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Conservative Therapy of Chronic Pancreatitis

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1. Introduction

Medical treatment of chronic pancreatitis is based on the three main characteristics of the disease, pain and exocrine and endocrine insufficiency. Pain is the leading symptom of chronic pancreatitis. Patients may suffer from continuous pain or relapsing pain in parallel with relapses of the chronic inflammatory process or complications. Pain may decrease over time due to what is called “burn out” disease. Treatment of pain should be based on its pathogenesis. However, in many instances the pathogenesis of pain remains unclear. Pain may be due to an inflammatory mass of the pancreatic head which doesn`t resolve over time and is best treated by resectional surgery; e.g. duodenum preserving pancreatic head resection. Pain due to obstruction of the main pancreatic duct by calcified protein plaques may be treated by ESWL (extracorporal shock wave lithotripsy) with or without endoscopic placement of a stent into the pancreatic duct. These options are discussed in other chapters. Complications of chronic pancreatitis such as development of pseudocysts, bleeding of a pseudoaneurysm of the splenic artery, obstruction of the bile duct leading to cholestasis are generally not amenable to conservative, medical treatment. Cholangitis due to obstruction of the bile duct is primarily treated by endoscopic drainage with sphincterotomy and placing a biliary stent usually in addition to antibiotics. Development of pancreatic cancer may require surgical resection and chemotherapy. Pain not responding to medical treatment may be treated by endoscopic ultrasound-guided celiac plexus blockade. Again, interventional endoscopic possibilities will not be discussed in this chapter. This review on medical treatment of chronic pancreatitis is based on two recent publications of the author (33, 46). Thus, some degree of overlap is inevitable. However, some new clinical studies on treatment are included as well.

Treatment of a severe acute inflammatory relapse of chronic pancreatitis is similar to treatment of acute pancreatitis. Thus, medical treatment of SIRS (systemic inflammatory response syndrome), MODS (multiorgan dysfunction syndrome) including treatment of renal insufficiency or sepsis are discussed in the section on “Acute Pancreatitis”. The role of enteral nutrition in acute relapses is similar to nutrition in acute pancreatitis as well.

2. Pain Syndrome

Clinical symptoms are often unspecific. Symptoms such as a belt-like upper abdominal pain and vomiting, together with a more than 3-fold rise in serum amylase or lipase levels above normal, point the way to the diagnosis of either acute pancreatitis or a relapse of chronic pancreatitis. Initially, it may not be possible to

differentiate acute alcohol induced pancreatitis with the potential for full recovery from an attack of previously unrecognized, yet already established chronic pancreatitis. The pain syndrome - either acute relapses of pain, chronic pain or relapses of pain with decreasing pain severity during the course of the disease - has been extensively described by Ammann and Melhaupt (3). According to a long-term study, the course of early-stage chronic pancreatitis is characterized by episodes of relapsing pain. Chronic pain is often associated with local complications such as pseudocysts. According to the Ammann study in advanced chronic pancreatitis all patients achieved complete pain relief. This observation has not been completely confirmed by others. However, in some patients pain may remit spontaneously due to the chronic inflammatory destruction of the pancreas ("burn out").

Pain score

A validated pain score, such as that published by Bloechle et al. in 1995 or the visual analogue scale (VAS), should be used as a tool for quantifying pain (7). Rated on a scale from 0 – 100 are: frequency of pain attacks (0 never, 100 daily), intensity of pain (1 – 100), use of analgesics (100 morphine, 1 acetylsalicyclic acid) and pain-related absence from work (100: permanent, 0: not in the last year). The review of Pezilli et al. describes measurements of quality of life comparing the SF-12 with the SF-36 (55). Both the SF-12 and the SF-36 have been assessed as valid, albeit only for the assessment of quality of life. The pain score published in 1995 is therefore the only validated score explicitly for pain in patients with chronic pancreatitis.

Pain medication

Analgesics

Analgesics are indicated to treat patients with pain from chronic pancreatitis in order to achieve pain relief or reduction of pain until spontaneous improvement due to cessation of a relapse or definitive treatment (e.g. endoscopy or surgery). Pain management in chronic pancreatitis follows the WHO three-step analgesic ladder. However, due to a lack of studies in chronic pancreatitis, the effectiveness of the WHO pain management plan cannot be answered at present.

