Chapter

Dietary Interventions for Pancreatitis

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Abstract

Pancreatic insufficiency, both acute and chronic, is an important cause of maldigestion and malnutrition caused by impaired exocrine pancreatic function. Many causes are able to determine pancreatic insufficiency which, depending on the severity, can manifest itself with very diversified symptoms. The chapter will illustrate the diagnostic and monitoring methods of pancreatic pathology in the acute and chronic phases. Great attention will be given to oral nutrition, in its various forms, including enteral and peranterior artificial nutrition. Finally, we will discuss the most appropriate pharmacological therapy to optimise food absorption in the different phases of the disease. Each of the aspects considered takes into account the most recent literature and the clinical experience of the authors.

Keywords: acute pancreatitis, chronic pancreatitis, artificial nutrition, pancreatic insufficiency, pancreas diet

1. Introduction

1.1 Symptoms and causes of acute pancreatitis

Pancreatitis is an inflammatory process, either acute or chronic, resulting from the outset, caused by digestive enzymes, of a process of self-digestion of the pancreas, and resulting in a complex inflammatory pattern which is extremely challenging for patients. Since even organs and systems located far from the pancreas can be variably involved in such pattern, the manifestations and the intensity of the disease may prove extremely severe, to the point of endangering the patient's life [1, 2].

A healthy pancreas synthesises over 10 digestive enzymes in the acinal cells, while the pancreatic ducts host the production of bicarbonate, whose function is that of neutralising the acid content of the stomach when it reaches the duodenum. The increased pH makes the duodenum the ideal environment for the pancreatic and the jejunal digestive brush border enzymes. Complex factors contribute to the stimulation of the exocrine pancreas, including the intake of highly caloric food (>500 kcal), the presence of free fatty acids in the duodenum, the intake of essential aminoacids (phenylalanine, valine, methionine, tryptophane) and solid rather than liquid or

semi-liquid dietary consumption (slower gastric emptying). The exocrine stimulation mainly occurs through the vagus nerve and the secretion of cholecystokinin (CCK) [3–5].

The onset of Acute Pancreatitis may be sudden, with pain ranging from mild to severe and often accompanied by fever, nausea and vomiting. The intensity of the pain, typically located in the epigastric area, is not always correlated with the disease severity and may radiate towards the back, the chest or the hips (**Tables 1** and **2**) [6, 7].

Data regarding the severity of the clinical picture and that of any complications are essential in the prognosis. Scores have been elaborated aimed at quantifying the severity of the clinical picture (Ranson's score; Harmless Acute Pancreatitis Score [HAPS]; Modified Glasgow Acute Pancreatitis Severity Score; Atlanta Score for Acute Pancreatitis 2013; Bedside Index for Severity in Acute Pancreatitis) [8–12]. These scores are frequently associated with systemic assessment scores such as the Marshall Score (**Table 3**) [13]. Predictive symptoms of clinical worsening in patients with Acute Pancreatitis are: body temperature < 36 o > 38°C (<96 or > 100°F), heart rate > 90/min, respiratory rate > 20/min, white blood cells <4 x 109/L or > 12 x 109 L (<4 or > 12 K/mm3).

SYMPTOMS	SIGNS
1. Pain: • generally sudden onset • mainly in the upper abdomen/epigastric area • persistent, progressively increasing intensity (not relieved by ordinary analgesics) • duration: from hours to a day • often radiated towards the back, the chest and the hips • often relieved by fetal position; 2. Associated symptoms: nausea, vomiting, anorexia, abdominal distension; 3. Aggravating factors: eating or drinking (especially alcohol); 4. Korte's sign: painful resistance in the epigastric area where the head of the pancreas is located, 6–7 cm above the navel.	1. General condition: distress, anxiety; 2. Vital signs: fever, tachycardia, hypotension, tachypnea; 3. Clinical signs: jaundice, cyanosis, dehydration 4. Abdominal pain: marked epigastric tenderness with voluntary and involuntary shielding +/− rigidity, abdominal distension, reduced peristalsis, sometimes palpable pseudocyst; 5. Possible pleural effusion; 6. Common signs associated with pancreatitis: • Voskresynskyy sign: absence of abdominal aortic pulsation in epigastric area; • Mayo-Robson sign: costovertebral angle (CVA) tenderness; • Razdolsky sign: tenderness during pancreas percussion; 7. Uncommon signs associated with severe Necrotizing Pancreatitis: • Cullen sign (presence of peri-umbilical oedema with bruising as a result of intraperitonal haemorrhage) • Grey-Turner's sign (brownish colouration of the flanks, generally between the last rib and the top of the hip, as a result of retroperitoneal haemorrhage) • Fox's sign (discolouration below the inguinal ligament or at the base of the penis) • Panniculitis, reddish skin nodules and Erythematosis (subcutaneous fat necrosis) 8. Systemic signs: • Arthritis and Sierositis resulting from the release of cytokines (a phenomenon which is not well defined from a rheumatological standpoint) • Purtscher Retinopathy (rare vasculopathy leading to sudden blindness due to retinal artery occlusion).

Table 1.
Symptoms and signs of acute pancreatitis.

Abdominal pain: 95–100%
Epigastric tenderness: 95–100%
Nausea and vomiting: 70–90%
Low-grade fever: 70–85%
Hypotension: 20–40%
Jaundice: 30%
Grey Turner/Cullen sign: <5%

Table 2.
Frequency of signs and symptoms in acute pancreatitis.

ORGAN SYSTEM	score				
	0	1	2	3	4
respiratory (PaO2/FIO2)	>400	301–400	201–300	101–200	<=101
renal (serum creatinine, mg/dL)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
cardiovascular (systolic blood pressure, mmHg)	>90	<90	<90	<90	<90

Note: score ≥ 2 over a period of more than 48 hours, for any one of the three organ systems: persistent organ failure; score ≥ 2 over a period of less than 48 hours: transient organ failure.

Table 3.
Modified Marshall system to evaluate organ failure.

The main aetiopathological mechanisms involved in Acute Pancreatitis are summarised in **Figure 1** [14]. Their main cause is the obstruction, due to the presence of gallstones, of the biliary tract or pancreatic duct (40–70% of cases). The second

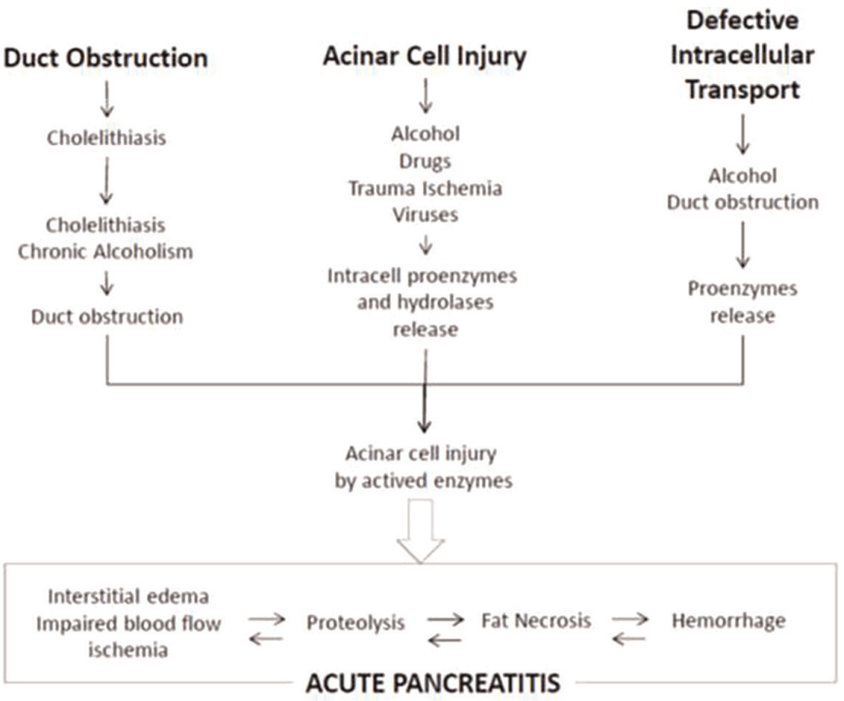

Figure 1.
Main mechanisms involved in acute pancreatitis.

