

Pancreatic Insufficiency

What is pancreatic insufficiency?

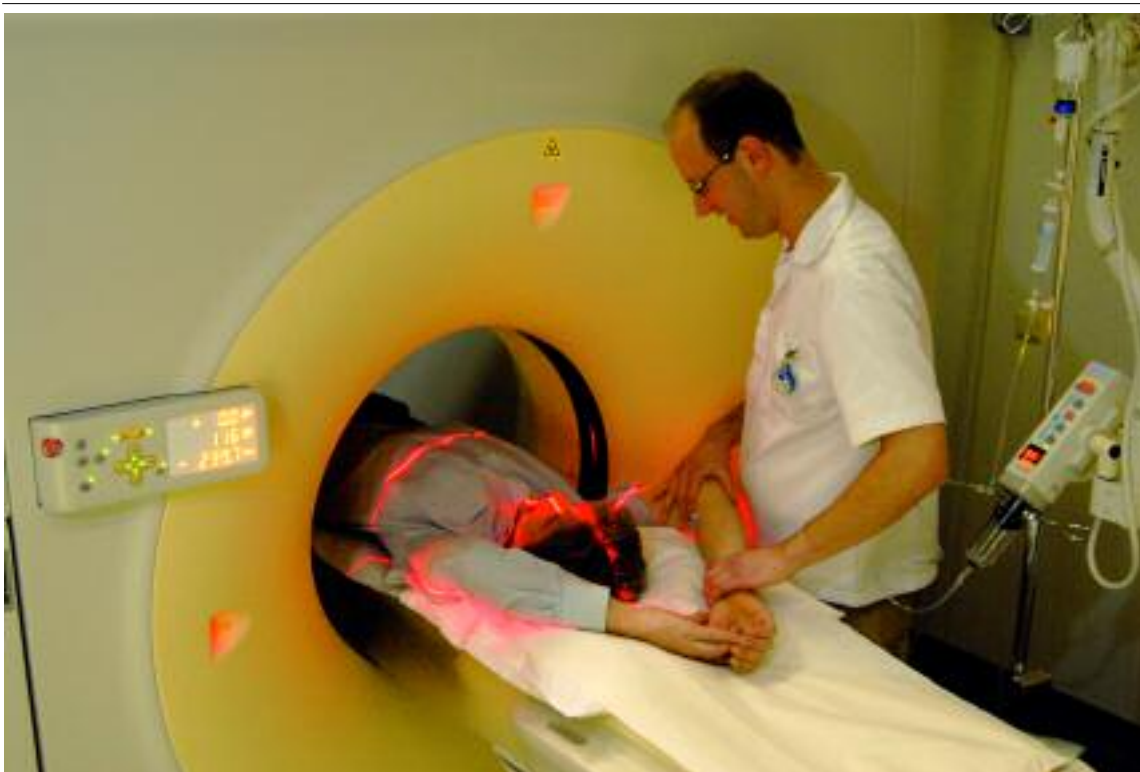
Pancreatic insufficiency occurs when the pancreas does not synthesise sufficient enzymes for proper digestion to take place. The organ produces and secretes digestive fluids containing enzymes, which help break down fats, carbohydrates and proteins. The islet cells of the pancreas secrete the hormones insulin and glucagon into the bloodstream. Insulin causes the body's cells to take up glucose from the blood, and glucagon causes the liver to release glucose into the blood.

Pancreatic insufficiency is a condition, not a disease. It is commonly associated with diseases such as pancreatitis or cystic fibrosis, in which patients have a shortage of the digestive enzymes necessary to break down food. It typically results from damage to the organ, such as chronic inflammation or after pancreatic surgery. Its main cause is alcohol dependence. Certain gastrointestinal diseases, such as stomach ulcers and Crohn's disease, and autoimmune disorders such as systemic lupus erythematosus (SLE), may also lead to the development of pancreatic insufficiency.

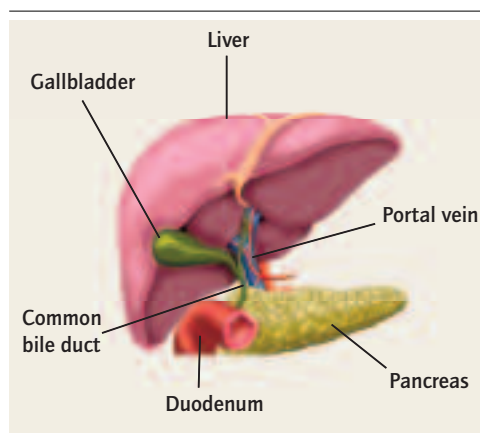
Malabsorption of fat is likely if an individual ingesting 100g of fat per day excretes more than 7g of fat in a 24-hour period. Malabsorption of protein is likely if nitrogen excretion is greater than 2.5g per 24 hours. In order for impairment of the digestion of fat to occur, pancreas secretion must be less than ten per cent of its normal output. This means that in severe pancreatic insufficiency, 90 per cent of the gland's tissue is affected.

Severe pancreatic insufficiency impairs absorption of nutrients by the intestines and may lead to malabsorption syndromes, resulting in deficiencies of essential nutrients. Decreased absorption of fat leads to increased amounts of fat in stools, or steator-

Pancreatic insufficiency occurs when the pancreas does not produce enough digestive fluids to break down food. It is a serious condition, often caused by alcohol. Research has helped patients with enzyme therapies to make their lives more bearable.



rhoea. A typical finding is pale, bulky, foul-smelling stools. The condition may cause pain, abdominal tenderness, loss of appetite or feeling of fullness, diarrhoea and weight loss. People with pancreatic insufficiency may also have bone pain, muscle cramps, night blindness, and be prone to bruising.



