Nutrition in pancreatic diseases

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The pancreas plays a major role in nutrient digestion. Therefore, in both acute and chronic pancreatitis, exocrine and endocrine pancreatic insufficiency can develop, impairing digestive and absorptive processes. These changes can lead to malnutrition over time. In parallel to these changes, decreased caloric intake and increased metabolic activity are often present. Nutritional deficiencies negatively affect outcome if they are not treated. Nutritional assessment and the clinical severity of the disease are important for planning any nutritional intervention.

In severe acute pancreatitis, enteral nutrition with a naso-jejunal feeding tube and a low molecular diet displays clear advantages compared to parenteral nutrition. Infectious complications, length of hospital stay and the need for surgery are reduced. Furthermore, enteral nutrition is less costly than parenteral nutrition. Parenteral nutrition is reserved for patients who do not tolerate enteral nutrition.

Abstinence from alcohol, dietary modifications and pancreatic enzyme supplementation is sufficient in over 80% of patients with chronic pancreatitis. In addition, oral supplements are helpful. Enteral nutrition can be necessary if weight loss continues. Parenteral nutrition is very seldom used in patients with chronic pancreatitis.

Key words: Acute pancreatitis; Chronic pancreatitis; Enteral nutrition; Parenteral nutrition; Nutritional state assessment.

The two major inflammatory diseases of the pancreas are acute and chronic pancreatitis. In both circumstances nutrient digestion and absorption can be impaired, both short-term or indefinitely. Nutritional support is different in acute and chronic pancreatitis. Under normal conditions, the pancreas plays an important role in the digestion and absorption of nutrients. An impaired pancreatic function has negative consequences for the patient. Nutritional deficiencies can occur in both acute and chronic pancreatitis. Malnutrition in acute pancreatitis can be caused by the acute
catabolic stress induced by the systemic inflammatory response, while in chronic pancreatitis malnutrition is due to pain and decreased nutrient digestion and absorption. This overview focuses on the consequences of impaired pancreatic function and the importance of nutritional support to decrease morbidity and mortality.

**PHYSIOLOGY OF THE PANCREAS**

Digestion and absorption of nutrients is a complex and well coordinated process involving multiple and interacting gastrointestinal secretory, absorptive, motor and circulatory systems. Normal functioning of the pancreas is a prerequisite for undisturbed processing and mucosal uptake of nutrients.

The normal human pancreas secretes more than ten different enzymes together with water, bicarbonate and other proteins. These enzymes are secreted in abundance and hydrolyse macronutrients within the intestinal lumen, of which lipids, proteins and carbohydrates are of particular importance. The regulation of human pancreatic secretion is part of an overall, integrated, motor-secretory response. A meal is the most important physiological stimulus for pancreatic secretion. Pancreatic secretion also occurs in the fasting (interdigestive) state in a coordinated regulated fashion. The postprandial pancreatic enzyme output reaches maximal rates following a mixed meal of 20 kcal/kg body weight. The duration of the response increases with greater caloric loads. The proportions of fat, carbohydrate and protein within a meal influence the duration and enzyme composition of the pancreatic response.

The tuned gastric emptying of small portions of pre-processed, liquid chyme into the duodenum starts the pivotal period of intraluminal digestion. The duodenal entry of nutrients is accompanied by bursts of pancreatic and biliary digestive secretions with which nutrients are instantly mixed. Exposed to a large mucosal area, digestion and subsequent absorption of the nutrients occurs rapidly.

The generation of absorbable products as a result of intraduodenal digestive processes is the major event for the regulation and integration of the postprandial gastrointestinal response. Multiple neuro-humoral mechanisms are involved in controlling gastric emptying, secretory and metabolic responses.

A vagally-mediated cephalic phase contributes to the overall response, but the most important mechanism inducing postprandial human pancreatic secretion is the presence of nutrients within the duodenal lumen. Postprandial stimulation of pancreatic secretion by duodenal nutrients involves the activation of neural pathways (vagal-cholinergic reflexes) and the release of regulatory peptides (e.g. cholecystokinin (CCK)) and secretin, with a tight interaction of neural- and humoral systems.

The regulation of human postprandial pancreatic secretion also involves inhibitory mechanisms that probably serve to modulate and eventually terminate the response. Somatostatin, pancreatic polypeptide (PP), peptide YY and glucagon-like peptide-1 are involved in this regulatory circuit.

In parallel with the induction of the postprandial pancreatic response, gastrointestinal motility changes from basal interdigestive into postprandial activity. Induction, maintenance and duration of fed intestinal motility and pancreatic secretion are tightly coupled and coordinated. In the fasting state, characterised by the absence of stimulatory nutrients within the lumen, the human pancreas is not quiescent but secretes in a characteristic pattern. Output of water, bicarbonate and enzymes occurs in parallel with the phases of interdigestive cyclical motility (migrating motor complex, MMC).
**Practise points**

In acute and chronic pancreatitis:

- the well coordinated secretion and motility patterns are disturbed
- nutritional status and the course of the disease are negatively influenced.

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**ACUTE PANCREATITIS**

**Epidemiology and aetiology of acute pancreatitis**

The true incidence of acute pancreatitis is not known exactly and it varies in different areas of the world. In the USA, Great Britain and Germany, 11–23 cases/100 000 people have been reported.\(^1\) Biliary lithiasis and chronic alcoholism are the two most important causes for acute pancreatitis (accounting for 80–90% of cases). After the exclusion of alcoholism and ductal obstruction, there are some less frequent aetiologies that should be considered (Table 1).