• Gallstones
• Alchol (Ethanol)
• Trauma
• Cancer
• Endoscopic Retrograde Cholangiopancreatography (ERCP)
• Surgical (Post-operative)
• Mumps, Coxsackie or Idiopathic infections
• Autoimmune (Polyarteritis Nodosa)
• Genetic (Serine Protease Inhibitor Kajal Type 1), PRSS1 mutation (cationic trypsinogen)
• Hypertriglyceridemia, Hypercalcemia
• Hypothermia
• Drugs (Corticosteroids, Thiazides, Valproate, Azathioprine, Oestrogen, Sulfonamides, Tetracycline, 6-Mercaptopurine, anti-HIV medications)

Table 4.
Main causes of acute pancreatitis.

most frequent cause is alcohol consumption (25–35% of cases). Other less common causes are hyper-triglyceridemia (>1.000 mg/dL) and the presence of benign or malign Pancreatic tumours (**Table 4**). The immune system appears to play an important role in the progression of Acute Pancreatitis, since the release of pro-inflammatory mediators during the self-digestion phase might result in Necrotizing Pancreatitis. In this context, the small intestine barrier may become permeable to the transit of bacteria (bacterial translocation) from the enteric lumen to the lymphatic and blood systems, allowing Multiple Organ Dysfunction Syndrome to occur (**Figure 2**) [15, 16].

1.2 General aspects of pancreatitis treatment

Acute Pancreatitis can be classified according to clinical severity (**Table 5**) [2]. While in cases of Mild or Moderate Acute Pancreatitis organ failure and/or pancreatic necrosis hardly occur, in Medium-Severe cases there may be pancreas tissue necrosis without persistent organ failure; in severe cases, the disease progression can have an initial phase with local inflammation of the pancreas associated with a systemic inflammatory response related to the syndrome/organ failure, and a later phase with local complications and/or persistent organ damage. It is estimated that about 15–20% of the patients present a Severe Pancreatitis profile with organ failure (>8 hours). Another 20% present a Necrotizing Pancreatitis profile defined as focal areas of non-viable pancreatic parenchyma (>3 cm in size or > 30% of the pancreas) [18].

Being this distinction among Mild, Medium and Severe Pancreatitis obviously reductive and not always immediate, Acute Pancreatitis is diagnosed, in presence of abdominal pain in patients with a medical history and/or familiarity for the disease, by monitoring pancreatic health (serum amylase or lipase at least three times higher than the highest value within the normal range). Abdominal Imaging (CT or MRI) is generally crucial for the diagnosis (**Table 6**) [19, 20].

The treatment is aimed at reducing the systemic inflammatory response so as to prevent, where possible, organ failure and systemic complications. There being no

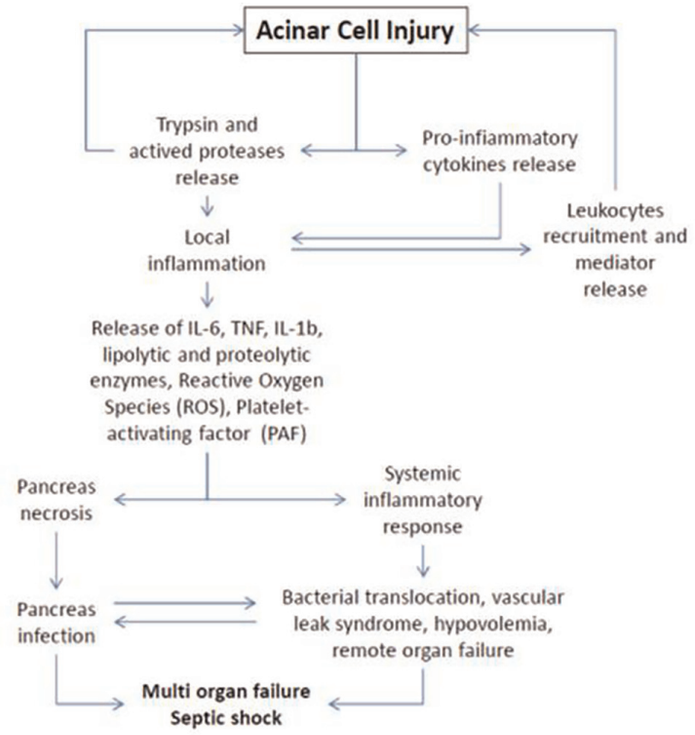

Figure 2.
Multi-organic mechanisms involved in acute pancreatitis.

Grade of Severity of Acute Pancreatitis	Criteria of Classification
Mild	No organ failure No local or systemic complications
Medium-Severe	Transient organ failure (that resolves within 48 hours) Local or systemic complications without persistent organ failure
Severe	Persistent organ failure (>48 hours) Local or systemic complications

Table 5.
Grading severity of acute pancreatitis according to Atlanta criteria 2012 [17].

• Transabdominal ultrasound should be performed in all patients with suspected Acute Pancreatitis;
• Hyper-triglyceridemia (>1.000 mg/dl), once ascertained, should be considered a major cause of the disease in the absence of gallstones and/or history of alcohol consumption/abuse;
• A neoplastic origin should always be considered in patients aged over 40 years;
• Patients with Idiopathic Pancreatitis should be re-evaluated over time and possibly sent to specialised centres;
• Genetic testing should be considered in young patients (<30 years) if there is no obvious cause or, conversely, if there is familiarity for pancreatic diseases.

Table 6.
Diagnostic aspects in patients with pancreatitis.

specific pharmacological treatment to this date, hydro-electrolyte re-balancing, use of analgesics, antibiotics and management of metabolic complications (hyperglycemia and hypocalcemia) are at the core of today's treatment.

Overall, Mild Acute Pancreatitis should be treated with fluids, analgesics and antibiotics for a few days only in presence of infectious complications (never for prophylactic purposes), whereas Severe Acute Pancreatitis requires an accurate inspection, since patients must undergo surgical removal of gallstones, re-activation of the bilious-pancreatic ducts and, in rare cases, elimination of the necrotic tissue through partial or total removal of the the pancreas and/or attached organs [21].

1.3 Evaluation of the nutritional status

Maximum catabolism with negative nitrogen balance is not uncommon, especially in the most severe cases of Acute Pancreatitis [22, 23]. The resulting high increase in calorie (Resting Energy Expenditure) and protein need might rapidly lead, if not promptly managed, to malnutrition (**Figure 3**) [24]. Malnutrition, being associated with severe weight loss, lean body mass loss and decreased functional capacity due to sarcopenia, is likely to affect quality of life and clinical outcomes [25]. Possibly asthenia and/or loss of appetite, leading to reduced calorie-protein intake, contribute to weight loss, hence to malabsorption and maldigestion. In case of sudden weight loss (10% of habitual weight in about 3–6 months), malnutrition might pair with the main disease, leading to acute or chronic complications which may worsen the patient's prognosis (**Table 7**).

Therefore, the aetiology of malnutrition is heterogeneous and may depend on the severity of the disease, the patient's ability to eat food and the catabolic state. Old age and immobilisation may contribute to raise the risk of malnutrition (**Figure 4**) [26]. Full-blown malnutrition becomes a disease which adds up to the underlying disease. Patients with Acute Pancreatitis should be considered at high risk of malnutrition.

To confirm this, literature shows that about 30% of patients with Acute Pancreatitis are malnourished and that they do not receive adequate nutritional support, which makes accurate Nutritional Screenings such as the Nutritional Risk Screening 2002 (NRS-2002) necessary in order to objectively evaluate the risk of hypo/malnutrition. **Table 8** shows some of the most employed Screening Tools.

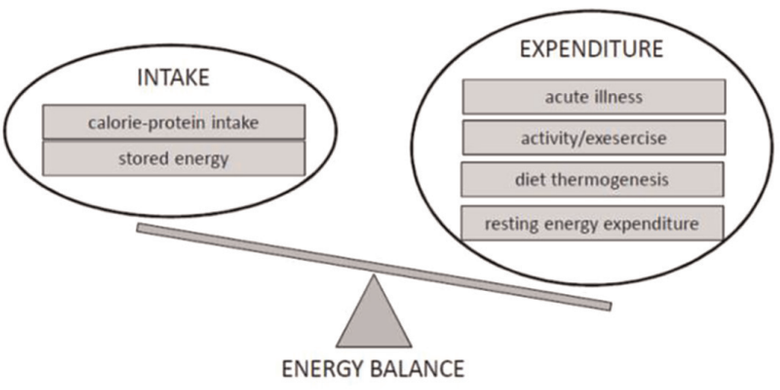

Figure 3.
Relationship between energy intake and expenditure (see text).

Short-term consequences	Long-term consequences
• Weight reduction with muscle and fat loss	• Decreased long-term survival
• Biochemical disorders (anaemia and hypoalbuminaemia)	• Risk of secondary tumours
• Late bone marrow recovery	• Higher mortality
• Changes in body composition	• Alteration of bone density and/or osteoporosis
• Immunodepression and slow wound healing	• Decreased life quality and productivity
• Increased susceptibility to infections	• Higher levels of psychological discomfort
• Longer hospitalisation stay and higher re-hospitalisation frequency	
• Increased healthcare costs	
• Decreased tolerance to chemotherapy	
• Adverse response to chemo-radio therapy	
• Delayed chemo-radio therapy	

Table 7.
Consequences of malnutrition.

