Nutritional Status in Patients with Chronic Pancreatitis

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Abstract: Chronic pancreatitis (CP) is defined as a continuing inflammatory disease of the pancreas that is characterized by irreversible morphological changes often associated with pain and the loss of exocrine and/or endocrine function, which may be clinically relevant. Maldigestion (absolute deficiency of pancreatic enzyme secretion) is a typical complication of CP of any etiology with long anamnesis. Fat malabsorption is considered to be the malnutrition base in CP patients. The purpose of this article is to evaluate the role of nutritive status and nutritive deficiency in CP patients, evaluate diagnostic approaches, correct nutritive status deviation with reference to previous experience, and explore the present situation and possible future perspectives.

Keywords: Chronic pancreatitis, exocrine pancreatic insufficiency, maldigestion, malnutrition, nutritive status.

INTRODUCTION

Chronic pancreatitis (CP) is defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes often associated with pain and the loss of exocrine and/or endocrine function, which may be clinically relevant [1]. The annual incidence of CP ranges from 5 to 12/100,000 individuals; the prevalence of CP is approximately 50/100,000 persons in the US [2]. The condition is most often caused by alcohol abuse over many years. Repeated episodes of acute pancreatitis can lead to chronic pancreatitis. Heredity may be a contributing factor in some cases, and sometimes the cause is not known.

Maldigestion (absolute deficiency of pancreatic enzyme secretion) is a typical complication of CP or acute necrotizing pancreatitis and can be a consequence of pancreatic resection or pancreatectomy in CP patients [3]. Exocrine pancreatic insufficiency (EPI) in CP patients leads to steatorrhea, body weight loss, malnutrition [4], and consequently a major reduction in quality of life [5].

The average time between the onset of the first symptoms of CP and the appearance of signs of maldigestion is 8–9 years in patients with alcoholic CP and over 15 years in patients with idiopathic non-alcoholic pancreatitis [6]. At present, many CP patients suffer from chronic pancreatic pain that often requires treatment with narcotic analgesics [7,8]. However, pain relief therapies are often not efficient and surgery is indicated (resection or complex methods with longitudinal pancreaticojejunostomy or total pancreatectomy with autotransplantation of pancreatic islet cells) [7], resulting in an additional increase in maldigestion.

The acute structural damage of the pancreas added to a deep functional insufficiency of this vitally important organ has a tremendous impact on the patient's metabolism: nutrients are not digested normally, leading to a progressive insufficiency of macronutrients and micronutrients; such damage is often associated with diabetes. Despite the attention paid by physicians to the probable nutritional insufficiency in CP patients, malnutrition develops frequently in clinical practice [9].

The underestimation of the nutrient deficiency and nutritive insufficiency in CP could be partly explained by the rather complicated malnutrition pathophysiology of the disease, including various limitations in nutrition other than maldigestion and diabetes. In particular, the postprandial strengthening of pain, specificity of the food ration associated with chronic alcoholism [6,10], and other pathophysiological aspects will be detailed in this article.

The purpose of this article is to evaluate the role of nutritive status and insufficiency in CP patients, to evaluate diagnostic approaches and to correct deviations in nutritive status in light of previous experience, current practice, and possible future perspectives.

NUTRITIVE STATUS AND CHRONIC PANCREATITIS

History of Studies

The aspects of nutritive status evaluation and characteristics of nutrition in CP patients were
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thoroughly examined in special planned studies performed in the 1980s [11,12] up to recent publications [13,14,15]. Objectively, few studies have estimated nutritive status in CP patients; however, the number of publications has definitely increased. Many studies have evaluated only a few markers [11,16,17] or a small combination of parameters [12,14,15,18-24]: the deficiency of fat- or water-soluble vitamins, microelements, protein transport in the blood, lipids, clinical blood analysis parameters and a few others. In some studies, malnutrition or its complications have been evaluated in combination with nutritional parameters [12-14,19,25,26], and others have assessed the efficacy of substitutive enzyme therapy on the dynamics of nutritional parameters in CP patients [12,13,27]. The main studies evaluating nutritive status in CP patients are presented in Table 1.

The Pathophysiology of Nutritive Insufficiency in CP

Fat malabsorption is considered to be the malnutrition base in CP patients [28]. The severity of malnutrition in CP patients correlates with three main pathogenetic factors [4,6]:

- Initial nutrient deficiency, which is caused by alcohol addiction and is revealed clinically by strong postprandial pain or other factors that limit food rations;
- Pancreatic maldigestion and secondary malabsorption syndrome (loss of nutrients);
- Hypermetabolism, the inflammation process that occurs in the pancreas and defines the severity of the disease (excessive calorie consumption).