In Germany, alcohol and biliary-induced acute pancreatitis have a similar frequency. In the USA, Australia, South Africa and Italy, alcohol is the dominant factor whereas in

<table>
<thead>
<tr>
<th>Table 1. Aetiology of acute pancreatitis.</th>
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<tbody>
<tr>
<td><strong>Toxic and metabolic factors</strong></td>
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<tr>
<td>Alcohol abuse</td>
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<tr>
<td>Hypertriglyceridaemia</td>
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<tr>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Azathioprine, sulfonamide, didanosine, thiazide, furosemide, pentamidine, tetracycline, valproic acid, oestrogens</td>
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<tr>
<td><strong>Vascular factors</strong></td>
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<tr>
<td>Periarteritis nodosa</td>
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<tr>
<td>Hypothermia</td>
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<tr>
<td>Malignant hypertension</td>
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<tr>
<td><strong>Mechanical factors</strong></td>
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<tr>
<td>Biliary stones</td>
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<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Endoscopic retrograde pancreatography (ERCP)</td>
</tr>
<tr>
<td>Pancreatic malignancy</td>
</tr>
<tr>
<td>Pancreas divisum</td>
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<tr>
<td><strong>Infectious diseases</strong></td>
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<tr>
<td>Viral (e.g. Coxsackie virus)</td>
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<tr>
<td>Ascaris lumbricoides</td>
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<td><strong>Idiopathic pancreatitis</strong></td>
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Great Britain biliary lithiasis is more often seen. Females appear to be more often affected than males. In female patients, a higher prevalence secondary to biliary stones is the most important aetiological factor, whereas in males the most frequent cause of acute pancreatitis is excessive alcohol consumption. Acute pancreatitis occurs more frequently in the population aged between 50 and 70 years. The highest mortality can be seen after age 60. Acute alcoholic pancreatitis is more frequently seen in males and the onset is earlier, between 30 and 45 years of age. Biliary-induced pancreatitis occurs between 50 and 70 years of age, with a higher proportion being female. In areas where alcohol consumption is increasing, the alcoholic aetiology of acute pancreatitis is also increasing. Alcoholic pancreatitis develops in only 5% of alcoholics and after at least 10 years of ethanol abuse.

### Practise points

The most common causes of acute pancreatitis are:

- alcohol abuse in men
- biliary stone obstruction in women.

### Diagnosis, classification and outcome of acute pancreatitis

Acute pancreatitis is an acute inflammatory process that may involve the peripancreatic tissue or even remote organs. Acute pancreatitis presents with abdominal pain, tenderness and elevation of serum pancreatic enzyme concentrations. A rise in concentration of serum amylase and lipase is typical. Acute pancreatitis can be characterised as either a mild or severe disease, with local or systemic complications. According to the Atlanta criteria, approximately 75% of patients have mild disease with a mortality rate of less than 1%. Mortality increases up to 20% if the disease progresses to its severe necrotising form; in the most severe cases, mortality can exceed 30–40%.

Assessment of the severity and prediction of the progress of acute pancreatitis at the time of admission can be difficult. Assessment at admission and during the course of the disease is crucial for planning the optimal treatment. Several prognostic scoring systems are available that include clinical aspects (e.g. Ranson score, Glasgow score, Atlanta classification), laboratory and radiological criteria. The Atlanta classification of severity defines severe acute pancreatitis on the basis of standard clinical manifestations: a score of 3 or more in the Ranson criteria or a score of 8 or more in the APACHE II criteria, as well as evidence of organ failure and intrapancreatic pathological findings (necrosis or interstitial pancreatitis). Laboratory markers include the measurement of serum C-reactive protein (CRP) or urinary trypsinogen activation peptide (TAP) concentration; both are useful in clinical practice. CRP concentration has an independent prognostic value. A peak of more than 210 mg/l on days 2 through 4, or more than 120 mg/l at the end of the first week has the same predictive value as multiple-factor scoring systems. Urinary TAP level has been shown to predict the severity of acute pancreatitis 24 hour after onset. Urinary TAP level is
suggested as a single marker for severity assessment, but it is not available as a routine test.23

The severity of acute pancreatitis can be graded using imaging on the basis of the Balthazar score (Table 3), which predicts severity from the computed tomography (CT) appearance, including the presence or absence of necrosis. An attack is defined as

### Table 2. Ranson criteria for severity assessment in acute pancreatitis.

<table>
<thead>
<tr>
<th>On admission</th>
<th>SI units</th>
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<tr>
<td>Age</td>
<td>&gt; 70 years</td>
</tr>
<tr>
<td>WCC</td>
<td>&gt; 18 x 10^9/l</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>&gt; 12 mmol/l</td>
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<tr>
<td>LDH</td>
<td>&gt; 400 IU/l</td>
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<tr>
<td>ASAT</td>
<td>(&gt; 210 IU/l)</td>
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### Table 3. CT grading of acute pancreatitis.

<table>
<thead>
<tr>
<th>Score</th>
<th>Necrosis</th>
<th>Score</th>
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<tr>
<td>Normal</td>
<td>A 0 0 0 0</td>
<td></td>
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<tr>
<td>Focal, diffuse enlargement.</td>
<td>Contour Irregularity</td>
<td></td>
</tr>
<tr>
<td>Inhomogeneous attenuation</td>
<td>B 1 &lt; 30% 2</td>
<td></td>
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<tr>
<td>B + peripancreatic haziness/steady densities</td>
<td>C 2 50% 4</td>
<td></td>
</tr>
<tr>
<td>B, C + ill-defined pancreatic fluid collection</td>
<td>D 3 &gt; 50% 6</td>
<td></td>
</tr>
<tr>
<td>B, C + 2 ill-defined pancreatic fluid collections</td>
<td>E 4</td>
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WCC, white cell count.

