017) explains, CCK:

- Inhibits gastric emptying;
- Helps prevent the duodenum overfilling;
- Stimulates the production of pancreatic enzymes;
- Stimulates the contraction of the smooth muscle wall of the gall bladder, prompting it to release bile;
- Relaxes the sphincter of Oddi, allowing bile and pancreatic juice to be released into the duodenum;
- Enhances the activity of Brunner's glands, increasing their output of bicarbonate-rich secretions;
- Reduces sensations of hunger, together with other hormones such as pancreatic polypeptide.

Gastric inhibitory polypeptide
Synthesised by the enteroendocrine K-cells of the duodenum and jejunum, GIP is a polypeptide comprising around 42 amino acids. As its name suggests, GIP inhibits the release of gastric secretions in the stomach, helping to avoid damage to the small intestine. It also promotes the release of insulin by the beta cells of the pancreas (Pederson and McIntosh, 2016).

Vasoactive intestinal peptide
VIP is a neuropeptide consisting of 28 amino acids and produced by nerve cells throughout the GI tract. Its role is poorly understood but it is thought to regulate the composition of pancreatic juice and bile, as well as blood flow in gut tissue. However, VIP also has effects outside of the GI tract: it induces peripheral vasodilation, thereby lowering blood pressure, while increasing the strength of myocardial contraction. It is also thought to play a role in regulating immune responses (Igarashi et al, 2017).

Chemical digestion in the duodenum
Chemical digestion in the duodenum relies on the secretions of the two major accessory organs of the GI tract, the:

- Liver, which produces bile;
- Pancreas, which produces pancreatic juice.

Bile and pancreatic juice are mixed and discharged into the duodenum every time the sphincter of Oddi opens under the influence of CCK.

Liver and bile production
The liver is the largest internal organ of the human body; it weighs around 1.3kg in women and 1.8kg in men. Located in the upper right quadrant of the abdomen, just below the diaphragm, it has over 500 documented functions. Its major role in

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**Systems of life**

**Fig 1. Physiology of the duodenum**

**Fig 2. Stomach, liver, pancreas and duodenum**
digestion is the production of bile, which is concentrated and stored in the gall bladder (Fig 2). In a healthy person, the liver releases around 600ml of bile into the duodenum each day. This is done in small amounts as the gall bladder contracts in response to CCK (Hundt et al, 2019).

Bile is a yellowish green fluid that contains mostly:
- Water;
- Bile salts, including sodium taurocholate and sodium glycocholate;
- Cholesterol;
- Phospholipids;
- Bile pigments bilirubin and biliverdin, which come from the breakdown of erythrocytes.

Bile salts play an important role in chemical digestion in the duodenum. They lower the surface tension of large fat globules, causing them to collapse into smaller droplets (Fig 3). This process is called emulsification, as it creates an emulsion of tiny fat droplets with a larger surface area for subsequent breakdown by fat-digesting enzymes (lipases). The digestion of fats by bile and lipases also allows the efficient absorption of fat-soluble vitamins such as vitamins A, D, E and K.

Pancreas and pancreatic juice production
The pancreas is a small, elongated gland around 15cm long and weighing around 110g; it is located in the loop of the duodenum and is covered by the lower portion of the stomach (Fig 2). The pancreas is an important organ in the endocrine and digestive systems, playing key roles in both the regulation of blood-glucose levels and digestion.

The endocrine portion of the pancreas consists of tiny clusters of cells called islets of Langerhans, which produce several key hormones involved in controlling blood-sugar levels and regulating appetite.

The digestive portion of the pancreas, or exocrine pancreas, takes up around 80% of the organ’s mass. It consists of thousands of acini, small berry-like structures that secrete pancreatic juice into tiny ducts. These connect and eventually fuse before discharging their secretions into the central pancreatic duct, which itself fuses with the common bile duct before entering the duodenum at the major duodenal papilla (Fig 2).

Around 1-2.5L of pancreatic juice is produced each day by an adult pancreas. As explained by Agrawal and Aoun, (2014), pancreatic juice consists mostly of:
- Water;
- Bicarbonate ions;
- Pancreatic enzymes.

One of its key roles is to neutralise acidity in the chyme coming through from the stomach. This is essential to prevent autodigestion and ulceration of subsequent sections of the GI tract.

Pancreas and pancreatic enzyme production
Beyond pancreatic juice, the pancreas also produces several enzymes that continue, in the duodenum, the chemical digestion started in the mouth and stomach.

Pancreatic lipase
Pancreatic lipase is the most active of the gut lipases. Like salivary and gastric lipases (see parts 1 and 2), it breaks down triglyceride fats into fatty acids and glycerol, working mostly on the emulsified fat droplets created by bile salts. For maximal activity on fat droplets, pancreatic lipase requires the presence of the small protein co-enzyme colipase, which is itself produced by the pancreas (Ross et al, 2013).

Weight-loss drugs such as orlistat inhibit pancreatic lipase, thereby reducing the digestion and absorption of fats. Orlistat is reported to reduce the absorption of dietary fat by up to 30%. However, the use of such drugs is often associated with side-effects such as abdominal bloating and diarrhoea, as undigested fats collect in the colon and irritate it (Qi, 2018; Al-Suwailem et al, 2006).