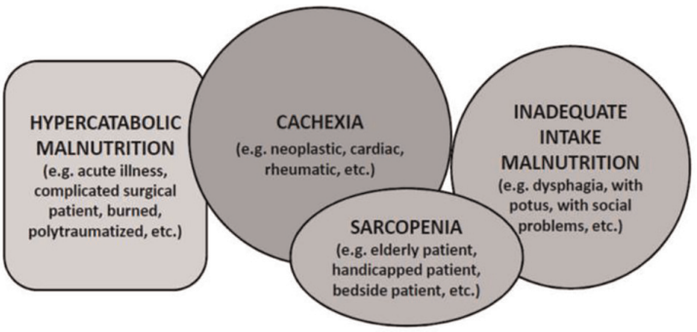

Figure 4.
A schematic overview of the different types of malnutrition.

Screening	• Malnutrition Screening Tool (MST). • Malnutrition Universal Screening Tool (MUST). • Nutritional Risk Index (NRI). • Nutrition Risk in Critically Ill (NUTRIC) score.
Diagnostic Assessment	• Subjective Global Assessment (SGA). • Patient Generated Subjective Global Assessment (PS-SGA). • Mini Nutritional Assessment (MNA). • AND (Academy of Nutrition and Dietetics)-ASPEN (American Society for Parenteral and Enteral Nutrition) Malnutrition Consensus Criteria (MCC). • Global Leadership Initiative on Malnutrition (GLIM).

Table 8.
Malnutrition screening and diagnostic assessment tools (used in the USA, Australia, New Zealand, Canada and Europe).

The employment of a Screening Tool permits to immediately evaluate the nutritional status and to monitor the progression of the disease. Unfortunately, these tools are scarcely used and patients' nutritional treatment is not adequate.

1.4 Nutritional treatment of acute pancreatitis

Acute Pancreatitis is traditionally treated with the suspension of food intake via mouth in order to rest the pancreas. This indication is suggested until pain is resolved or until the normalisation of the flogoses indices and/or until the pancreatic enzymes fall within acceptable normal values. However, the nutritional treatment should be planned and monitored over time, and it should include: (1) accurate evaluation of the severity of the disease; (2) proper assessment of the nutritional state; (3) correct identification of the patients with special nutritional needs. As shown in the previous paragraphs, Acute Pancreatitis may present itself very differently in clinic, thus requiring differentiated nutritional approaches.

1.4.1 Energy and protein need in acute pancreatitis

The Resting Energy Expenditure (REE) in patients with Acute Pancreatitis depends on the severity of the disease. In the most severe cases it is highly increased, thus entailing a high mortality risk linked to increased catabolism. In patients with septic complications the REE may be increased by decreased splanchnic blood flow, acidosis and bacterial translocation, as a result of which the REE assessed via indirect calorimetry (REEm) may exceed up to 110–150% of the energy expenditure theoretically calculated using Harris-Benedict (REEc) formulas. A realistic evaluation at the patient's bed should assess the energy expenditure by means of REEc multiplied by a constant of 1,3 or 1,5, depending on the clinical severity. As a result of this huge energy consumption, skeletal muscle proteolysis might increase up to 80% with nitrogen losses of 20–40 g per day, hence requiring the energy and the protein need to be estimated around, respectively, 25 kcal/kg/die and 1,2–1,5 g/kg/die [24, 27, 28].

1.4.2 Oral vs. artificial nutrition in moderate acute pancreatitis

Oral feeding is recommended when abdominal pain, nausea and vomiting have disappeared and, according to some authors, food intake may also take place regardless of serum lipase concentrations [29]. In this context the ideal diet includes a gradual intake of solid food and calories. Traditional diets with clear liquids and low fats (< 30% of total energy intake) have proved completely ineffective if not worsening in terms of malnutrition [30]. Early oral feeding (within 24–48 hours) should be administered also to patients undergoing minimally invasive necrosectomy, as long as haemodynamically stable, in the absence of septic complications and with normal gastro-enteric function. The use of Oral Nutritional Supplements (ONS) aimed at increasing the caloric-protein content is also recommended for these patients [31].

Being a negative prognostic factor of the disease, hyperlipaemia should be treated early with low-fat diets or, in the most severe cases, with hypolipidaemic drugs including insulin, heparin and plasmapheresis if necessary (**Figure 5**). Careful management of hyperglyceridemia appears to reduce the risk of acute pancreatitis recurrence.

Oral Nutrition has not proved less effective than Enteral Nutrition (EN) in preventing infection or death in these patients. Instead, **Table 9** shows a list of the cases in which EN after placement of nose-gastric probe is recommended.

Despite there being few data comparing it to Oral Nutrition, EN is very likely to improve these patients' prognosis, as we will see later. It should therefore be suggested early even when the development of Pancreatitis is initially uncertain (**Table 10**) [32].

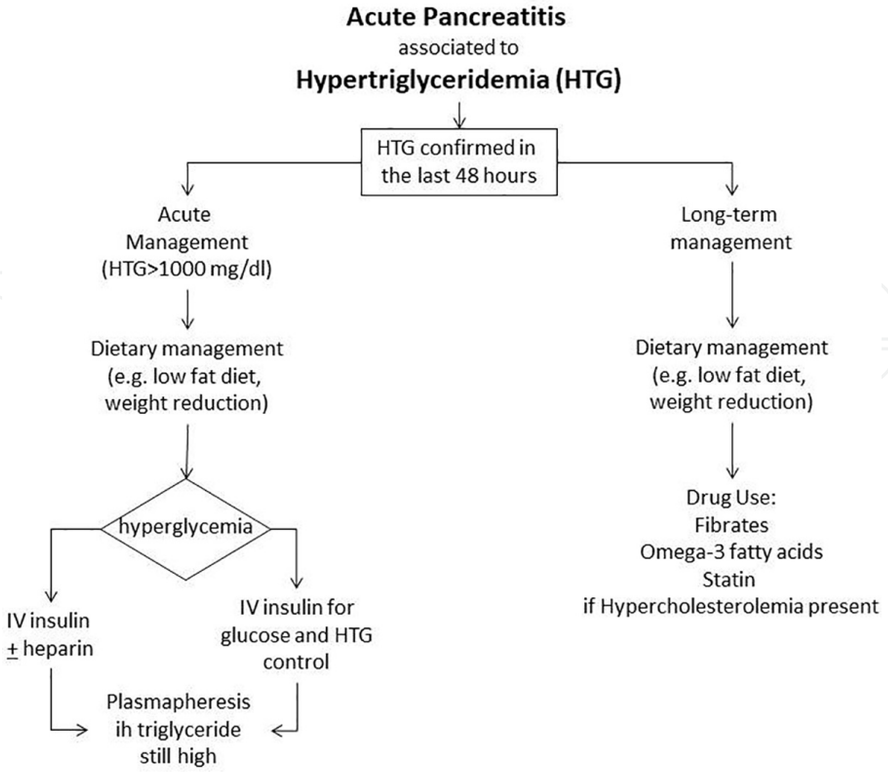

Figure 5.
Overview of management of hypertriglyceridemia.

• if Oral Nutrition is is not feasible within 24–72 hours;
• if caloric intake (also by support of Oral Supplements) does not cover at least 75% of the caloric-protein need, calculated on current weight;
• if a patient reports a rapid weight loss in the last few months (10% in the last 3–6 months);
• if Nutritional Screening strongly suggests malnutrition risk (e.g. alcohol-addicts or elderly)
• if BMI upon admission is <19 kg/m2, regardless of the clinical presentation;
• if mild painful symptoms, with nausea or vomiting, persist for a few days.

Table 9.
Indications for the use of EN during acute pancreatitis.