**Practise points**

**Acute pancreatitis:**
- presents as mild or severe disease
- has a mortality range of between < 1–40% depending on severity
- can be assessed for outcome using clinical, laboratory and imaging methods.
severe if more than 50% of the pancreatic gland does not show an enhancement of the parenchyma during the arterial phase of an intravenous contrast-enhanced CT scan.\textsuperscript{24}

**Pathogenesis of acute pancreatitis**

The initial acute pancreatitis-inducing event has not yet been clarified in detail. The first stage in the initiation of acute pancreatitis is acinar cell injury with subsequent activation of trypsinogen to trypsin, which leads to autodigestion of the gland. Most patients have mild disease with minimal organ dysfunction and recover in a few days. In severe cases, a systemic inflammatory response syndrome (SIRS) develops, leading to pancreatic necrosis and multiorgan failure. Inflammatory cytokines cause macrophages to migrate into tissues that are distant from the pancreas, including the kidneys and lungs. Some of the cytokines (e.g. interleukin-1 and tumor necrosis factor (TNF) etc.) are involved in the disease progression. Mast cells are very important in mediating both the local and systemic effects. The local effects include alteration in microvascular and endothelial barrier function. The systemic effects are mediated by the over-expression of cytokines. The clinical presentation of the systemic effects are fever, tachycardia, tachypnoea, hypovolaemia, hypoxia, acute respiratory distress syndrome (ARDS), shock and ultimatively multiorgan failure.\textsuperscript{25} Furthermore, these mechanisms are involved in the hypermetabolic, hyperdynamic process that leads to catabolic stress associated with nutritional deficiencies. This will have negative consequences, especially in patients already malnourished at the time of the initial attack.

**Nutritional consequences during acute pancreatitis**

Malnutrition is often seen in patients with acute pancreatitis prior to the first attack.\textsuperscript{26} Protein-calorie malnutrition arises or worsens due to the depletion of nutrients and to

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<tr>
<td>In acute pancreatitis:</td>
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<tr>
<td>• nitrogen balance can become negative and may have an adverse effect on outcome</td>
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<td>• adequate nutritional support is of great importance.</td>
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<tr>
<td>In acute pancreatitis:</td>
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<tr>
<td>• multiple mechanisms lead to autodigestion of the gland</td>
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<tr>
<td>• the degree of the systemic inflammatory response syndrome predicts the severity of the disease and the clinical outcome.</td>
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the hypermetabolic state during the acute attack. Specific and non-specific metabolic changes occur during acute pancreatitis. A variety of proinflammatory cytokines increase the basal metabolic rate. This results in increased energy consumption. If patients develop sepsis, 80% of them show a marked elevation in protein catabolism and an increased nutrient demand. A negative nitrogen balance affects the clinical outcome. Sitzmann et al. reported a tenfold increase in the mortality rate when the nitrogen balance was negative, compared with those patients with a positive balance. As yet, no study has been stratified according to disease severity and nitrogen balance.

Alteration of substrate metabolism during acute pancreatitis

Carbohydrates
Glucose metabolism in acute pancreatitis is determined by an increase in energy demand. Endogenous gluconeogenesis is increased as a consequence of the metabolic response. Glucose is an important source of energy and can partially counteract the intrinsic gluconeogenesis from protein degradation. This can compensate to a certain degree the deleterious and unwanted effects of protein catabolism.

The maximum rate of glucose oxidation is approximately 4 mg/kg per minute. The administration of glucose in excess of this can be harmful, because of lipogenesis and glucose recycling. Furthermore, hyperglycaemia and hypercapnia can occur. Hyperglycaemia is also associated with an increase in infections and metabolic complications. Glucose levels can also be increased due to the frequently impaired insulin secretion. There is little evidence that insulin supplementation is beneficial to these patients.

Proteins and amino acids
A negative nitrogen balance is often seen in severe acute pancreatitis. Protein loss should be minimised in these patients, thus the increased protein turnover must be compensated for. Deficiency in certain amino acids may enhance pancreatic inflammation.

Lipids
Hyperlipidaemia is often seen in acute pancreatitis. Increases in cholesterol and free fatty acid serum concentrations have been reported. The mechanism for these changes in lipid metabolism is not entirely clear. Alterations in lipid oxidation and lipid clearance may both play a role. Serum lipid concentration returns to normal ranges if the patient recovers. In some patients with pre-existing hyperlipidaemia, an increased risk of
developing acute pancreatitis has been reported. Hyperglyceridaemia, ranging up to 80–100 mmol/l has been seen in these patients. Several mechanisms have been suggested as explanations for the harmful effects, but none of them has been accepted.

Are nutrients harmful in acute pancreatitis?

Intravenous glucose administration does not stimulate exocrine pancreatic secretion. Enteral perfusion of glucose into the jejunum is only a weak stimulus for exocrine pancreatic secretion. Intravenous administration of protein hydrolysates either inhibits the exocrine pancreatic secretory response, or has no effect. However, amino acids can stimulate gastric acid secretion, which in turn may stimulate the pancreatic secretory response. Jejunal perfusion of elemental diets containing defined amounts of protein or amino acids is well tolerated and does not significantly stimulate exocrine pancreatic secretion. Regardless of whether an elemental diet is ingested orally or infused into the duodenum or the jejunum, the elemental diet results in lower stimulation than a standard diet infused at the same level. Elemental diets have been studied in patients with acute pancreatitis and they were regarded as safe. However, clinical experience with the infusion of intact proteins into the jejunum has not been shown to induce major negative effects on outcome.