It is well known that CP patients often restrict their food rations because of postprandial pain. As a result of the smaller rations of food and dietary fibers, steatorrhea and diarrhea increase [6]. A low BMI (<20 kg/m²), diarrhea and steatorrhea occur in 32%, 57% and 24% of CP patients, respectively, and these patients need medical rehabilitation [29]. Other studies have demonstrated a nutritive deficiency in CP patients who require surgery; this deficiency persists for an extended period during the postoperative period [30-32]. A recent study demonstrated a reduction of thin body mass with fat layer retention in alcoholic CP patients and a deficiency of magnesium and vitamin D with lower cholesterol levels in persons without pancreatitis who are addicted to alcohol [24].

Maldigestion develops after pancreatic parenchymal injury and progressive fibrosis, leading to a deficiency of bicarbonate secretion in patients with CP. Maldigestion restricts the patient to a vicious circle of pathogenesis in which the patient cannot digest and assimilate sufficient and balanced food rations in the absence of substitutive enzyme therapy [33].

Hypermetabolism in CP patients develops concurrently with the inflammation process in the pancreas. Attacks of pancreatitis are accompanied by a metabolic reaction, which is rather difficult to differentiate from acute pancreatitis [34] or sepsis [35, 36]. The resting energy expenditure in CP patients is 30–50% higher than normal [37] and confirms the hypermetabolism status in CP patients [38]. The proteolysis of skeletal muscles in hypermetabolism is accompanied by a decrease of 40% in amino acid levels and a loss of 15% of the total volume of muscle mass [10]. This persistent negative nitrogen balance has an important impact on the survival of patients who suffer from acute pancreatitis [39]. Patients with CP often undergo catabolic stress and have increased levels of catecholamines and cortisol as well as an abnormal insulin/glucagon secretion balance that results from beta cell dysfunction, leading to the development of insulin resistance [10,40]. Fat metabolism in CP patients can also change with respect to lipolysis activation and acceleration of lipid peroxyl oxidation processes [34,41] when lipid clearance decreases as a result of hypercholesteremia and hypertriglyceridemia [10,34,42].

Hypermetabolism in CP can cause gradual exhaustion of the nutrient reserves, and persistent symptomatology (pain, nausea and vomiting, gastrostasis, and continued alcohol intake) will cause nutrition abnormalities and intensify deficiencies in macronutrients and micronutrients [33, 43].

In addition, other mechanisms may participate in the development of malnutrition in CP patients, but the role of such mechanisms is less well supported. Glycosuria, as a cause of nutrient loss and secondary nutrition limitation as well as the accompanying gastrointestinal diseases, may be additional causes of nutrient loss or insufficient nutrient supplies. Patients with alcohol addiction typically have hypokinesis, a physical inertness that will be the background for progressive muscle hypotrophy [29].

Nutritive Deficiency and Clinical Course of CP

Malnutrition in CP patients is not only a complication of the disease but also influences its course. CP
### Table 1: Clinical Studies of the Nutritive Status of CP Patients