Adequate pain management is essential. Patients with an acute exacerbation of pancreatitis often suffer from severe visceral pain. Analgesia is therefore one of the most important and often most urgent aims of treatment. The argument that morphine or its analogues possibly cause contraction of the duodenal papilla, thus creating an additional obstruction for pancreas secretion, is obsolete. This effect either does not occur when using the majority of analgesics of this group or is so inconsequential that it does not play any clinical role (34, 65, 70). Some morphine analogs are successfully used for pain control both in acute and chronic pancreatitis. The question whether oxycodone is a stronger analgesic than morphine has to be proven by a larger study (64). One small study found that transdermal fentanyl is useful but not the ideal first-choice analgesic (49). Tramadol is generally not preferred because it often causes nausea and vomiting in patients with acute pancreatitis. However, the use of tramadol is associated with less gastrointestinal side effects (76). Some centers have achieved good results by the use of thoracic epidural analgesia (EPA) (5, 50). This does not only lead to rapid analgesia but, in addition, prevents or treats paralytic ileus. A prerequisite for the use of EPA is an alert patient and coagulopathy is a contraindication.

The duration of medical therapy with various combinations of pain relievers can be decided on a case by case basis. However, re-evaluation should be made regularly in unsuccessful cases in order to augment the treatment with either an endoscopic or surgical procedure. There are no data to guide the duration of pain therapy using conservative means or when endoscopic or surgical treatment is indicated.

Weaning patients from pain medication again can follow the WHO three-step analgesic ladder in

reverse order. Conservative pain management follows the WHO three-step analgesic ladder, although its effectiveness was not specifically tested in chronic pancreatitis.

Somatostatin

Inhibition of exocrine pancreatic secretion by somatostatin in order to decrease intrapancreatic ductal pressure has not been shown to be successful in decreasing pain. Thus, octreotide should not be used to treat pain associated with chronic pancreatitis. Apart from single case reports and retrospective case series, there are only a double-blind crossover study (40) and an unblinded crossover study comparing octreotide with octreotide long acting release (LAR) (38). In both studies, pain was measured by the VAS. The double-blind crossover study comparing octreotide with saline administration was unable to detect reduction in pain or analgesic requirement while effectively blocking pancreatic secretion. The unblinded crossover study showed no difference between octreotide and octreotide LAR with regard to pain reduction. The effects of somatostatin in acute pancreatitis are controversial as well as its claimed effect in reducing the complication rate after pancreatic surgery.

Pancreatic Enzymes

Inhibition of exocrine pancreatic secretion by porcine pancreatic extracts (negative feedback inhibition) seems also not be successful in treatment of pain. Thus, pancreatic enzymes should not be used to treat pain associated with chronic pancreatitis (39, 47, 60). The rationale behind pancreatic enzyme therapy for pain relief is based on the assumption of a negative feed-back mechanism for the release of cholecystokinin releasing peptides. This in turn leads to a reduced release of cholecystokinin and by this mechanism reduced exocrine pancreas secretion. In a systematic review of the Cochrane Collaboration published in 2009, ten RCTs with a total of 361 patients were identified, which examined the various aspects of the effectiveness of pancreatic enzyme supplements (60). Six of the studies compared enteric encapsulated preparations with placebo, one compared an unencapsulated preparation with placebo, two examined different preparations, and one study examined different dosage regimens. The heterogeneity of the selected dependent variables and the lack of statistical characteristic variables do not allow the data to be pooled. Three of five studies using a pain score showed a significant reduction in pain; two did not. One of four studies which quantified analgesic usage reported a reduction in the consumption of analgesics. No study examined long-term effects of the various types of treatment. Thus, one may conclude that the use of pancreatic enzyme supplements has no proven positive effect on pain symptoms. Furthermore, no improvement in the quality of life was detected. Due to different inclusion criteria, which often are not clearly explained in the studies, it is not possible to clarify whether the cause of pancreatitis, the presence of exocrine pancreatic insufficiency or a certain formulation of the used preparations was responsible for the lack of therapeutic success. Finally the negative feedback inhibition of exocrine pancreatic secretion may either not exist in humans or not play a role in the pathogenesis of pain (48).