Pancreatic secretion is not stimulated by intravenous lipids. However, case reports have been published in which acute pancreatitis developed after the intravenous infusion of fat emulsions. In all of these cases it was not clear whether the increase in serum triglycerides was a direct cause of the acute pancreatitis, or whether it was caused by other factors (e.g. comorbidities and/or other drug therapies). The stimulation of exocrine pancreatic secretion by enteral administration

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<th>Research agenda</th>
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<td>Detailed studies are necessary:</td>
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<tr>
<td>• to elucidate the negative effect of amino acid deficiencies on pancreatic inflammation</td>
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<td>• to define the mechanism of disturbed lipid metabolism in acute pancreatitis.</td>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>In severe acute pancreatitis:</td>
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<tr>
<td>• due to the catabolic state, the metabolism is altered for all three macronutrients</td>
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<tr>
<td>• energy expenditure and protein catabolism are increased.</td>
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of lipids depends on the anatomical site of administration. If lipids are given into the proximal jejunum, only a minimal stimulation of exocrine pancreatic secretion occurs. Thus, there is no convincing evidence that would suggest that the use of glucose, proteins and triglycerides or other fats is contraindicated in patients with acute pancreatitis, provided that those patients are monitored for hyperglycaemia and hypertriglyceridaemia.

**NUTRITIONAL TREATMENT IN ACUTE PANCREATITIS**

Until recently, enteral nutrition, given either orally or by enteral tubes, was believed to have a negative impact on the progression of the disease due to stimulation of exocrine pancreatic secretion and the consequent worsening of the autodigestive processes. Even so, nutritional deficits are frequent in severe acute pancreatitis and nutrition as a part of therapy was neglected for a long time.

Oral feeding can increase abdominal pain in patients with acute pancreatitis. To overcome these problems, patients were either fasted or nutritional support was provided by the parenteral route. Parenteral nutrition (PN) was considered to be the standard treatment with two main goals: (1) to meet the nutritional requirements and (2) to avoid stimulation of exocrine pancreatic secretion. A clear benefit of PN has, however, not been shown in various trials. Two studies in patients with mild to moderate severe acute pancreatitis compared parenteral nutrition to no nutritional support or to tube feeding. In the trial by Sax et al no difference in the mortality rate could be demonstrated. Catheter-induced septicaemias, as well as hyperglycaemia, occurred significantly more often in the PN group. McClave et al compared early enteral nutrition (EN) via a jejunal tube to PN in a randomised controlled prospective study. Enteral nutrition was initiated within 48 hour after admission to the hospital. The
outcome in both groups revealed no statistical differences in infectious complications, length of intensive care unit (ICU) stay, length of hospital stay, or days to oral food intake. A small advantage of PN was seen in the endpoint of reaching the caloric target. This was achieved in 86% of patients having PN compared to 72% having EN. All patients in both groups survived. In the PN group, significantly higher glucose concentrations were found in the first 5 days and PN was four times more expensive than EN. PN is, in general, associated with more cases of hyperglycaemia and other metabolic disturbances. It has become clear that this complication was often the consequence of overfeeding. Van Den Berghe et al. provided clinical evidence that irrespective of the route of nutritional support, controlling hyperglycaemia with insulin reduced mortality in critically ill patients.

Compared to mild acute pancreatitis, the feeding support in severe acute pancreatitis is different. A prospective, randomised trial compared naso-jejunal tube feeding using a semi-elemental diet with PN. Enteral feeding was well tolerated without adverse effects on the course of the disease. Patients who received EN experienced fewer septic complications and fewer total complications than those receiving PN. Furthermore, the costs of nutritional support were three times higher in patients receiving PN. Windsor et al. later confirmed these data. PN was compared with EN in patients with mild to moderate pancreatitis (peripheral PN versus sip feeds) and severe pancreatitis (total PN versus tube feeding). The SIRS was significantly attenuated in all enteral fed patients. Sepsis and multiorgan failure as well the incidence of surgery were reduced. Two patients died in the parenteral group, whereas no death occurred in the enteral group. A major weakness of this study was the low number of patients with severe pancreatitis and the total amounts of nutrient delivered, revealing marked differences between the enteral and the parenteral group. A further trial by Powell et al. could not demonstrate the same positive results. They compared early tube feeding in patients with a severe acute pancreatitis to patients without artificial nutrition.

Abou-Assi et al. treated 156 patients with acute pancreatitis during the first 48 hour with only intravenous (iv) fluid and analgesics. Of the 156 patients, 87% had mild, 10% had moderate and 3% had severe disease. Those patients who improved were orally fed. The non-responders were randomised to receive nutrients either by naso-jejunal tube or by PN; 75% of the initially enrolled patients improved with the initial regimen and were discharged within 4 days. In the randomised group, 54% of the EN group \( n = 26 \) and 88% in the PN group \( n = 27 \) had an adequate energy intake. However, the patients in the enteral group were fed for a significantly shorter period and had significantly fewer metabolic and septic complications. Hyperglycaemia requiring insulin therapy was significantly higher in the parenterally fed patients. Mortality was not different between the two groups.