Liver and pancreas

Who does pancreatic insufficiency affect?

Based on estimates from hospital discharge data in several cities around Europe, the overall frequency of pancreatic insufficiency – expressed as number of cases per 1,000 hospital admissions – was calculated between three and four. When the data from several centres are compared over time, the incidence of the condition from 1945-1985 appeared to be increasing. No exact data exist on the extent of disability resulting from pancreatic insufficiency.

In population studies, males are affected twice as often as females. Rates in males peak at the age group 45-54 and then decline, and female rates reach a plateau which remains stable after the age of 35 years. Sex differences with respect to the causes of the condition also exist. Alcohol-induced illness is more prevalent in males, idiopathic and hyperlipidemic-induced insufficiency of the gland is more prevalent in females, and equal sex ratios are observed in chronic insufficiency associated with hereditary causes, such as in cystic fibrosis.

Present treatments

Until a cure for pancreatic insufficiency is found, the goals of medical treatment are to modify behaviours that may exacerbate the natural history of the condition, to enable the pancreas to heal itself, to restore digestion and absorption, and to diagnose and treat endocrine insufficiency. When possible, treatment is directed at the underlying cause of pancreatic damage. In early-stage alcohol-induced pancreatic insufficiency, pain relief can occur after abstinence from alcohol and giving up smoking, but recommending abstinence from alcohol and smoking cessation alone may not be sufficient for recovery.

If the patient has lost weight and has diarrhoea or has a daily fat excretion of greater than 15g, pancreatic enzyme replacement therapy is recommended. Pancreatic enzymes include three classes of enzymes: proteolytic enzymes needed to digest protein, lipases needed to digest fat, and amylases needed to digest carbohydrates. At least 30,000 units of lipase activity must be taken with a meal to correct malabsorption, and total correction of steatorrhoea may not occur. Several studies have demonstrated pain relief with high-dose pancreatic enzymes, as high as three times replacement doses.

The enzymes in standard tablets can be inactivated by a low pH; therefore, the addition of a histamine 2 receptor (H_2) blocking compound or a proton pump inhibitor is occasionally needed to reduce stomach acid. Special microsphere capsules have been developed which have the advantage of better mixing with pancreatic fluids.

Initial analgesic therapy consists of pain-relieving medicines or non-steroidal anti-inflammatory drugs (NSAIDs). An amino acid sequence containing the active portion of somatostatin is also used to provide analgesia. For refractory severe pain, narcotic pain-killers are required. Antioxidant vitamin and micronutrient supplementation may have a role in facilitating pancreatic healing in the early stage of the condition. In severe cases, it may be recommended to replace unabsorbed fat soluble vitamins A, D, E, and K via intravenous nutritional supplements. A low fat diet helps to control steatorrhoea.

Surgery is indicated when an anatomical complication exists that is correctable by a mechanical intervention. Depending on the individual case, the appropriate interven-

tion may involve endoscopic, radiological, or surgical techniques. In selected patients, the long-term morbidity caused by diabetes following total surgical removal of the pancreas can be avoided by harvesting the islet cells from the resected pancreas and injecting them into the portal system of the patient, which then lodges them in the liver.

What's in the development pipeline?

Two research groups have joined forces for the development of a new biotechnologically engineered microbial enzyme tailored to treat pancreatic insufficiency. There is the intention of launching a variety of new generation digestive enzymes derived from a microbiological source. The lipase, protease and amylase under development should show an efficacy comparable to that of pancreatic enzymes. Development is in early stages, with the first toxicology studies under preparation, to be followed by clinical phase 1 and 2 studies. The first data from clinical studies are expected in 2007.

A preparation consisting of three active ingredients is in phase 3 clinical development as an orally delivered enzyme replacement therapy for the treatment of malabsorption as a result of pancreatic insufficiency. The medicine has been granted orphan drug status and fast-track designation by the USA Food and Drug Administration (FDA). Another product in development is a gastric lipase used in the treatment of pancreatic insufficiency, in particular for cystic fibrosis and chronic pancreatitis patients and is in phase 1 clinical trials.



The longer-term future

Basic and clinical studies will have to address the identification of genetic factors predisposing individuals to pancreatic insufficiency. Such investigations would include: (i) genetic screening studies to identify gene mutations in candidate genes or their regulatory elements associated with pancreatic structural or functional abnormalities; (ii) the identification of biological or molecular mechanisms of pancreatic injury; (iii) the generation of new animal models of abnormal pancreatic function by expression of mutant genes associated with pancreatic disease; and (iv) identification of environmental factors that influence the development and course of pancreatic insufficiency in susceptible individuals.

Recent evidence indicates involvement of distinct chemokines in the initiation and perpetuation of chronic inflammation of the pancreas. In contrast to healthy pancreatic tissues, pancreatic lobules in mild-to-moderate chronic pancreatitis express messenger ribonucleic acid (m-RNA) of monocyte chemoattractant protein-1 in the ducts of the organ, in endothelial cells, fibroblasts, macrophages, and T lymphocytes. In more advanced disease stages, interleukin (IL)-8 is detected in pancreas cells. Further research is needed to understand the complexity of this area, and, hopefully, research will lead to new treatment approaches.

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