Pancreatic amylase
Carbohydrate digestion starts in the mouth with salivary amylase (see part 1). Like salivary amylase, pancreatic amylase attacks the glycosidic bonds between adjacent glucose molecules in polysaccharides, breaking down starch into maltose. As it catalyses starch digestion in the duodenum lumen (inside space of the duodenum), it is also called luminal amylase (Williams, 2009).

Pancreatic amylase can function over a broad neutral-to-alkaline pH range. Amylases are most efficient in an environment with a neutral-to-alkaline pH. The activity of salivary amylase slows down in the acidic environment of the stomach, but the enzymatic digestion of carbohydrates resumes in the alkaline environment of the duodenum.

Pancreatic proteases
Protein digestion starts in the stomach, where pepsin attacks the peptide bonds of large molecules, breaking down proteins into smaller chains of amino acids termed polypeptides (see part 2). The next stage of protein digestion relies on several pancreatic proteases:
- Trypsin;
- Chymotrypsin;
- Carboxypeptidase;
- Elastase.

Trypsin is the major protease present in pancreatic juice. To avoid autodigestion and damage to the pancreatic acini and ducts, it is initially secreted as the inactive precursor (orzymogen) trypsinogen. Once in the duodenal lumen, trypsinogen is converted into trypsin by the action of the enzyme enteropeptidase (or enterokinase), which is produced by the mucosal cells of the duodenum and jejunum. Trypsin then catalyses the activation of the other pancreaticzymogens into their active forms chymotrypsin, carboxypeptidase and elastase (Goodman, 2010).

Carboxypeptidase – an exopeptidase – catalyses the removal of single amino acids...
from the ends of protein and polypeptide molecules, gradually reducing their length. Trypsin, chymotrypsin and elastase – all endopeptidases – attack the peptide bonds in the central portions of proteins and polypeptides. This results in the generation of smaller chains of amino acids called peptides (Fig 4), which are subsequently digested in the jejunum and ileum by the action of intestinal peptidase (see part 4).

Pancreatic nucleases
All food consumed by humans comes from plant, animal, fungal or bacterial sources. As all cells, whatever their origin, contain deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), the human body can digest these by breaking them down into their building blocks, which are called nucleotides. DNA is composed of four major nucleotide bases: adenine, cytosine, guanine and thymine; RNA has the same bases, except that thymine is replaced by uracil (Knight and Andrade, 2018).

Pancreatic juice contains the pancreatic nucleases DNase and RNase, enzymes that break down DNA and RNA (VanPutte et al, 2017). The digestion of nucleic acids allows some of the nucleotide bases to be recycled and used as building blocks for human DNA synthesis during cell division, and for RNA during the process of transcription that precedes protein synthesis.

Mineral absorption in the duodenum
The duodenum is primarily dedicated to digestion, but the presence of short villi in relatively small numbers indicates that some nutrient absorption does also take place here. Small amounts of sugars, amino acids and fats, but large amounts of minerals (iron, calcium, phosphorus and trace elements of zinc and copper) are absorbed in the duodenum (Kiela and Ghishan, 2016). Patients who have had extensive ulceration or cancer that has required the removal of all or part of the duodenum may need to take mineral supplements to compensate for reduced mineral absorption.

Common problems
Duodenal ulceration
‘Peptic ulcer’ is an umbrella term used to describe ulcers in the stomach or duodenum. Gastric and duodenal ulcers used to be attributed to stress and poor diet – particularly the consumption of greasy and spicy foods – but it is now accepted that infection with Helicobacter pylori is the major precipitating factor (see part 2). The use of non-steroidal anti-inflammatory drugs significantly increases the risk of peptic ulcers (Kaur et al, 2012).

Symptoms of gastric and duodenal ulcers are very similar. Patients often experience a burning epigastric pain, often described as ‘gnawing’, and can point to its location. Some with duodenal ulcers experience pain either on an empty stomach or occurring two to three hours after food consumption, which tangles with gastric emptying times. However, the only way to locate a peptic ulcer with absolute certainty is to visualise it, usually via endoscopy.

Duodenal ulcers must be treated because of the risk of perforation and life-threatening complications such as peritonitis and sepsis. As with gastric ulcers (see part 2), treatment relies on the combination of a proton pump inhibitor to reduce stomach acid secretion and two antibiotics to eradicate H. pylori infection (triple therapy) (Narayanan et al, 2018).

Gallstones
Gallstones are one of the most common pathologies of the GI tract, usually forming as a result of the consolidation of bile salts and cholesterol. Many people have, in their gall bladder, a collection of gritty deposits resembling wet sand, known as biliary sludge. Over time, the particulates can aggregate to form a gallstone. Many textbooks quote the ‘five Fs’ – female, fair, fat, forty and fertile – as major risk factors for developing gallstones, but these criteria are now regarded as poor indicators of risk. However, being female, being overweight and being middle-aged are recognised risk factors (Bit.ly/NHSGallstones).