The meta-analysis of Marik and Zaloga compared PN versus EN in patients with acute pancreatitis and concluded that EN should be the preferred route of nutritional support in patients with acute pancreatitis, because it was associated with a significantly lower incidence of infections, a reduced rate of surgical interventions and a reduced length of hospital stay. There were no significant differences in mortality and non-infectious complications.

Many studies in the last decade in patients with trauma, terminal injury and after major gastrointestinal surgery have shown a reduction in septic complications with enteral feeding. Enteral nutrition helps to maintain mucosal functions and limits the absorption of endotoxins and cytokines from the gut. Four prospective studies have shown that jejunal delivery of nutrients is possible in most patients with acute pancreatitis. Proximal migration of the feeding tube and a subsequent pancreatic
stimulation can aggravate acute pancreatitis, but this is a rare occurrence.\textsuperscript{71} The placement of feeding tubes either by pushing blindly, with the aid of fluoroscopy or by endoscopy is feasible most of the time.

With the publication of Eatock et al,\textsuperscript{72} it seems that naso-jejunal feeding in severe acute pancreatitis may not be necessary all the time. They compared naso-gastric feeding with naso-jejunal feeding in a randomised study. The results showed that naso-gastric feeding was safe, with no differences in pain scores, analgesic requirements, serum CRP concentrations, or clinical outcome. If there are no problems with gastric emptying, naso-gastric feeding can be tried.

Enteral nutrition has been possible in most patients with acute pancreatitis that have been studied in controlled prospective trials. In a more general population, dealing with large patient groups or including all treated patients, this was not found to be the case. Oleynikov et al\textsuperscript{73} have reported that EN was not possible in most patients with severe acute pancreatitis with a mean APACHE II-score of 17.2 and a mean Ranson-score of 4.3 on admission. This was probably due to severe retroperitoneal inflammatory changes.

Two studies using specific enteral formulations have been published recently. In a small study, Halley et al\textsuperscript{67} reported a beneficial effect of a glutamine-rich multifibre diet compared to a standard fibre diet on the recovery of IgG and IgM-proteins, with a shorter disease duration. In a second study, the enteral administration of the probiotic strain \textit{Lactobacillus plantarum} 299 and prebiotic oat fibre was examined in patients with severe acute pancreatitis.\textsuperscript{74} Twenty-two patients received live bacteria and 23 patients received the same formulation with heat-killed bacteria. In the live bacteria group, only one patient developed a septic pancreatic complication requiring surgery compared to the control group where seven patients required surgery. Furthermore, the incidence of infected necrosis and abscesses were significantly lower (4.5 versus 30.4%). These new data are exciting, but the approach cannot be recommended outside clinical trials at this time. Larger trials are needed to confirm these findings.

Not all patients with acute pancreatitis need specific nutritional support. There is no evidence that nutritional support (enteral or parenteral) has a beneficial effect on clinical outcome in patients with mild acute pancreatitis. In mild acute pancreatitis, the clinical course is usually uncomplicated and patients can consume an oral diet low in fat within 3–7 days. The disease does not have a major impact on nutritional status, or on energy and substrate metabolism. It is not clear whether this is true in cases with pre-existing malnutrition. It is crucial for patients with signs of malnutrition that their requirements are met by providing artificial nutrition.

The European Society of Parenteral and Enteral Nutrition (ESPEN) Guidelines recommend three steps for the nutritional support of patients with mild acute pancreatitis, if they can consume an oral diet within 5–7 days (Figure 1).\textsuperscript{75}

- In the first 2–5 days fasting, analgesics, iv fluid and electrolyte replacement is the treatment of choice.
- If pain is controlled and enzymes are regredient, a diet rich in carbohydrates and moderate in protein and fat can be started.
- Normally these patients can be discharged to home after 4–7 days with a normal diet.

In acute severe pancreatitis, early EN by a jejunal tube is recommended as the first step. If side-effects occur, or the caloric goal cannot be reached, EN should be combined with PN. There is substantial experimental evidence to support the notion that enteral feeding in severe acute pancreatitis can down-regulate the systemic inflammatory response and promote beneficial effects on gastrointestinal functions. EN may prevent the colonisation
Severe acute pancreatitis

NPO (2-5 days)

Jejunal tube placement
Elemental diet (Polymeric diet?) (Immune-enhancing diet?) (Probiotics?)

PN and in addition continuous small amounts of an enteral diet (10-30 ml/h) perfused to the jejunum

Add PN and continue with EN

Oral Re-feeding
• Diet rich in CH
• Diet moderate in protein and fat

Normal diet

Discharge

Figure 1. Nutritional support in acute pancreatitis.
of the intestine by pathogenic bacteria and reduce bacterial translocation in the intestinal wall, with a reduction in superinfection of the pancreatic necrosis. For this reason, a low volume of enteral solution continuously perfused to the jejunum (10–30 ml/hour) should be started and, if necessary, given in parallel with PN. Nutrient delivery (enteral or parenteral) should be determined by the patient’s tolerance. This approach allows the nutritional goals to be reached in the most efficient way.

In patients with severe acute pancreatitis who have complications or who need surgery, the ESPEN Guidelines recommend the following (Figure 1):75

- Begin early with a continuous enteral feeding by a jejunal tube as soon as the clinical signs predict severe pancreatitis.
- An elemental diet is used most often, but standard enteral or immune-enhancing formulations are also given.
- At present, due to the lack of controlled trials, no recommendation for a specific nutrient formulation can be given.
- If EN is insufficient, PN should be added.
- The administration of fat in PN can be regarded as safe.
- Hyperglycaemia (<10 mmol/l) and hyperglyceridaemia (<12 mmol/l) should be avoided.