Antioxidants

Increased levels of free oxygen radicals have been detected in the serum and pancreatic juice of patients with chronic pancreatitis. Thus, treatment with antioxidants could help to prevent and treat pain by reducing cellular damage from pancreatitis. One initial study involving patients with recurrent acute and chronic pancreatitis demonstrated a significant improvement in the number of acute exacerbations as well as in chronic pain. However, per protocol analysis only 20 of the initial 28 patients could be assessed (73). In another study an improvement of pain could also be demonstrated. However, the number of patients who could be analyzed was much too low to draw any conclusions (36). In a double-blind placebo-controlled study from India, 71 patients were treated with antioxidants and 56 with placebo over a period of six months. There

was a reduction of the days with pain in the treatment arm (6), but these results were not confirmed in a recent controlled trial carried out in the U.K. (62). A later study, again from India, found a reduction of serum surrogate markers of fibrosis and a reduction of pain in patients treated with antioxidants (19). A combination of pregabalin (see below) and antioxidants caused an amelioration of pain recurrence in patients who were still free of narcotics and whose pancreatic duct has been cleared of stones (67). According to a recent meta-analysis the authors recommend antioxidant supplements for patients with low antioxidant levels in their blood (78). Another meta-analysis came to the conclusion "that antioxidants can reduce pain slightly in patients with chronic pancreatitis. The clinical relevance of this small reduction is uncertain, and more evidence is needed" (2). However, "adverse events in one of six patients may prevent the use of antioxidants. Furthermore, the effects of antioxidants on other outcome measures, such as use of analgesics, exacerbation of pancreatitis and quality of life remain uncertain because reliable data are not available" (2). The pathogenesis of pain in chronic pancreatitis is rather complex and often not understood in the individual patient to be treated. Pain may be due to inflammatory infiltration of sensory nerves, ductal hypertension due to ductal scars or protein precipitates, an inflammatory mass or pseudocysts with compression of adjacent organs etc. Duration of the disease, concomitant smoking, or alcohol abuse, prior therapy such as interventional endoscopy or surgery, need for narcotics as pain medication, and numerous further factors may have had an influence in the studies which tested the effect of an additional supplementation with antioxidants (25). In summary, convincing evidence that antioxidants have a role in the treatment of pain from chronic pancreatitis is still lacking. Furthermore in most of the studies mentioned, antioxidant medication contained beta-carotene; application of beta-carotene may be associated with the development of bronchial carcinoma in smokers who comprise the majority of patients with alcoholic chronic pancreatitis (1, 53).

Electro-acupuncture and transcutaneous electrical nerve stimulation

Electro-acupuncture and transcutaneous electrical nerve stimulation (TENS) is not effective for treatment of pain in chronic pancreatitis (4).

Inhibition of leukotrienes, radiotherapy

Treatment with a leukotriene receptor antagonist was not effective in chronic pancreatitis. A three-month treatment with montelukast did not reveal a significant reduction in pain (15). Radiotherapy cannot be recommended for treatment of pain. In a pilot study, significant reduction in pain and avoidance of acute exacerbations were achieved with one session of radiotherapy in 12 of 15 patients (26). However, in view of an increased risk of developing pancreatic cancer in chronic pancreatitis, radiation may have the potential to increase this risk.

Pregabalin

Pregabalin displays effects similar to gamma aminobutyric acid (GABA). However, it does not bind to GABA receptors. Pregabalin binds to a subunit of voltage dependent calcium channels in the central nervous system (CNS). Pain processing by the CNS seems to be abnormal in patients with chronic pancreatitis. The additional role of alcohol in pain processing is only partly understood. In a randomized, double-blind, placebo-controlled trial in 64 patients with pain due to chronic pancreatitis, pregabalin as an adjuvant analgesic was superior to placebo after 3 weeks of treatment (52). The same group finds that these inhibitory effects on central sensitization may be due to inhibition of spreading hyperalgesia (9).

3. Exocrine and endocrine insufficiency

With ongoing destruction of pancreatic acini and pancreatic ducts, inhibition of outflow of digestive

enzymes due to e.g. scars or protein plaques and the destruction of the islets of Langerhans, exocrine and endocrine insufficiency will develop. The destruction of exocrine acini and endocrine islets does not always proceed in parallel. Thus, exocrine insufficiency may precede the development of diabetes or vice versa. However, most patients with long lasting chronic pancreatitis develop so called type 3c diabetes.