Nutrition Route	Pros	Cons
Oral	• No procedures or devices required • Nutrition regimen/caloric intake more easily adjustable • Easier transition to home regimen	• Increased risk of worsening Pancreatitis • Increased risk of morbidity/mortality • Wider range of variation in caloric intake day to day • Difficult to ensure adequate intake at home
Nasogastric (NG)	• Easy bedside access • No need for enteral pump • Permits higher feeding rates and bolus feeds	• Possible increased risk of pancreatic stimulation and worsening Pancreatitis • Nasal necrosis or sinusitis • Not suitable in patients with gastric outlet obstruction and/or need for gastric venting

Nutrition Route	Pros	Cons
Nasojejunal (NJ)	• Potentially reduced risk of aspiration • Permits enteral access beyond points of duodenal compression from inflamed pancreas • Possibly reduced risk of pancreatic stimulation	• Post pyloric placement may be difficult • Requires pump for feeding • Bolus feeding not possible • Increased risk of tube clogging/ dislodgement • Nasal necrosis or sinusitis • May migrate back into stomach
Percutaneous Gastrostomy with Jejunal Extension (PEG-J)	• Durable enteral access • No risk of nasopharyngeal injury • Permits gastric venting in outlet obstruction • May be placed endoscopically, radiologically, surgically	• Risk associated with tube placement (bleeding, infection, perforation) • Peristomal tube leak, bleeding, infection • Relatively contra-indicated in patients with ascites, bleeding diatheses or poor window for PEG placement • J-arm may migrate back into stomach
Parenteral Nutrition (PN)	• Direct Nutrition that bypasses need for luminal absorption • Can be used for patients with bowel obstruction or perforation • Can be used for patients with intractable nausea and vomiting	• Requires peripheral/central venous access • Increased risk for line related infections and DVT vein thrombosis • Increased risk of mucosal barrier dysfunction with resultant bacterial translocation/infection • Increased morbidity/mortality compared with EN • Increase risk of hyperglycaemia

Table 10.
Pros and cons on nutrition route in severe acute pancreatitis.

1.4.3 Artificial nutrition in severe acute pancreatitis

Being the risk of malnutrition in Severe Acute Pancreatitis particularly worrying, Parenteral Nutrition (PN) has been widely considered a first choice therapy in the past, aimed at providing such a caloric-protein intake able to maintain lean mass without stimulating the pancreas [33, 34]. However, more recent data show that PN is associated with higher risk of infections (especially from the venous catheter), besides triggering electrolyte imbalance, leading to – or aggravating – Pancreatitis-induced hyperglycaemia and increasing the risk of multi-organ dysfunction. Since PN administration does not involve enteric transit, the intestinal mucosa is at risk of atrophy, with consequent reduction of its barrier function, especially in the small intestine, thus leading to bacterial translocation [35]. All these phenomena may worsen the clinical picture.

Given these considerations, EN through nose-gastric probe should be carried out early (within 24–72 hours) in haemodynamically stable patients who do not tolerate Oral Nutrition, so as to protect the intestinal mucosa, prevent the proliferation of bacteria and stimulate bowel motility (**Figure 6**) [36, 37]. Many studies and meta-analyses show that EN significantly decreases the rate of infection (with lower levels of cytotoxic CD4 T lymphocytes and C-reactive protein), the risk of multi-organ failure, the necessity for operation and the mortality, compared to PN. Gastric EN does not lead to higher incidence of complications (such as diarrhoea, abdominal distension or increased pain), although the indication to use anti-secretory agents (somatostatin, octreotide) so as to reduce the nutrients-induced secretory action of the pancreas remains questioned.

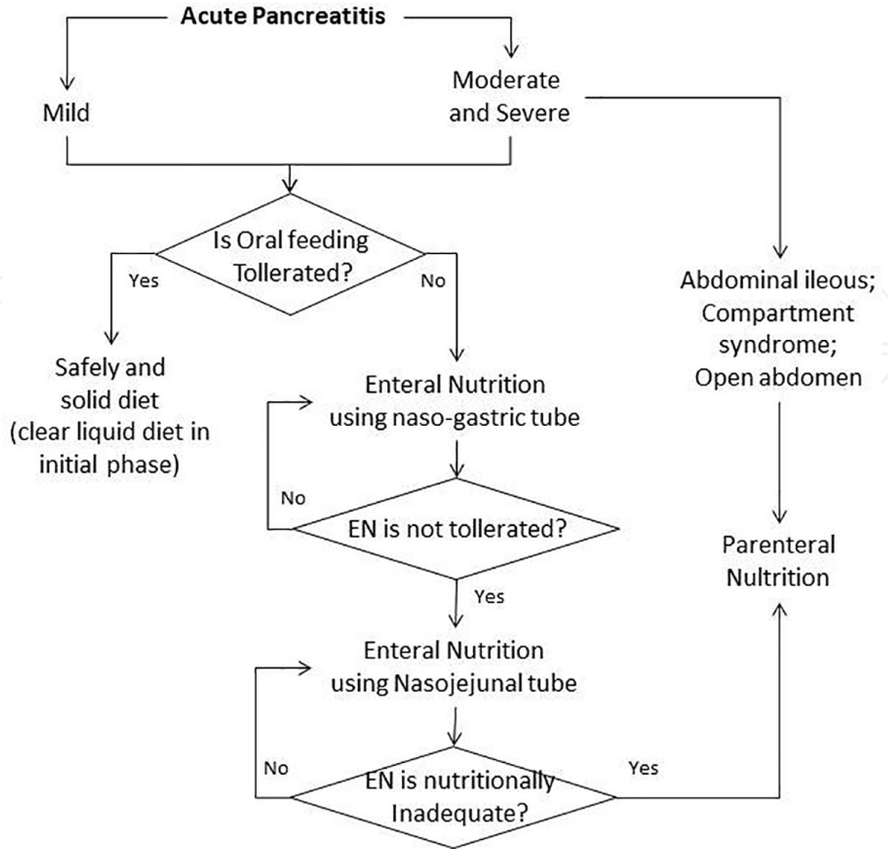

Figure 6.
Route of nutrition treatment in acute pancreatitis.

In cases where the enteric function appears uncertain, it is recommendable not to infuse nutrients, but only a 5% low-speed glucosate solution (10–20 ml/hour for 24 hours) through the standard gastric-nose probe. The evaluation of the gastric stagnation or the distension of the loops, in addition to the use of instrumental techniques, will permit to assess the state of the enteric transit. The use of a nasojejunal probe (NJ) is recommended in patients with gastroparesis, gastric obstruction due to oedema or pancreatic pseudocyst. Since the tip of this probe, which is indicated also in case of significant regurgitation, ideally overcomes the Treitz ligament, its insertion may prove difficult, often requiring repeated positioning by endoscopy and resulting in frequent spontaneous displacement. In Severe Necrotizing Pancreatitis or in Nasopharyngeal Disorder precluding NJ placement, some scholars suggest the placement of a percutaneous gastrostomy tube with jejunal extension (PEG-J) in case of EN lasting over 4–6 weeks. These invasive techniques should be used only with complicated patients in whom the prognosis appears to be severely impaired. Finally, jejunostomy should be performed in patients undergoing surgery (**Table 11**) [38].

A possible side effect of EN is the increased Intra-Abdominal Pressure (IAP), due to which the use of boluses is never recommended, especially in case the patient is feverish or reports nausea or vomiting. On the contrary, a low flow of nutrients (20 ml/hour to be increased very slowly depending on the patient's tolerance) can guarantee, especially in the early stages, a progressive normalisation of the intestinal function.

In the most severe cases, measurement of Pulmonary Pressure is recommended. When it reaches or exceeds 15 mmhg, EN should be administered with caution. In

Management of severe Pancreatitis	Nutritional Recommendations
Enteral vs. Parenteral Nutrition	Enteral preferred
Timing of feeding	Enteral feeding within 48 hours
Gastric vs. jejunual route	No difference
Oral food composition	No difference were observed using normal fat, low-fat, soft diet with liquid or solid
Enteral formula	No benefit of semi-elemental or elemental formula vs. polymeric formula
Enteral infusion	Continuous low-flow feeding (no bolus)
Probiotics use	Not recommended

Table 11.
Overall nutritional recommendations for severe acute pancreatitis.

patients with pressures above 15 mmhg, in which a picture of abdominal hypertension is possible (e.g. no peristalsis, abdominal distension, elevated gastric stagnation, etc.), the development of a picture of Abdominal Compartment Syndrome (ACS) should never be excluded [39]. In this context, the use of a nasojejunal tube for EN should be preferred, although the transition to NP should always be considered. In case of IAP with pressure higher than 20 mmhg, the use of EN should be interrupted for precautionary purposes. Clinical data are reported where early EN was possible in about 30% of cases with excellent clinical results (e.g. open abdomen with rapid fascial closure, low rates of fistulation, reduction of nosocomial infections and lower hospital costs), as long as the medical staff is highly skilled in managing minimal complications and able to monitor and manage the metabolic aspects of the disease. In summary, when nutritional objectives are not attainable with EN alone, a partial or total PN should be ensured especially in hyper-catabolic patients, patients with negative nitrogen balance, patients whose gastro-enteric tract is not usable, or for whom a surgical decompression (open abdomen) is required. In these cases the additional use of glutamine (0.20 g/kg/day) appears to increase albuminaemia, decrease C-reactive protein, reduce the frequency of infections and the risk of death [40].

The use of NP should also be recommended in patients with chylous ascites not responding to a fat-free diet nor to an elemental EN diet.