### Research agenda

For future studies, there are several unanswered questions that need clarification:

- Is gastric feeding safe? If so, when and in which patients?
- Which is the best formula for enteral nutrition (EN) in severe acute pancreatitis?
- What is the role of pre- and probiotics in patients with acute pancreatitis?
- Could immune-enhancing formulas be more beneficial?

Oral refeeding can be started if the patient is stable, gastric outlet obstruction has resolved, pain has ceased and amylase and lipase values are decreasing.76 Oral refeeding with a diet that is rich in carbohydrates and moderate in proteins and in fat is recommended, but no clinical trials are available to support this strategy. If the diet is well tolerated, oral nutrition can be increased continuously. Specific products do not have to be used.

The nutrient requirements depend on the severity of the disease. Patients with severe acute pancreatitis are hypermetabolic. If the disease is complicated by sepsis or multiorgan failure, the resting energy expenditure is significantly increased.27,77 In patients with severe acute pancreatitis, it is recommended that over- or underfeeding should be avoided. For EN or PN, 25–35 kcal/kg body weight/day are recommended. In severely ill patients, indirect calorimetry can be helpful for assessing the resting energy expenditure properly. It is important to avoid hyperglycaemia. Blood glucose concentration should not exceed 10 mmol/l. Insulin treatment is then recommended. The dose should not be higher than 4–6 units/hour, because the impaired glucose oxidation rate cannot be normalised by insulin administration or by increasing glucose administration. Normally 3–6 g/kg body weight/day of carbohydrates are sufficient.
The optimal goal for supplying protein is to administer between 1.2 and 1.5 g/kg body weight/day. A higher protein intake should only be given to patients with a severe negative nitrogen balance. A lower protein intake is sometimes necessary in patients with severe renal or hepatic failure.

Fat can be given safely up to 2 g/kg body weight/day, but triglyceride levels must be monitored carefully. The level should not exceed 12 mmol/l. Ideally fat serum levels should be kept within normal ranges.

Nutrient recommendations are easier to obtain with PN than with EN. Enteral solutions contain fixed amount of the different nutrients. The enteral intake of the different nutrients can only be regulated by changing the application time. Today a 24-hour continuous jejunal feeding regimen is most commonly used.

**CHRONIC PANCREATITIS**

**Epidemiology and aetiology of chronic pancreatitis**

There have been only a few population-based studies on the frequency of chronic pancreatitis. The estimated incidence varies between 5 and 10/100 000 per year. Chronic pancreatitis is more frequent in males than in females. In Western countries, the most common cause of chronic pancreatitis, in up to 80% of patients, is intake of alcohol. The frequency of chronic pancreatitis is, however, considerably lower than the frequency of heavy alcohol drinking. It is not known why only a few heavy drinkers develop chronic pancreatitis. Compared to alcohol-induced liver cirrhosis, chronic pancreatitis is significantly less frequent. An additional important co-factor may be smoking. The mean age of patients with chronic pancreatitis is about 45 years. Apart from alcohol-induced chronic pancreatitis, pancreatic duct obstruction, pancreas divisum, hereditary pancreatitis and tropical pancreatitis are other aetiologies, but clearly less common in Western countries. In 10–20% no apparent underlying disease (idiopathic chronic pancreatitis) can be identified (Table 4).

**Diagnosis, classification and outcome of chronic pancreatitis**

Chronic pancreatitis is an inflammatory disorder that causes irreversible anatomical changes and damage, including infiltration of inflammatory cells, fibrosis and calcification of the pancreas. The diagnosis of chronic pancreatitis is based on ductal changes observed using imaging procedures such as abdominal ultrasound, endoscopic ultrasound, endoscopic retrograde pancreatography (ERCP), magnetic resonance pancreatography or CT scans. Furthermore, functional evaluation of the pancreas can

<table>
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<th>Table 4. Aetiology of chronic pancreatitis.</th>
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<td>Alcohol (60–70%)</td>
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<td>Obstruction</td>
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<td>Hereditary</td>
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<tr>
<td>Tropical</td>
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<td>Idiopathic (15–35%)</td>
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confirm pancreatic insufficiency. Several non-invasive tests are available such as the pancreolauryl test, as well as several breath tests using $^{13}$C-labelled substrates. In addition, pancreatic enzyme concentration (elastase) can be measured in faeces. Finally, exocrine pancreatic function can also be indirectly assessed by means of faecal fat quantification. This test reflects fat digestion and, therefore, indirectly the capacity of pancreatic lipase activity. The non-invasive pancreatic function tests are simple and routinely applicable in a clinical setting.82,83

Data on the natural history of chronic pancreatitis are rare and conflicting. In the early stage of chronic pancreatitis, episodes of recurrent acute pancreatitis predominate. Severe persistent pain is typically associated with local complications. Maldigestion is a late complication of chronic pancreatitis and depends on the underlying disease. The medium latency between onset of first symptoms and signs of maldigestion is about 8–9 years in alcoholic chronic pancreatitis and more than 15 years in idiopathic non-alcoholic pancreatitis.84

Pathogenesis of chronic pancreatitis

In the development of chronic pancreatitis the pancreatic glands undergo morphological changes. These include oedema, acute inflammation and necrosis, superimposed on a background of chronic changes that include fibrosis, calcification, inflammation and the loss of exocrine tissue. The pancreatic ducts can be dilated and contain intraductal protein plaques, which can be calcified.85,86 Pancreatic stones can be seen in chronic alcoholic, tropical, hereditary and idiopathic pancreatitis.87 A different pathophysiological feature is seen in tropical pancreatitis. This non-alcoholic, fibrocalcific type of chronic pancreatitis develops at a young age and is associated with severe early diabetes. A major risk factor for tropical pancreatitis is believed to be malnutrition in childhood.88

During the evolution of chronic pancreatitis, enzyme secretion is gradually decreased, resulting in maldigestion with steatorrhea and azotorrhea when more than 90% of the pancreatic tissue is destroyed. In the late course of chronic pancreatitis, diabetes will develop due to the loss of insulin producing beta-cells in the pancreas. The acinar cells are usually affected before the islet cells.