Definition of exocrine insufficiency

Exocrine pancreatic insufficiency develops when the decrease of digestive enzyme and bicarbonate secretion no longer allows full digestion of dietary intake. The main causes of exocrine pancreatic insufficiency in adults are chronic pancreatitis, pancreatic carcinoma, and a previous pancreas resection. Cystic fibrosis is the main cause of maldigestion already developing in childhood. A functional impairment of digestion, so called pancreato-cibal asynchrony, may be a consequence of (sub-)total gastrectomy, and some forms of bariatric surgery. as well as in patients with atrophy of the duodenal/jejunal mucosa due to celiac disease. Rare causes include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome and congenital enzyme deficiencies such as trypsinogen, amylase, lipase, enteropeptidase (enterokinase), or α1-antitrypsin deficiencies.

Clinical features of exocrine pancreatic insufficiency

Typical symptoms of exocrine insufficiency are abdominal symptoms such as cramps, gas, bloating, flatulence, steatorrhea and signs of malnutrition. The development of steatorrhea and other symptoms of exocrine pancreatic insufficiency are to be expected once the diagnosis of chronic pancreatitis has been made. In patients with alcoholic chronic pancreatitis, clinically manifest exocrine pancreatic insufficiency usually appears approximately 10 – 15 years after development of the first symptoms such as abdominal pain. In patients with early onset of idiopathic or hereditary chronic pancreatitis exocrine pancreatic insufficiency may develop after even longer periods. The relatively late manifestation of exocrine insufficiency, well after pancreatic tissue destruction has begun, reflects the large functional reserve capacity of the pancreas. It is widely agreed that decompensation associated with steatorrhea and creatorrhea (abnormal excretion of muscle fibers in the feces) does not occur until secretion of the corresponding enzymes has been reduced by more than 90 – 95% (20). However, this study has not been reproduced. There is no clinical symptom that unequivocally confirms exocrine pancreatic insufficiency or, conversely, excludes it. Clinically, steatorrhea cannot be reliably detected. Inspection of the stools is also unreliable, even when performed by an experienced practitioner (37). Exocrine pancreatic insufficiency, even without symptomatic steatorrhea, can have a negative effect on nutrition parameters such as body weight (29). Further studies substantiate reduced absorption of fat-soluble vitamins already in patients with only mild to moderate exocrine insufficiency (35, 41, 42). In patients with osteoporotic fractures reduced fecal elastase levels has been observed. This finding correlates with low vitamin D_3 levels (37). In the majority of patients with chronic pancreatitis there is a correlation between the extent of morphological and functional disturbances (10).

Therapy of exocrine pancreatic insufficiency

The indication for pancreatic enzyme replacement therapy is weight loss of more than 10% of the body weight, steatorrhea with fecal fat excretion of more than 15 g / d, dyspeptic symptoms with severe gas or diarrhea. Pancreatin should also be supplemented even when the increase in fecal fat excretion is modest (7 – 15 g / day) if there are signs of malassimilation (e.g. weight loss) or the patient presents abdominal symptoms, which can be attributed to maldigestion and malabsorption. As the quantitative measurement of fecal fat is often no longer performed, the indication for

replacement is also present with any pathological pancreatic function test in combination with clinical signs of malabsorption. This includes weight loss and abdominal pain with dyspepsia, severe gas or diarrhea. Therapy with pancreatin as an empiric trial for up to 4 – 6 weeks may also be beneficial if the source of symptoms is uncertain (33, 46).

The majority of enzyme supplements contain pancreatin, a pulverized extract from porcine pancreas with the main components: lipase, amylase, trypsin, and chymotrypsin. Pancreatin is not absorbed from the gastrointestinal tract, but is inactivated by enteric bacteria and digestive juices and eliminated in the feces (18, 31, 44, 54). Encapsulated microsphere formulations which protect from gastric acid clearly improve efficiency of replacement with pancreas ferments (8, 11, 21, 77). The measure of success of treatment is improvement of the disease symptoms. Pancreatic enzyme replacement therapy improves quality of life (17). Several studies which compared enteric coated porcine pancreatic extracts with placebo showed their superiority (58, 71, 72, 75).