1.4.4 Enteral nutrition formulations

In patients with AP, a standard polymeric diet shall be used, although some studies express concern about the possibility for these nutritional formulations to induce insufficiency of exocrine pancreas (manifesting with alteration of faecal elastase and faecal fat) especially in cases of Alcoholic or Necrotizing Pancreatitis. However, polymeric diets should always be the first choice [41]. Feeding with semi-elemental diet should be performed only if persistent steatorrhea appears and absence of clostridium-difficile infection can be proved. In case of steatorrhea the use of pancreatic enzymes should be considered. The use of semi-elemental or elemental products is appropriate in cases where, despite the severity of the clinical picture (e.g. necrotizing pancreatitis), total or partial EN is possible [42]. The enteral formulations should be chosen according to the doses of faecal elastase. Despite there being several different techniques, EN in patients with Acute Pancreatitis is mostly performed with nasogastric probe.

2. Chronic pancreatitis

2.1 Causes and symptoms of chronic pancreatitis

Chronic Pancreatitis is a fibroinflammatory syndrome of the pancreatic gland histologically characterised by irreversible morphological changes. The evolution towards a picture of Chronic Pancreatitis usually occurs due to recurring episodes of Acute Pancreatitis with permanent organ damage [43, 44]. The use of alcohol and tobacco, as well as the chronic presence of hypercalcaemia and the use of certain drugs, may contribute to the progression of the disease (**Table 12**) [46–49]. Recent studies show the persistence of a chronic inflammation process also in Chronic Pancreatitis (with the involvement of: interleukins 4, 6, 8, 10, 12; tumour necrosis factor

Class	Examples
Toxin-metabolic	Alcohol
	Tobacco smoking
	Hypercalcemia
	Hyperlipidemia
	Chronic renal failure
	Medications
	Toxins
Idiopathic	Early onset (slower development of calcification and exocrine and endocrine insufficiency)
	Late onset (faster development of calcification and exocrine and endocrine insufficiency)
	Tropical calcific pancreatitis
Anatomical obstruction	Pancreatic divisum
	Post irradiation
Autoimmune	Autoimmune pancreatitis
Recurrent and severe acute pancreatitis	Recurrent acute pancreatitis
Genetic pancreatitis	PRSS1 mutation
	PRSS2 mutation
	CFTR mutation
	SPINK 1 mutation
	CTRC mutation
	Cationic trypsinogen mutation
	α-1 antitrypsin deficiency

CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; PRSS1, serine protease 1; PRSS2, serine protease 2; SPINK 1, serine peptidase inhibitor, Kazal type 1; TIGAR-O, Toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, obstructive.

Table 12.
Causes of chronic pancreatitis by TIGAR-O classification (LIST 1 - version 2001) [45]).

[TNF-alfa]; transforming growth factor [TGF-beta]; interferon [IFN-gamma]; macrophage activity; etc.) able to increase the REE [50–52].

The prevailing symptom in over 80% of patients is epigastric pain radiating towards the column or the left upper quadrant of the abdomen [53, 54]. The pain is often postprandial and is accompanied by nausea, vomiting, diarrhoea with or without oily appearance, malodorous faeces and weight loss. However, symptoms may vary and pain might be absent in case the degenerative process affects the nerve endings. On the contrary, persisting pain might manifest in presence of the worst complications of chronic pancreatitis such as fibrosis, diabetes or tumours. A major symptom of this disease is postprandial pain, which induces a progressive reduction of the caloric-protein intake, thus leading to malnutrition, and in severe cases must be treated with opiates. Weight loss could therefore be the combined result of a progressive reduction in food intake and the increase in energy expenditure induced by chronic inflammation. Less frequent causes of chronic pancreatitis are those associated with auto-immune pathologies such as coeliac disease or inflammatory bowel diseases where, however, pain may be absent or masked by intestinal inflammation. In these patients, genetic predisposition to Pancreatitis may be proved, for example, by the presence of variants of the CFTR gene responsible for cystic fibrosis, the Serine Peptidase Inhibitor Kazal Type 1 gene (SPINK1), the Serine Protease 1 gene (PRSS1) and other genes still under study [55].

Another relevant clinical aspect is the delayed gastric emptying, perceived by a high percentage of patients. The causes of this symptom are not clear, especially in patients not undergoing surgery or not taking opioids. In patients undergoing surgery this symptom is believed to be secondary to the resection of the vagus nerve or part of the duodenum [56].

2.2 Treatment overview

The treatment of Chronic Pancreatitis is based on pain control and management of complications. In Chronic Pancreatitis, as well as in Acute Pancreatitis, it is useful to divide the clinical picture into at least three stages: a) clinical picture without complications, caused by recurring episodes of Acute Pancreatitis; b) presence of pain and local complications (pancreatic pseudocysts, calcifications and minimal involvement of adjacent organs); c) end-stage with insufficiency of exocrine and/or endocrine function (**Table 13**).

Typically, these patients will need to implement the enzyme replacement therapy and be gastro-protected with proton pump inhibitors to reduce the denaturation of

AETIOLOGY	MECHANISM
Chronic Pancreatitis, cystic fibrosis, diabetes	Altered lipase production or destruction
Pancreatic cancer	Pancreatic duct obstruction
Coeliac disease, Crohn's disease, Shwachman–Diamond syndrome	Decreased endogenous lipase stimulation and production
Gastrectomy, gastric by-pass, extensive small bowel resection	Motility disorders (interaction with chyme, decrease stimulation of pancreatic enzymes)

Table 13.
Causes of pancreatic dysfunction.

pancreatic lipase by stomach acid. The nutritional intervention, which is accompanied by hydro-electrolyte rebalancing, has proved effective not only in the prevention and treatment of malnutrition, but also in reducing the systemic inflammatory process, with reduced complications and improved prognosis of the disease.

2.3 Treatment of the endocrine insufficiency

Over 50% of patients with Chronic Pancreatitis develop Diabetes Mellitus due to mass loss of beta-cells, although Endocrine Insufficiency, which manifests in Chronic Pancreatitis, may have a double aetiology: on the one hand it is secondary to a reduced production of insulin, on the other it could depend on insulin resistance (Pancreatogenic Diabetes, or type 3 Diabetes) [57]. The diagnosis of Diabetes is obviously carried out with the same techniques used in the other types of Diabetes (fasting blood sugar dosage, load curve, C-peptide, dosage of glycosylated haemoglobin). However, the differential diagnosis is carried out by assessing the severity of the pancreatic picture and the the absence of antibodies associated with type 1 diabetes, as well as by detecting pancreatic disease via Imaging. The evaluation of the beta cell reserve function, attained by dosing a fasting C-peptide, is crucial in choosing the best drug. The treatment of patients with Pancreatogenic Diabetes could be more complex than those with type 2 Diabetes due to the concomitant presence of malabsorption, impaired secretion of counter-regulatory hormones and potential lack of compliance in the case of alchol-induced Pancreatopathy. Furthermore, the use of many antidiabetic agents is often contraindicated. There are not randomised clinical trials on hypoglycaemic treatment for diabetes associated with pancreatic disease. In case of preserved beta cell function, metformin is the first choice treatment. Side effects as nausea, weight loss, diarrhoea or the increased risk of lactic acidosis should be carefully assessed and metformin stopped if present. The use of DPP4-inhibitors or GLP1-receptor agonists is not recommended due to the reportedly increased risk of worsening the pancreatic disease.

The use of sulfonylureas as a front-line therapy is not recommended due to both the increased risk of hypoglycaemia and the dependence of intact islet cell function. Also the use of thiazolidinediones is discouraged because of their side effects (weight gain, fluid retention) and their role in increasing the risk of osteoporosis, especially in patients with calcium malabsorption. Given the progressive impairment of insulin secretion, insulin therapy with rapid and basal analogues is frequently required. Insulin therapy should be initiated without delay in case of: symptomatic hyperglycaemia (>180 mg/dl), catabolic state secondary to uncontrolled diabetes, history of diabetic keto-acidosis, hospitalisation for uncontrolled diabetes. Special attention must be paid to the management of hypoglycaemia and the gradual adjustment of insulin dose, as these patients are more likely to be insulin sensitive and to present a loss of counter regulatory hormones. Other important factors are hepatic glycogen storage deficit, carbohydrate malabsorption and malnutrition, inconsistent eating patterns due to pain or nausea, and possibly underlying alcoholic liver disease and enhanced peripheral insulin sensitivity. Diabetic education or glucose self-monitoring and glucagon utilisation should be provided to all patients. A valid alternative to capillary glycaemic control is the use of continuous or flash glucose monitoring. There are currently no studies available comparing glycaemic control in patients with pancreatic disease using self glucose blood monitoring and flash/continuous glucose monitoring. Lifestyle modifications, such as stopping smoking and drinking alcohol, are essential to reduce the risk of recurrence, since alcohol and tobacco smoking contribute to keeping the inflammatory process high, thus favouring the risk of pancreatic cancer and diabetes [58].