Nutritional consequences during chronic pancreatitis

A late symptom of chronic pancreatitis is malnutrition. The severity of malnutrition is correlated with complications and outcome, but specific studies investigating this issue are not available. The two major factors causing malnutrition are depletion of nutrients and increased metabolic activity. Persistent alcohol intake, pain after a meal and maldigestion are the main causes of weight loss. Resting energy expenditure is increased by up to 30–50% in patients with chronic pancreatitis.89 Weight loss is strongly associated with maldigestion of fat. Clinical steatorrhea is seen when over 90% of the pancreatic exocrine secretory function is lost.90 Steatorrhea is more severe and develops earlier than maldigestion of protein and carbohydrates. A deficiency in vitamins A, D, E and K occurs in parallel with the severity of steatorrhea. Specific deficiencies in calcium, magnesium, zinc, thiamine and folic acids have also been reported.
Alteration of substrate metabolism during chronic pancreatitis

Carbohydrates

In exocrine pancreatic insufficiency, carbohydrate digestion is maintained for a long time by salivary amylase and brush-border oligosaccharidases. The loss of endocrine function leads to glucose intolerance. Glucose intolerance occurs in 40–90% of all cases with severe chronic pancreatitis. In 20–30% of all patients an insulin-dependant diabetes develops associated with impaired glucagon release.

Proteins

Protein digestion is initiated by intragastric proteolytic activity, it is continued by intestinal brush-border peptidases and is maintained even in the absence of luminal pancreatic proteolytic activity. Azotorrhea is a very late symptom in chronic pancreatitis.

Lipids

Luminal lipid digestion within the small intestine depends on the combined action of pancreatic lipase and cofactors such as colipase and bile acids. There are no triglyceride-digestion enzyme systems within the intestinal brush-border membrane. Lipid digestion is decreased by insufficient lipase secretion and reduced luminal bile acid concentration. In chronic exocrine pancreatic insufficiency, bicarbonate secretion is also diminished. Postprandial intraduodenal pH may fall below 4. It is known that lipase is more sensitive to acid destruction than are other enzymes. Luminal lipase degradation occurs more rapidly than that of other enzymes due to its greater instability when proteolysis occurs. The small residual quantities of lipase secreted into the duodenum may be further inactivated by low intraluminal pH. All these actions lead to a decrease in fat digestion and overt steatorrhea. Gastric lipase potentially compensates for the lack of pancreatic lipase.

Nutritional treatment in chronic pancreatitis

Chronic maldigestion of macronutrients is the major cause of progressive nutritional and metabolic impairment in patients with chronic pancreatitis. Nutritional interventions depend on the degree of maldigestion and the nutritional status.

It is necessary to assess the nutritional status in patients with chronic pancreatitis. Nutritional assessment is easy to perform. Weight loss over time, body mass index, anthropometry and some laboratory values are useful parameters. Furthermore, several nutritional screening scores, e.g. subjective global assessment (SGA), ESPEN-nutritional risk score (ESPEN-NRS) and the minimal nutritional assessment (MNA), are available for detecting those patients with nutritional deficiencies who are at risk of developing complications.92–95

The main goals for nutritional interventions are to decrease maldigestion and malabsorption in order to prevent malnutrition.

The treatment of exocrine deficiency begins with dietary recommendations and pancreatic enzyme supplementation. About 80% of patients can be managed by analgesics, dietary recommendations and pancreatic enzyme supplements, while
10–15% need oral nutritional supplements, 5% need enteral tube feeding and around 1% require PN.

Adequate nutritional therapy and effective pain treatment have a positive impact on the nutritional status. Often, calorie intake increases after an attenuation of postprandial pain.

Dietary recommendations begin with total abstinence from alcohol. In addition, an adequate number of calories should be taken because of increased resting energy expenditure. Frequent meals (4–5 times a day) should be given. The diet should be rich in carbohydrates and proteins. The carbohydrate intake should be limited when an overt diabetes mellitus is present. A protein diet of 1.0–1.5 g/kg body weight/day is generally sufficient and well tolerated. Fat must also be given to reach the necessary caloric goal. Usually, if 30–40% of the calories are given as fat this is well tolerated, especially when the foods are rich in vegetable fats. If weight gain is insufficient and/or steatorrhea persists, medium chain triglycerides (MCT) can be tried to increase fat absorption. MCT are absorbed directly across the small bowel into the portal vein, even in the absence of lipase, colipase and bile salts. The drawbacks of MCT are their low energy density and unpalatable taste. Sometimes MCTs also cause cramps, nausea and diarrhoea. Fat soluble vitamins (A, D, E and K), vitamin B12 and other micronutrients should be supplemented if serum levels indicate deficiencies. In general, a low fibre diet is recommended, because fibre may absorb enzymes and delay the absorption of nutrients.