<table>
<thead>
<tr>
<th>Author Reference</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalvaria [11]</td>
<td>1986</td>
<td>case-control study</td>
<td>44 CP patients/83 controls (44 healthy + 39 Crohn’s disease)</td>
<td>Low vitamin E level in 75% CP patients without association to pancreatic exocrine insufficiency</td>
</tr>
<tr>
<td>Twersky [12]</td>
<td>1989</td>
<td>review of small studies</td>
<td>-</td>
<td>Low fat-soluble vitamins, B12, calcium, zinc, selenium levels in CP patients 10–20% decrease in BMI as a result of diet + pancreatic exocrine insufficiency Impossible to normalize the nutritive status by administering pancreatin 50% lethality in 12 years</td>
</tr>
<tr>
<td>Glasbrenner [16]</td>
<td>1991</td>
<td>case-control study</td>
<td>137 CP patients/58 controls; 89.8% with pancreatic exocrine insufficiency</td>
<td>5.7% of cases of vitamin B12 deficiency and 3.6% of cases of folic acid deficiency in CP patients without association to pancreatic exocrine insufficiency grade</td>
</tr>
<tr>
<td>Marotta [21]</td>
<td>1994</td>
<td>case-control study</td>
<td>44 CP patients/83 controls (44 healthy + 39 Crohn’s disease)</td>
<td>Decrease level of vitamin E: 75% (gen.)/91% (by steatorrhea) in CP patients Decrease level of vitamin A: 16% (gen.)/38% (by steatorrhea) in CP patients</td>
</tr>
<tr>
<td>Morillas Ariño [26]</td>
<td>1997</td>
<td>cross-sectional non-comparative study</td>
<td>40 with pancreaticexogenous diabetes</td>
<td>Malnutrition in 29 patients (72.5%), hybrid (protein-energy) insufficiency in 19 patients (47.5%)</td>
</tr>
<tr>
<td>Haaber [25]</td>
<td>2000</td>
<td>cross-sectional study</td>
<td>32 without pancreatic exocrine insufficiency/26 with pancreatic exocrine insufficiency; all with normal BMI</td>
<td>Reduction of mineral bone density: 56% in CP patients and 69% in patients with pancreatic exocrine insufficiency; median serous concentrations of vitamin D below the normal value in both groups</td>
</tr>
<tr>
<td>Hartmann [22]</td>
<td>2007</td>
<td>case-control study</td>
<td>58 CP patients/92 controls (proteomics)</td>
<td>Retinol-binding protein, apolipoprotein A-II (ApoA-II), ApoC-I, ApoC-II, ApoC-III, transthyretin reduced in CP vs. control</td>
</tr>
<tr>
<td>Dujisikova [19]</td>
<td>2008</td>
<td>cross-sectional study</td>
<td>73 CP patients (Instantaneous)</td>
<td>Osteopathy in 39%, osteopenia in 26%, osteoporosis in 5%, and late rickets in 8% of cases</td>
</tr>
<tr>
<td>Girish [17]</td>
<td>2009</td>
<td>prospective cohort study</td>
<td>101 CP patients (34 alcoholic, 67 tropical)/89 controls</td>
<td>Evident reduction of zinc levels in erythrocytes in CP patients compared with control (P &lt; 0.001) especially in alcoholic CP (P = 0.001) Zinc levels were significantly lower in diabetic patients than in non-diabetics (P = 0.036). Correlation of zinc levels with pancreatic elastase in feces (r = 0.587, P &lt; 0.001) in CP patients with exocrine insufficiency</td>
</tr>
<tr>
<td>Schnitzler [23]</td>
<td>2010</td>
<td>case-control study</td>
<td>13 alcoholic CP patients</td>
<td>Vitamin D, vitamin C reduced in CP vs. control</td>
</tr>
<tr>
<td>Sobral-Oliveira [24]</td>
<td>2011</td>
<td>case-control study</td>
<td>48 subjects with chronic alcoholic pancreatitis, alcoholics without visceral disease, and 60 healthy never-drinking adults (controls)</td>
<td>Both alcoholic populations suffered from reduced lean body mass (P = 0.001), with well-maintained body fat. Magnesium was depleted, and values of vitamin D and B12 correlated with alcohol abuse. LDL and total cholesterol were increased in alcoholics without pancreatitis (P = 0.04), but not in those with visceral damage. C-reactive protein and serum amyloid A correlated with the duration of excessive drinking (P = 0.01)</td>
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patients with severe malnutrition demonstrate a reduction of pancreatic enzymes in duodenal content, stool, and blood along with a decrease in total protein and albumin in the blood. Visualization methods reveal a substantial reduction of the pancreas in such patients, a tendency that is observed in all clinical types of trophological insufficiency and is more severe in the case of marasmus. Complex treatment of trophological insufficiency and correct and step-by-step nutritive correction restore pancreatic dimensions, which correlate with the volume of secretion and increase in BMI [44-46] but not with the primary form of insufficiency (marasmus, kwashiorkor, mixed form) [45].

The severity of malnutrition correlates with the level of hypotrophy of the pancreatic endocrine apparatus and insulin secretion levels. An adequate nutritive correction therapy can partially reverse the hypertrophy and restore higher insulin secretion levels; however, diabetes resulting from severe trophological insufficiency is not reversible [47].

The importance of malnutrition in the development of severe exocrine pancreatic insufficiency and fibrosis was demonstrated in early morphological studies. The canonical work reported by Volk B.W. and Lazarus S.S. (1960) [48] demonstrates the development of pancreatic acinar atrophy and the reduction of zymogenic granule quantities in rabbits fed a low-calorie diet using optical microscopy. The same authors confirmed these results in 1964 using electron microscopy [49]. The next important milestone in the connection between malnutrition and pancreatic morphological alterations was the demonstration of pancreatic fibrosis. W.R. Blackburn and K. Vinjchaikul (1969) used electron microscopy to demonstrate pancreatic fibrosis in addition to atrophy in the kwashiorkor model of severe malnutrition [50]. Later studies demonstrated that atrophic and fibrotic alterations of the pancreatic parenchyma in kwashiorkor patients are combined with fat dystrophy in the pancreas and are highly expressed in the liver. Fibrosis was observed in all segments of the pancreas, but no severe fibrotic alterations were found. Fibrotic alterations in the pancreas were only observed in patients with marasmus and kwashiorkor-marasmus at a frequency of 32% and 29.2%, respectively [51].