2.4 Nutritional assessment in chronic pancreatitis

A reduced exocrine function, especially if under-diagnosed, may on its own induce a state of hypo- or malnutrition, possibly secondary to a malabsorption of macro and micro-nutrients [59]. It is estimated that a picture of pancreatic dysfunction develops in about ten years in patients with potus and in about 20 years in those with idiopathic aetiology and that it is extremely frequent in people with autoimmune diseases. Enteric symptoms (malabsorption, bloating, diarrhoea, steatorrhea, weight loss, abdominal discomfort) are usually present when enzymatic secretion is 10% lower than normal. Since this situation is mainly linked to inadequate lipid digestion, it may result in a malabsorption of fat-soluble vitamins (vit. A: 1–16% of cases; vit. D: 33–87%; vit. E: 2–27%; vit. K: 13–63%), with loss of micro-nutrients and reduction of circulating lipoproteins (**Table 14**) [60]. In Severe Chronic Pancreatitis, the use of parenteral fat-soluble vitamins is absolutely indicated. Much less frequent is the lack of hydro-soluble vitamins with the exception of thiamine (vit. B1), which is often deficient in alcoholics. A shortage of zinc, copper and selenium has also been observed in patients who do not consume alcohol, so the use of specific supplements is recommended by a number of scholars.

The state of chronic inflammation, also variably present in Chronic Pancreatitis, can interfere with the protein synthesis and catabolism by the body. Insufficient levels of pancreatic protease may lead to protein malnutrition and be a cause of vitamin B12 deficiency. The absorption of vitamin D, calcium and folic acid, whose deficiency causes significant changes in the clinical picture, requires a separate discussion. In fact, a picture of osteopathy (osteoporosis, osteomalacia, osteopenia) is present in about a quarter of patients with Chronic Pancreatitis. Vitamin D deficiency, which is often underestimated, may present itself with not clearly defined bone pain and may trigger other diseases (**Table 15**) [61]. However, hyper-secretion of the parathyroid hormone (PTH) may be one of the first signs of vitamin D deficiency. Densitometric studies (dual-energy x-ray absorptiometry) should always be implemented to prevent or monitor any skeletal damage. Exocrine pancreas dysfunction requires a change in lifestyle (e.g. no smoking, no alcohol) and the intake of pancreatic enzymes during meals in order to reduce the effects of malabsorption-induced malnutrition. A supplementation of protein or macro-nutrients should be recommended particularly to patients who reduce their food intake or undertake unbalanced low-calorie and low-protein diets because of pain or fear of pain. Early enzymatic and vitamin supplementation should be associated with careful clinical evaluation over time.

VITAMIN	SOURCES	MAIN FUNCTIONS	DEFICIENCY
A (retinol)	fish liver oil, milk, cheese, eggs, carrots, apricots, broad-leaved vegetables	Precursor of rhodopsin, protective antitumoural action	Visual impairment, increased cancer incidence
D (cholecalciferol)	fish liver oil, eggs, milk, oily fish	Regulation of the metabolism of calcium	Rickets in children, osteomalacia in adults
E (tocopherol)	broad-leaved vegetables, oily seeds and fruits, liver, eggs, dairy products	Lipid protection from oxidation (antioxidant effect), anticancer, anti-sclerotic, additive	Accumulation of lipid peroxides, anaemia, chronic-degenerative diseases
K	Intestinal flora, vegetables	Prothrombin activation, calcium metabolism	Haemorrhages

Table 14.
Dietary sources and functions of fat-soluble vitamins.

APPARATE	DISEASE
Neuropsychiatric diseases	Schizophrenia Major depressive disorders Neurodegenerative disorders
Infections	Respiratory infections Covid-19 Sepsis Tuberculosis
Vascular diseases	Hypertension Cardiovascular diseases
Muscular diseases	Muscle pain Proximal muscle weakness
Bone diseases	Osteoporosis Osteomalacia Osteopenia Osteoarthritis
Skin diseases	Epidermolytic ichthyosis Autosomal recessive congenital ichthyosis
Allergic diseases	Asthma Wheezing diseases Urticaria Atopic dermatitis
Autoimmune diseases	Type 1 diabetes Rheumatoid arthritis Inflammatory bowel diseases Multiple sclerosis Psoriasis Vitiligo
Cancer	Breast Colon Prostate

Table 15.
Diseases secondary to vitamin D deficiency.

Figure 7 summarises the essential components of an adequate nutritional assessment [62]. If malnutrition develops, the symptoms described in **Table 5**, often blurred, or simply vitamin deficiency signs may be present. Although sarcopenia has been poorly studied in patients with Chronic Pancreatitis, it may, as in neoplastic patients, increase the risk of complications and hospitalisation. An accurate nutritional assessment is therefore always appropriate in patients with Chronic Pancreatitis.

2.5 Nutritional requirements in chronic pancreatitis

2.5.1 Oral nutrition

Low-fat oral diets are widely used in clinical practice especially for the purpose of reducing postprandial abdominal pain. However, these diets, in addition to being poorly accepted by patients, can induce a state of malnutrition [63]. In fact, it is estimated that a patient with Chronic Pancreatitis has a REE 30–50% higher than healthy patients. As an indication, diets with high energy (35 kcal/kg/24 hours), high

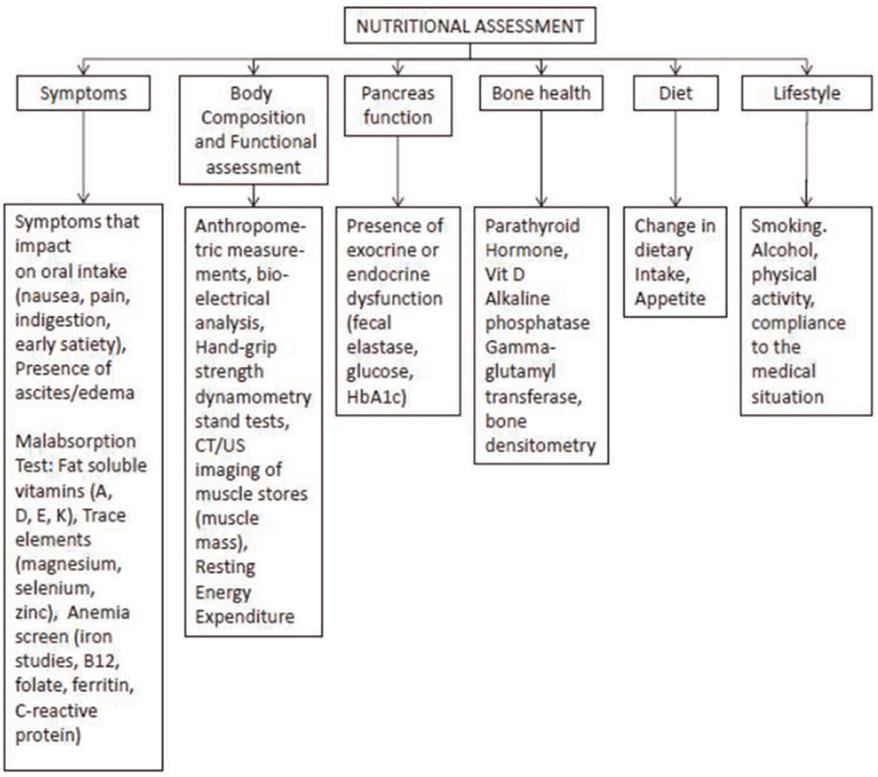

Figure 7.
Nutritional assessment in chronic pancreatitis.

protein (1.0 to 1.5 g/kg/24 hours), rich in carbohydrates, and with moderate amounts of fat (0.7 to 1.0 g/kg/24 hours) should be recommended. Low-fat diets are discouraged by a number of scholars, since they may reduce steatorrhea, thus masking the onset of fat malabsorption, induce a weight loss due to insufficient caloric intake and cause deficiencies in fat-soluble vitamins. Fats should be limited if it is not possible to control steatorrhea (generally associated with flatulence, bloating, dyspepsia, urgency to pass stools, cramping, abdominal pain) with proper oral Pancreatic Enzyme Replacement Therapy (PERT). Typically, 500 units/lipase/kg are recommended for each meal and adapted to the symptoms or the type of diet recommended for the patient. The dose can be doubled or even tripled but should never exceed 10,000 units/kg/day or 4000 units/g of fat per day [64].