An adequate quantity of exogenous pancreatic enzymes is necessary to correct protein and lipid malabsorption. Steatorrhea is usually more difficult to correct than azotorrhea. Therefore, a suitable amount of lipase per meal is necessary to provide adequate lipolysis. There is no defined dose for these enzyme supplements and patients will need to take 2–6 pills with each meal. Weight control, symptomatic relief of steatorrhoea, or a decrease in 72-hour faecal fat excretion are practical endpoints for this therapy. It is important to give the enzymes before the meal to ensure adequate mixing. If the enzyme treatment response is not satisfactory, the addition of an acid inhibitor (proton pump inhibitor) can be tried. Decreasing the duodenal acid load can prevent the inactivation of lipase in the small bowel. Several enzyme supplements are available that differ in enzyme content as well as in the galenical formulation. There is no evidence that encapsulated formulations are superior to standard enzyme supplements.

In 10–15% of patients oral supplements can help to attenuate weight loss and delay the use of enteral tube feeding.

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<td>In chronic pancreatitis:</td>
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<td>• more than 80% can be treated with normal food supplemented by pancreatic enzyme supplements</td>
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<tr>
<td>• 10–15% of all patients require enzyme supplements</td>
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<tr>
<td>• adequate nutritional therapy as well pain treatment may have a positive effect on nutritional status</td>
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<tr>
<td>• caloric intake increases if postprandial pain is controlled.</td>
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EN is generally indicated when patients do not have a sufficient calorie intake. The cause for inadequate calorie consumption can be anatomical (pyloro-duodenal-stenosis), inflammatory with acute complications (new attack of acute pancreatitis or development of fistulas) or prior to a surgical intervention. It is recommended that the calories are given via naso-jejunal tube. For long-term therapy a percutaneous endoscopic gastrostomy (PEG) with a jejunal tube is probably more convenient. It has been shown that continuous overnight delivery of the nutrients is suitable. There are no studies available that show an improvement in the nutritional status by enteral feeding. A semi-elemental diet can be recommended. The use of a polymeric diet can be tried, but there are no clinical data available that show a beneficial effect.

Enteral nutritional support can be very useful before pancreatic surgery. Data from patients undergoing general abdominal surgery have provided evidence that a preoperative enteral or oral nutritional support with an immune-enhancing diet improved outcome (1) by reducing postoperative infection complications and (2) by a reduction in the length of hospital stay. Furthermore, early enteral nutrition with a fine-needle catheter-jejunostomy or a naso-jejunal tube after major abdominal surgery can be beneficial.

PN is seldom used in patients with chronic pancreatitis. PN should be instituted when gastric emptying is blocked, when the patient needs gastric decompression, when a tube can not be introduced into the jejunum, or when a complicated fistula is present. There are no reported series of patients with chronic pancreatic insufficiency who have been treated with intravenous nutrition for a long period. PN is mainly performed over the short term, e.g. in apparent severe malnutrition prior to pancreatic surgery if enteral feeding is not possible.

**Research agenda**

- In chronic pancreatitis it is necessary to study the impact of malnutrition on complications.

**Practise points**

In chronic pancreatitis:

- 5% of patients need tube feeding
- in less than 1% parenteral nutrition (PN) is necessary.

**Research agenda**

Future questions to be answered are:

- is gastric or jejunal feeding necessary?
- which type of nutrients (semi-elemental or polymeric diets) are most beneficial?
- what is the benefit of using medium chain triglycerides (MCTs).
SUMMARY

Severe acute and chronic pancreatitis interferes with nutrient digestion and absorption. Inadequate food supply and increased demands lead to nutritional deficiencies and weight loss.

In both diseases, it is crucial to assess the nutritional status, because the severity of a pre-existing or developing malnutrition affects outcome. Several easy methods for a nutritional assessment are available.

Severe acute pancreatitis is associated with autodigestion of the pancreatic gland, protein catabolism, metabolic instability and increased nutritional requirements. In the last decade, nutritional support in acute pancreatitis has changed. It has been shown that in mild and severe acute pancreatitis, parenteral nutrition was not beneficial. In addition, it was shown that PN increased complications due to overfeeding and uncontrolled hyperglycaemia. Several studies have demonstrated that enteral nutrition via a naso-enteral tube is possible and beneficial in patients with severe pancreatitis patients. EN is safer and less expensive than PN. Although EN can sometimes not reach the estimated caloric and protein needs, the clinical results clearly show a superiority of EN over PN. Specific nutritional support is only necessary in severe acute pancreatitis with local and systemic complications. In mild acute pancreatitis enteral and parenteral nutritional support has shown no beneficial effect. These patients can be fed orally very early and can be discharged in less than a week. PN should be reserved for patients with severe pancreatitis not tolerating EN, those that have an exacerbation of their disease with enteral feeding and before pancreatic surgery if the patient has severe signs of malnutrition.

Abstinence from alcohol, dietary modification and pancreatic enzyme supplements are the corner stones of nutritional management in patients with chronic pancreatitis. There are no good trials available to document a beneficial effect of EN or PN in patients with chronic pancreatitis and severe maldigestion and malnutrition. EN can be useful, when dietary recommendations fail or before, and after, pancreatic surgery. Jejunal applications of low molecular diets are well tolerated. The recommendations on EN and PN are still empirical, because prospective trials in patients with chronic pancreatitis using enteral or parenteral feeding protocols are lacking.

REFERENCES