Complete normalization of digestion and absorption of nutrients is usually not attainable. A rapid release of pancreatic enzymes from encapsulation may be hampered by a low pH in the duodenum due to a decrease of bicarbonate secretion in chronic pancreatitis. The success of pancreatin replacement therapy should be monitored primarily using clinical parameters (weight gain, long-term normalization of the vitamin status, disappearance of abdominal symptoms). If there is any doubt whether persistence of symptoms can be explained by a lack of efficacy of enzyme replacement, then fecal fat excretion or pancreatic function tests to measure nutrient digestion under therapy (e.g. breath tests with ^{13}C-labelled lipids) should be applied. The disappearance of clinical signs of malabsorption is the most important criterion for the success of pancreatic enzyme therapy.

Pancreatin should be taken with meals. The effectiveness of pancreatic enzyme supplements presupposes mixing of pancreatin and chyme. If more than one capsule / tablet per meal is to be taken, it may be beneficial to take one part of the dose immediately at the beginning of, and the rest distributed throughout, the meal (22). Because mixing of chyme and pancreatin is required for optimal effectiveness, preparations should be chosen which consist of acid-protected particles with a diameter of ≤ 2 mm. This critical value is in principle only relevant for patients with a preserved pylorus (45). However, there are no double blind prospective randomized trials comparing the efficacy of acid protected microtablets or microspheres with larger acid protected tablets / capsules. In a randomized study of patients with chronic pancreatitis and steatorrhea the coefficient of fat absorption was measured after application of either acid protected minimicrospheres (> 90% diameter < 1.25 mm, range 0.7 – 1.6 mm) with minispheres (> 70% diameter > 1.25 mm, range 1 – 2 mm). Both preparations were efficacious and at least equivalent (30). The number of patients studied was not large enough to determine whether minimicrospheres are superior to minispheres. The administered pancreatin dose should contain adequate enzymatic activity for the digestion of one meal. The dose of pancreatin preparations is based on lipase activity. 20,000 to 40,000 units (Ph. Eur.) per main meal should be administered as an initial dose; approx. 10,000 (to 20,000) lipase units for the digestion of smaller in-between meals. The enzyme dose should be doubled, if necessary tripled, if the effect is inadequate. Former studies showed an improvement of the efficacy of pancreatic enzymes by adding a H2-receptor blocker (12, 14, 23). Adding a PPI (proton pump inhibitor) may be more efficacious (12). However, a complete resolution of steatorrhea may not be achieved. Thus, pancreatin powder or granulate should be combined with a PPI if the effect is still inadequate. The clinical efficacy of pancreatin preparations is determined by the administered dose, the time point of intake, acid protection and

size of the pancreatin particles, specific biochemical properties of the preparation, which depend on its origin, as well as past and concomitant disorders of the patient to be treated.

Almost all pancreatic enzyme supplements available contain porcine pancreatin. Preparations with fungal (Rhizopus oryzae, Aspergillus oryzae) enzymes have less favorable biochemical properties (higher acid stability, but rapid deactivation in the presence of low bile acid concentrations) and are therefore of only limited clinical value. Bacterial enzymes and human lipase produced using gene technology are not yet of relevance in the treatment of exocrine pancreatic insufficiency. However, microbial lipase may be efficacious and seems to be safe (32). Given that some religions prohibit the consumption of pork, the patient should be made aware of the origin of the preparations.

Long term treatment with porcine pancreatic extracts is generally safe (27, 56). Minor side effects such as abdominal symptoms (in < 10% abdominal pain, bowel movement changes, nausea / vomiting) are possible. as well as allergic reactions (in < 1% of patients). Very high doses of enzymes (> 10,000 – 20,000 units of lipase per kg body weight per day) should be avoided if possible. Fibrosing colonopathy, a rare disorder, has been reported to occur after the administration of extremely high doses of pancreatin in children with cystic fibrosis. Causality has not been established and is rather unlikely (16, 59, 63, 68, 74). One may consider that ingredients of the encapsulation rather than enzymes itself are responsible.

In patients with diabetes mellitus and newly initiated or increased pancreatic therapy, blood glucose levels should be monitored more closely for a short time because the improved uptake of carbohydrates can result in hyperglycemia. Patients with chronic pancreatitis and associated diabetes mellitus may encounter more significant problems with controlling their blood sugar levels if pancreatin therapy is initiated or discontinued. This includes emergency situations requiring treatment: In a study by O'Keefe et al. symptomatic hypoglycemia developed during placebo treatment and ketoacidosis after recommencing pancreatic therapy (51).