In some circumstances (i.e: mixture of enzymes with meal; gastric emptying with meal; rapid release of enzymes in duodenum by chyme and bile acids) enzymatic supplementation appears scarcely effective, so it is necessary to accurately educate patients to use these products according to the quality of food intake, to its rate of intake, to its distribution and time of consumption. Benefits have also been observed by combining these therapies with antagonist H2 drugs or Proton pump inhibitor to prevent enzymatic degradation [65, 66]. To counteract the patient's weight loss, a supplementation of medium-chain triglycerides (MCT) that are absorbed in the absence of lipases, co-lipases, and bile salts is also suggested in combination with increased caloric intake. However, their use is limited by their poor palatability and the possibility of prescribing them up to a maximum of 50 g/day. Higher dosages may induce ketogenesis and intestinal disorders (cramps, nausea, diarrhoea). MCTs are found in coconut oils or in the form of oral supplements. In Chronic Pancreatitis carbohydrates and proteins should not be limited. Only in case of Diabetes should the proportion of carbohydrates, which will be balanced according to the hypoglycaemic

therapy, be evaluated. A number of scholars recommend high-calorie and high-protein diets, divided into five or six small meals throughout the day, and discourage diets very rich in fibres, being fibres able to absorb or block the action of pancreatic lipase, thus modifying the absorption of nutrients, due to a still poorly known mechanism. Pancreatic enzymes are thought to be possibly absorbed or trapped by fibres and be inactivated by anti-nutrient compounds present in some foods (i.e.: aponins, trypsin end lectins in soybeans; lectins and trypsin inhibitors in legumes; polyphenols in extracts of citrus fruits, Grape seeds, tea, peanut shells and apples). Finally, it is worth remembering that in about 10% of patients the use of caloric-protein supplementation by means of oral nutritional supplements enriched with micro-nutrients and vitamins in order to prevent a significant weight loss is recommended before considering artificial nutrition treatment of enteral or parenteral type. In patients with hyperglycaemia, the treatment is similar to that described for Acute Pancreatitis. In case of preserved beta cell function, metformin is the first choice treatment also in Chronic Pancreatitis. Given the higher risk of pancreatic tumour in patients with Chronic Pancreatitis and Diabetes, the choice of metformin is further supported by its anti-neoplastic effect. Data on SGLT2-inhibitors use in Chronic Pancreatitis are still controversial; since this class of drugs could increase the risk of euglycaemic ketoacidosis in insulin-deficient patients and induce catabolic effects and dehydratation, it should be used with caution.

2.5.2 Enteral nutrition or parenteral nutrition

It is estimated that 5% of patients must regularly undergo EN to prevent or reduce malnutrition [67]. The indications for acute pancreatitis summarised in the **Table 9** also apply to Chronic Pancreatitis. Fibres should similarly be reduced to avoid interference with pancreatic enzymes.

Finally, it is estimated that only 1% of patients with Chronic Pancreatitis undergo Parenteral Nutritional treatment. Usually this treatment is reserved to patients with stenotic complications or enteric fistulas waiting for surgery.

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References

[1] Crockett SD, Wani S, Gardner TB, et al. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. Gastroenterology. 2018;**154**:1096-1101. DOI: 10.1053/j.gastro. 2018.01.032

[2] Jablonska B, Mrowiec S. Nutritional support in patients with severe acute pancreatitis-current standards. Nutrients. 2021;**13**:1498. DOI: 10.3390/nu13051498

[3] Singh VK, Bollen TL, Wu BU, et al. An assessment of the severity of interstitial pancreatitis. Clin Gastroent Hepatol. 2011;**9**:1098-1103. DOI: 10.1016/j.cgh.2011.08.026

[4] Fusco R, Cordaro M, Siracusa R, et al. Biochemical evaluation of the antioxidant effects of hydroxytyrosol on pancreatitis-associated gut injury. Antioxidants. 2020;**9**:781. DOI: 10.3390/antiox9090781

[5] Weiss FU, Laemmerhirt F, Lerch MM. Etiology and risk factors of acute and chronic pancreatitis. Visc Med. 2019;**35**:73-81. DOI: 10.1159/000499138

[6] Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ. 2004;**328**:1407. DOI: 10.1136/bmj.38118.593900.55

[7] Pan LL, Li J, Shamoon M, et al. Recent advances on nutrition in treatment of acute pancreatitis. Frontiers in Immunology. 2017;**8**:762. DOI: 10.3389/fimmu.2017.00762

[8] Ranson JH. Acute pancreatitis. Current Problems in Surgery. 1979;**16**: 1-84. DOI: 10.1016/s0011-3840(79)80012-x

[9] Lankisch PG, Weber-Dany B, Hebel K, et al. The harmless acute pancreatitis score: A clinical algorithm for rapid initial stratification of nonsevere disease. Clinical Gastroenterology and Hepatology. 2009;**7**:702-705. DOI: 10.1016/j.cgh.2009.02.020

[10] Corfield AP, Cooper MJ, Williamson RC, et al. Prediction of severity in acute pancreatitis: Prospective comparison of three prognostic indices. Lancet. 1985;**2**: 403-407. DOI: 10.1016/s0140-6736(85)92733-3

[11] Park JY, Jeon TJ, Ha TH, et al. Bedside index for severity in acute pancreatitis: Comparison with other scoring systems in predicting severity and organ failure. Hepatobiliary & Pancreatic Diseases International. 2013; **12**:645-650. DOI: 10.1016/s1499-3872(13)60101-0

[12] Probst P, Haller S, Bruckner T, et al. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS pancreas). The British Journal of Surgery. 2017;**104**:1053-1062. DOI: 10.1002/bjs.10525

[13] Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: A reliable descriptor of a complex clinical outcome. Critical Care Medicine. 1995; **23**:1638-1652

[14] Alkareemy EAR, Ahmed LAW, El-Masry MA, et al. Etiology, clinical characteristics, and outcomes of acute pancreatitis in patients at Assiut university hospital. Egypt. Journal of Internal Medicine. 2020;**32**:24. DOI: 10.1186/s43162-020-00025-w

[15] Steinberg W, Tenner S. Acute pancreatitis. The New England Journal of Medicine. 1994;**330**:1198-1210. DOI: 10.1056/NEJM199404283301706

[16] Yadav D. Recent advances in the epidemiology of alcoholic pancreatitis. Current Gastroenterology Reports. 2011; **13**:157-165. DOI: 10.1007/s11894-011-0177-9

[17] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Acute pancreatitis classification working group. Classification of acute pancreatitis–2012: Revision of the Atlanta classification and definitions by international consensus. Gut. 2013;**62**: 102-111. DOI: 10.1136/gutjnl-2012-302779

[18] Ferreira Ade F, Bartelega JA, Urbano HC, de Souza IK. Acute pancreatitis gravity predictive factors: Which and when to use them? Arquivos Brasileiros de Cirurgia Digestiva. 2015; **28**:207-211. DOI: 10.1590/S0102-67202015000300016

[19] Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: Value of CT in establishing prognosis. Radiology. 1990;**174**:331-336

[20] Shinagare AB, Ip IK, Raja AS, et al. Use of CT and MRI in emergency department patients with acute pancreatitis. Abdom Imaging Abdominal Imaging. 2014;**40**(2):272-277. DOI: 10.1007/s00261-014-0210-1

[21] Olson E, Perelman A, Birk JW. Acute management of pancreatitis: The key to best outcomes. Postgraduate Medical Journal. 2019;**95**:1-6. DOI: 10.1136/postgradmedj-2018-136034

[22] Ramanathan M, Aadam AA. Nutrition management in acute pancreatitis. Nutrition in Clinical Practice. 2019;**34**:S7-S12. DOI: 10.1002/ncp.10386

[23] Lakananurak N, Gramlich L. Nutrition management in acute pancreatitis: Clinical practice consideration. World Journal of Clinical Cases. 2020;**8**:1561-1573. DOI: 10.12998/wjcc.v8.i9.1561

[24] Dickerson RN, Vehe KL, Mullen JL, Feurer ID, et al. Resting energy expenditure in patients with pancreatitis. Critical Care Medicine. 1991;**19**:484-490. DOI: 10.1097/00003246-199104000-00005

[25] Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. Internal and Emergency Medicine. 2012;**7**:S193-S199. DOI: 10.1007/s11739-012-0802-0

[26] Baeza-Zapata AA, García-Compeán D, Jaquez-Quintana JO, et al. Acute pancreatitis in elderly patients. Gastroenterology. 2021;**161**:1736-1740. DOI: 10.1053/j.gastro.2021.06.081

[27] Bouffard YH, Delafosse BX, Annat GJ, et al. Energy expenditure during severe acute pancreatitis. JPEN Journal of Parenteral and Enteral Nutrition. 1989;**13**:26-29. DOI: 10.1177/014860718901300126

[28] Hill GL, Jonathan E: Rhoads Lecture. Body composition research: Implications for the practice of clinical nutrition. JPEN Journal of Parenteral and Enteral Nutrition. 1992;**16**:197. DOI: 10.1177/014860719201600319 7