CP patients and patients with nutritive insufficiency may be at a higher risk for complications and a worse prognosis [52], but to date, no high-quality studies have confirmed these observations [53]. Data on nutritive insufficiency have been collected during the prolonged postoperative period from CP patients who needed surgery [30-32]. CP patients or patients suffering from nutritive insufficiency before their operation have a worse postoperative prognosis after pancreatoduodenal surgery.
denal resection or pancreatectomy [31,32]. This observation might be explained by the immunodeficiency that occurs in patients with CP and malnutrition [52]. A recent study reported a chance of 4.81 (95% CI 2.04–8.23) of developing complications (pseudocystis, parapancreatic exudate, and apostasis) in patients with a low BMI [18].

In summary, severe nutritive insufficiency can intensify the course of CP and the severity of exocrine and endocrine pancreatic insufficiencies. Early diagnosis of malnutrition and initiation of adequate substitute enzyme therapy with nutritional support are key to the success of the treatment of CP patients.

**Nutritive Status Evaluation in CP Patients**

Nutritive status research in CP patients is based on a multidisciplinary method that includes the following procedures [6,53]:

- Evaluation of the clinical presentation,
- Diagnosis of exocrine and endocrine pancreatic functions,
- Assessment of the body composition, bone tissue density, and biochemical and clinical blood counts,
- Definitions of food rations and lifestyle,
- Psychological evaluation focusing on the dependent symptoms of nutritive status and risk factors (nausea, anorexia, sitophobia, pain, alcohol addiction, and smoking).

Biochemical nutritive status markers should be evaluated 1-2 times per year and should include a fat-soluble vitamin and the microelement contents of the blood [6].

Although body mass and BMI are important parameters in estimating nutritive status, the food ration of CP patients cannot be based on these parameters alone. Fluid retention in a patient with hypoproteinemina and nutritive insufficiency is characterized by the absence of weight dynamics or even an increase of body mass and BMI (ascites, hypostasis). Therefore, an anthropometric examination that includes a bioimpedance analysis is recommended every 3–6 months. Protein deficiency in CP patients with a normal and relatively stable BMI could progress with a gradual decrease in muscle mass, resulting in muscle weakness, fatigue, and deterioration of the prognosis [30].

To evaluate the food ration, anthropometric parameters, including the volume of the upper arm muscles, thickness of the dermal-fat fold above the triceps, and lean body mass, must be used to evaluate the nutritive status, especially in patients with hypostases and ascites. Age and gender should also be considered [53].

Bioimpedance is an easy, reproducible, portable, non-invasive, and relatively cheap method to evaluate body composition and nutritive status. Bioimpedance analysis of healthy people and patients with various diseases reported in the ESPEN guidelines [54-56] demonstrates the possibility to evaluate the fat-free body mass, functioning somatic cell mass, and contents of the intracellular and extracellular liquid. Although the methodology of bioimpedance is objective in healthy people and patients with a stable hydro-electrolytic balance and is well correlated to age, gender, and ethnic affiliations, its clinical use for routine examination is not recommended in patients with a significant deviation from normal BMI or with hypostatic ascetic syndrome [6].

Whereas the function of skeletal muscles correlates with the total protein volume and body cell mass, a decrease in muscle mass will result in morphological alterations of the skeletal muscles and functional abnormalities [57]. Various studies have demonstrated a correlation between muscle power and the outcomes of acute and chronic diseases [57-59]. Patients with significant malnutrition and who are provided with intensive nutritional support regenerate muscle power initially; in contrast, the body composition regenerates slowly. Therefore, a long period of individualized nutritional support could stimulate the development of muscle mass and power and could further facilitate the gradual regeneration of nutritive status [56,60].

Calculation of the power expenditure at rest could provide an estimation of the energy level needed to regenerate the mass and optimize the nutritional support to prevent complications; [61] however, this technology is not available in most clinics. Instead, the equations of Harris–Benedict (with parameters of height, body mass, gender, and age) are the most frequently used methods in the clinic [62].