Many people who have gallstones are unaware of them, as they do not usually cause symptoms unless they start to travel out of the gall bladder. Each year, around 2-4% of people with gallstones experience symptoms (Gurusamy and Davidson, 2014). Biliary colic – the pain associated with gallstones – usually occurs when gallstones leave the gall bladder and begin to scrape their way along the highly innervated bile ducts. It is usually experienced in the upper right quadrant and commonly radiates to the back, particularly around the right shoulder blade. Biliary colic, described as agonisingly painful, with episodes typically lasting 1-5 hours, is often associated with nausea, vomiting and bloating. The pain is so intense that opioids are often required to alleviate it.

A gallstone that is stuck in the bile duct can lead to obstructive jaundice. The two bile pigments bilirubin and biliverdin accumulate in the liver and overspill into the blood, causing the urine to be dark coloured. They eventually turn the skin and the sclera (whites of the eyes) to the greenish-yellow colour that is typical of jaundice.

In patients who have asymptomatic gallstones, watchful waiting is usually the approach that should be adopted, while the National Institute for Health and Care Excellence (2014) recommends the removal of the gall bladder (cholecystectomy) for those with symptoms; this is usually done by laparoscopy (Gurusamy and Davidson, 2014).

Patients who have had their gall bladder removed are less efficient when it comes to digesting fats; this means that undigested fat is carried over into the large intestine, where it may irritate the mucosa. These patients are susceptible to recurrent diarrhoea with copious amounts of foul-smelling, pale-coloured and oily stools (steatorrhoea).
Pancreatitis

Pancreatitis is an inflammation of the pancreas that can lead to permanent scarring and structural damage to soft tissue and life-threatening complications. Acute pancreatitis is commonly caused by gallstones that have travelled along the common bile duct and have become trapped in a position where they obstruct the pancreatic duct. Pancreatic juice becomes trapped in the pancreas and pancreatic enzymes may start to digest the internal pancreatic tissue, triggering severe inflammation and pain.

Acute pancreatitis may also be caused by excessive consumption of alcohol and is particularly associated with binge drinking. The exact mechanism is unclear, but it is thought that alcohol may activate pancreatic enzymes while they are still in the pancreas, leading to autodigestion and inflammation. Pancreatitis is also often seen in patients with cystic fibrosis and can be triggered by certain drugs, such as the antibiotic tetracycline.

The symptoms of pancreatitis are similar to those of gallstones, with upper abdominal pain radiating into the back. The pain often becomes worse after eating and may be associated with a fever. Some patients experience relief when they lean forward (Bit.ly/NHSPancreatitis). Most cases of mild pancreatitis will resolve and symptoms gradually disappear after about a week. However, severe cases often require hospital admission, possibly in a high-dependency unit, and opioids for pain relief. Even with treatment, acute pancreatitis has an overall mortality of around 10-15%, rising to 30-40% in patients with severe disease (Meher et al, 2015).

Unresolved acute pancreatitis can turn into chronic pancreatitis, most often seen in patients with alcohol dependency. This is characterised not only by chronic pain, but also by long-term inflammation of the pancreas that can lead to progressive tissue fibrosis as a result of the deposition of collagenous scar tissue. Chronic pancreatitis can damage both the exocrine and endocrine pancreas; when more than 90% of the exocrine pancreas is destroyed, pancreatic exocrine insufficiency (PEI) develops and normal digestion can no longer take place. PEI most frequently manifests as poor digestion of fats leading to steatorrhea.

Around 50% of patients with chronic pancreatitis also experience significant damage to the endocrine pancreas and a progressive loss of pancreatic islets, which can lead to diabetes (Pham and Forsmark, 2018). Poor digestion of fats — whether resulting from PEI, gall bladder disease or cholecystectomy — may impair the absorption of key fat-soluble vitamins, so patients may need to take supplements to avoid deficiencies.

Pancreatic cancer

Each year, around 8,800 people are diagnosed with pancreatic cancer, which causes around 5-7% of cancer deaths in the UK. It is the most deadly of the common cancers, with five-year survival rates below 5% (Pancreatic Cancer UK, 2015). Pancreatic cancer is predicted to overtake breast cancer as the fourth most common cause of cancer death by 2030 (Pancreatic Cancer UK, 2015). Age is the main risk factor and most cases are diagnosed after the age of 50. Modifiable risk factors include smoking, obesity and inactivity.

Around 95% of pancreatic cancers arise in the exocrine pancreas. The remaining 5% affect the endocrine pancreas; they are generally less aggressive and have a better prognosis. Symptoms associated with pancreatic cancer are not usually present until the disease is fairly advanced; they include unexpected weight loss, abdominal discomfort and/or pain, steatorrhea, nausea and, sometimes, diabetes.

Pancreatic cancer is usually treated with surgery, which may be curative (if the tumour is discovered early) or palliative. Many patients may also undergo chemotherapy or radiotherapy with the aim of reducing the size of the tumour (Kleeff et al, 2016). Treatments specifically targeting pancreatic tumour cells have been recently developed but are not yet widely available (Amanam and Chung, 2018). NT

For more on this topic online

- Anatomy and physiology of ageing 3: the digestive system

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