[29] Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand Nasoenteric tube feeding in acute pancreatitis. The New England Journal of Medicine. 2014;**371**:1983-1993. DOI: 10.1056/NEJMoa1404393

[30] Sathiaraj E, Murthy S, Mansard MJ, et al. Clinical trial: Oral feeding with a

soft diet compared with clear liquid diet as initial meal in mild acute pancreatitis. Alimentary Pharmacology & Therapeutics. 2008;**28**:777-781. DOI: 10.1111/j.1365-2036.2008.03794.x

[31] Doley RP, Yadav TD, Wig JD, et al. Enteral nutrition in severe acute pancreatitis. Journal of the Pancreas: JOP. 2009;**10**:157-162

[32] Wu P, Li L, Sun W. Efficacy comparisons of enteral nutrition and parenteral nutrition in patients with severe acute pancreatitis: A meta-analysis from randomized controlled trials. Bioscience Reports. 2018;**38**. DOI: 10.1042/BSR20181515

[33] Mirtallo J, Canada T, Johnson D, et al. Task force for the revision of safe practices for parenteral nutrition. Safe practices for parenteral nutrition. JPEN Journal of Parenteral and Enteral Nutrition. 2004;**28**:S39-S70. DOI: 10.1177/0148607104028006S39

[34] Jaber S, Garnier M, Asehnoune K, et al. Anaesth Crit Care Pain Med. 2022; **41**:101060. DOI: 10.1016/j.accpm.2022.101060

[35] Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: Results of a randomized prospective trial. The British Journal of Surgery. 1997;**84**:1665-1669. DOI: 10.1046/j.1365-2168.1997.02851.x

[36] Li JY, Yu T. Chen GCet al: Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: A meta-analysis. PLoS One. 2013;**8**: e64926. DOI: 10.1371/journal.pone.006

[37] Petrov MS, van Santvoort HC, Besselink MG, et al. Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: A meta-analysis of randomized trials. Archives of Surgery. 2008;**143**:1111-1117. DOI: 10.1001/archsurg.143.11.1111

[38] Chang YS, Fu HQ, Xiao YM, Liu JC. Nasogastric or nasojejunal feeding in predicted severe acute pancreatitis: A meta-analysis. Critical Care. 2013;**17**: R118. DOI: 10.1186/cc12790

[39] Smit M, Buddingh KT, Bosma B, et al. Abdominal compartment syndrome and intra-abdominal ischemia in patients with severe acute pancreatitis. World Journal of Surgery. 2016;**40**:1454e61. DOI: 10.1007/s00268-015-3388-7

[40] Dong S, Zhao Z, Li X, et al. Efficacy of glutamine in treating severe acute pancreatitis: A systematic review and meta-analysis. Frontiers in Nutrition. 2022;**9**:865102. DOI: 10.3389/fnut.2022.865102

[41] Endo A, Shiraishi A, Fushimi K, et al. Comparative effectiveness of elemental formula in the early enteral nutrition management of acute pancreatitis: A retrospective cohort study. Annals of Intensive Care. 2018;**8**:69. DOI: 10.1186/s13613-018-0414-6

[42] Petrov MS, Loveday BP, Pylypchuk RD, et al. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. The British Journal of Surgery. 2009;**96**: 1243-1252. DOI: 10.1002/bjs.6862

[43] Kunovsky L, Díte P, Jabandžiev P, et al. Causes of exocrine pancreatic insufficiency other than chronic pancreatitis. Journal of Clinical Medicine. 2021;**10**:5779. DOI: 10.3390/jcm10245779

[44] Machicado JD, Yadav D. Epidemiology of recurrent acute and

chronic pancreatitis: Similarities and differences. Digestive Diseases and Sciences. 2017;**62**:1683-1691. DOI: 10.1007/s10620-017-4510-5

[45] Whitcomb DC, The North American Pancreatitis Study Group. Pancreatitis: TIGAR-O version 2 risk/etiology checklist with topic reviews, updates, and use primers. Clin Translational Gastroent. 2019;**10**: e-00027. DOI: 10.14309/ctg.0000000000000027

[46] Singh VK, Haupt ME, Geller DE, Hall JA, Diez PMQ. Less common etiologies of exocrine pancreatic insufficiency. World Journal of Gastroenterology. 2017;**23**:7059-7076. DOI: 10.3748/wjg.v23.i39.7059

[47] Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World Journal of Gastroenterology. 2013;**19**:7258-7266. DOI: 10.3748/wjg.v19.i42.7258

[48] Uc A, Fishman DS. Pancreatic disorders. Pediatric Clinics of North America. 2017;**64**:685-706. DOI: 10.1016/j.pcl.2017.01.010

[49] Pandol SJ, Gorelick FS, Gerloff A, et al. Alcohol abuse, endoplasmic reticulum stress and pancreatitis. Digestive Diseases. 2010;**28**:776-782. DOI: 10.1159/000327212

[50] Rasch S, Valantiene I, Mickevicius A, et al. Chronic pancreatitis: Do serum biomarkers provide an association with an inflammageing phenotype? Pancreatology. 2016;**16**:708-714. DOI: 10.1016/j.pan.2016.08.004

[51] Robinson SM, Rasch S, Beer S, et al. Systemic inflammation contributes to impairment of quality of life in chronic pancreatitis. Scientific Reports. 2019;**9**: 7318. DOI: 10.1038%2Fs41598-019-43846-8

[52] O'Brien SJ, Omer E, et al. Chronic pancreatitis and nutrition therapy. Nutrition in Clinical Practice. 2019;**34**: S13-S26. DOI: 10.1002/ncp.10379

[53] Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology. 1999;**116**:1132-1140

[54] Fasanella KE, Davis B, Lyons J, et al. Pain in chronic pancreatitis and pancreatic cancer. Gastroenterology Clinics of North America. 2007;**36**:335-64, ix. DOI: 10.1016/j.gtc.2007.03.011

[55] Pham A, Forsmark C. Chronic pancreatitis: Review and update of etiology, risk factors, and management. F1000Res. 2018;**7**:F1000 Faculty Rev. DOI: 10.12688/f1000research.12852.1

[56] Gianotti L, Besselink MG, Sandini M, et al. Nutritional support and therapy in pancreatic surgery: A position paper of the international study group on pancreatic surgery (ISGPS). Surgery. 2018;**164**:1035-1048

[57] Ewald N, Kaufmann C, Raspe A, et al. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). Diabetes/Metabolism Research and Reviews. 2012;**28**:338-342. DOI: 10.1002/dmrr.2260

[58] Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Archives of Internal Medicine. 2009;**169**:1035-1045

[59] Rasmussen HH, Irtun Ø, Olesen SS, et al. Nutrition in chronic pancreatitis. World Journal of Gastroenterology. 2013;**19**:7267-7275. DOI: 10.3748/wjg.v19.i42.7267

[60] Bhardwaj P, Thareja S, Prakash S, Saraya A. Micronutrient antioxidant intake in patients with chronic pancreatitis. Gastroenterol. 2004;**25**:69-72

[61] Reid IR. What diseases are causally linked to vitamin D deficiency? Arch Dis Childhood. 2016;**101**:185-189. DOI: 10.1136/archdischild-2014-307961

[62] Plewka M, Rysz J, Kujawski K. Nutrition and malnutrition in chronic pancreatitis. J Food Sci Tech. 2018;**3**: 431-439. DOI: 10.25177/JFST.3.5.4

[63] Duggan SN, Smyth ND, O'Sullivan M, et al. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. Nutrition in Clinical Practice. 2014;**29**:348-354. DOI: 10.1177/0884533614528361

[64] de la Iglesia-García D, Huang W, Szatmary P, et al. NIHR pancreas biomedical research unit patient advisory group 1; efficacy of pancre-atic enzyme replacement therapy in chronic pancre-atitis: Systematic review and meta-analysis. Gut. 2017;**66**:1354-1355. DOI: 10.1136/gutjnl-2016-312529

[65] Imrie CW, Connett G, Hall RI, Charnley RM. Review article: Enzyme supplementation in cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer. Alimentary Pharmacology & Therapeutics. 2010;**32**: 1S-25S. DOI: 10.1111/j.1365-2036.2010.04437.x

[66] Bruno MJ, Rauws EA, Hoek FJ, Tytgat GN. Comparative effects of adjuvant cimetidine and omeprazole during pancreatic enzyme replacement therapy. Digestive Diseases and Sciences. 1994;**39**:988-992. DOI: 10.1007/BF02087549

[67] Skipworth JR, Raptis DA, Wijesuriya S, et al. The use of nasojejunal nutrition in patients with chronic pancreatitis. Journal of the Pancreas: JOP. 2011;**12**:574-580