Therapy of endocrine insufficiency

Endocrine insufficiency in chronic pancreatitis has been designated diabetes type 3c. Endocrine insufficiency will develop in most cases sooner or later as the inflammatory processes progress. There is some correlation with the development of exocrine insufficiency. Therapy of this type of diabetes is often more difficult due to several reasons: 1) In addition to a lack of insulin due to the inflammatory destruction of islets there is also a lack of counter-regulatory islet hormones such as glucagon and somatostatin; 2) postprandial serum glucose levels depend on the sufficiency of food digestion which is dependent on the efficiency of treatment with porcine pancreatic enzymes; and 3) compliance, especially in alcoholics, may play a major negative role to control metabolism. Thus in patients whose daily food intake varies due to their life style or due to abdominal pain, treatment with insulin needs cautious supervision. The risk of late complications as a consequence of insufficient treatment of diabetes has to be counterbalanced by the risk of severe hypoglycemia. Intensified insulin therapy by patient measurements of preprandial serum glucose and individual selection of the appropriate dosage of insulin may not be possible in many of these patients. However, in patients having a good adherence as is usually the case in patients with hereditary and idiopathic chronic pancreatitis and patients with a rather stable disease course may be managed with an intensified diabetic regimen. Unfortunately there are no evidence-based data regarding treatment of diabetes type 3c in patients with alcohol induced chronic pancreatitis.

4. Nutrition in chronic pancreatitis

Nutrition during acute relapses of chronic pancreatitis is discussed under "Acute

Pancreatitis". The value of so-called "pancreas diets" or "bland" diets for pancreas patients is unproven. Indeed, a randomized trial led to initial fasting for mild acute pancreatitis no longer being recommended (24). Thus, a reduction in the length of hospital stay and a more rapid recovery can be achieved with oral refeeding (69). Malnutrition in patients with chronic pancreatitis may not only be the result of exocrine pancreatic insufficiency, but also due to a reduced food intake secondary to pain or continued alcohol consumption. Nutritional treatment should provide an adequate supply of nutrients, vitamins and trace elements. Usually patients should receive a normal isocaloric diet together with adequate pancreatic enzyme replacement. To improve the response, the nutrition intake should be distributed over appropriately 4 – 6 smaller meals. There is no established specific pancreas diet. Data from animal studies indicate that diets with a high fat and protein content plus adequate enzyme replacement can improve the effectiveness of fat absorption (66). A low fat diet cannot be generally recommended. Only when clinical symptoms of fat maldigestion occur with further progression of exocrine pancreatic insufficiency, despite adequate oral enzyme replacement, the amount of oral fat may be reduced, depending on tolerability. Fat is important as a central source of energy for avoiding and treating catabolism. If dietary fat has to be reduced for reasons of intolerability, despite adequate enzyme replacement therapy, it is necessary to ensure that the compensatory oral supply of other sources of energy (carbohydrates, proteins) are appropriately increased to maintain isocaloric nutrition. Medium-chain triglycerides (MCT) can be absorbed without prior digestion by lipase. MCT may improve fat absorption in patients with exocrine insufficiency not receiving enzyme replacement therapy. However, MCT should not be recommended in conjunction with enzyme administration. In a small study on patients with severe steatorrhea MCT alone were not superior to regular fat intake together with pancreatic enzyme application (13). Diet counseling is very important and as efficient in malnourished patients as supplementation with MCT (61). Alcohol consumption should be avoided in chronic pancreatitis. Alcohol consumption is an important pathogenetic factor for the progression of exocrine pancreatic insufficiency (28). There are numerous studies demonstrating that continuous smoking accelerates the progression of the disease course (57). Deficits of vitamins and trace elements should be specifically replaced. Patients with chronic pancreatitis and exocrine pancreatic insufficiency usually have an intake of vitamins and trace elements less than recommended for daily consumption. Thus deficiencies of the fat-soluble vitamins A, D, E and K as well as of calcium, magnesium, zinc, thiamine and folic acid are often detected (43). A reduced intake has also been reported for riboflavin, choline, copper, manganese and sulfur. The indication to replace vitamins and trace elements should be established in adults primarily according to clinical symptoms of deficiency.

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