With the high frequency of bone tissue pathology in CP patients, densitometry could be recommended
Micronutrient deficiency accentuates the severity of exocrine pancreatic insufficiency; diagnostic methods for pancreatic insufficiency can be developed by evaluating the micronutrient levels in the blood serum. Recent research by Lindkvist et al. [20] included 114 CP patients, and among various markers of nutritional deficiency, confirmed the specificity of several markers to exocrine pancreatic insufficiency using the 13C-inspiratory test with mixed triglycerides. These markers included hemoglobin, hematocrit, prothrombin time, lymphocytes, total protein, albumin, prealbumin, retinol-binding protein, cholesterol, triglycerides, amylase, folic acid, vitamin B12, glycohemoglobin A1C, transferrin, ferritin, magnesium, and zinc. Exocrine pancreatic insufficiency is also associated with lower values for magnesium, hemoglobin, albumin, prealbumin, and retinol-binding protein. A serum magnesium value of <2.05 mg/dl is strongly associated with exocrine pancreatic insufficiency (OR 14.3; 95% CI 2.76–74.2) [63]. The new A.S.P.E.N. recommendations do not include serum albumin and prealbumin as main markers of nutritive insufficiency because they are more indicative of inflammation and are not associated with a decrease in weight, caloric limitation of the food ration, or the nitrogen balance [64].

Nutritive Insufficiency Correction

Diet

According to the program of nutritional risk screening (NRS 2002; [65]), detailing of current and usual food habits must be conducted by a dietician for patients at risk of nutritive insufficiency. Daily food rations are evaluated by means of a 24-hour food diary or by using a special software for food anamneses, which provide detailed information about the supply of energy, protein, fat, and micronutrients. A food frequency questionnaire can be used to investigate commonly consumed food products [66].

A rational diet and scheduled clinic appointments allow patients to reconcile the recommended and actual calorie and protein consumption [6]. A randomized study using this method with nutritive support showed an increase in body mass and BMI and a decrease in fecal fat excretion in patients with CP and nutritive insufficiency [67].

The first dietary recommendation is total alcohol abstinence. One should calculate the necessary 24-hour calorie ration. The calculation of resting energy expenditures, especially in patients with a low BMI (<20 kg/m2), is necessary for an optimal 24-hour calculation of calories due to increased resting energy expenditures. A 24-hour calorie ration calculated as 35 kcal/kg/day is considered capable of compensating for the increase in resting energy expenditures in approximately 80% of patients [4].

Frequent meals (4–8 times a day) with carbohydrate limitation are recommended, especially in the case of incretory pancreatic insufficiency [4,6]. A protein content of 1.0–1.5 g/kg/day is well tolerated by CP patients. A fat content of 30–40% in the calorie ration, especially of vegetable origin, is well tolerated.

In patients with a body mass deficiency and/or persistent steatorrhea, the addition to the food of medium chain triglycerides (MCT) may facilitate the absorption of fat [4,6]. MCTs in the unaltered form are absorbed in the small gut in the absence of lipase, colipase, and bile salts, and they subsequently reach the portal blood stream. MCTs could be used in theory, but they have a low energetic value and bad organoleptic qualities (e.g., bitter taste). The recommended amount of MCT consumption is 50 g/day; a higher dose could induce abnormal levels of ketone bodies and cause unwanted effects (fits, nausea, and diarrhea) [68]. Thus, MCTs must be used carefully by patients with CP and diabetes [4]. The following items are prescribed to patients with clinical or laboratory characteristics of micronutrient deficiency:

- Fat-soluble vitamins (A, D, E, and K) and/or
- Vitamin B12 and/or
- Other micronutrients (such as zinc, calcium, magnesium, and folic acid).

Traditionally, the diet recommended for CP patients consists of small amounts of dietary fiber because it may lead to enzyme absorption and increased malabsorption. Enzyme medication will compensate for the deficiency in fiber-sorbed enzymes [9,69-71] and aid in building a healthy nutritional status in CP patients. Adequate substitutive enzyme therapy provides weight stabilization in 10–15% of CP patients, making nutritive correction unnecessary [72,73]. The universal clinical markers for long-term follow-up CP patients are good health and an increase in body mass [6].
**Lifestyle Modification**

To minimize nutritive insufficiency risks and CP progression, it is necessary to avoid smoking and to estimate compliance (use of enzyme medication and dosing schedule maintenance) and pain control. Balanced physical activity is necessary to achieve optimal results in nutritive correction [57-59].

**Nutritive Correction**

Malnutrition is the main cause of progressive nutritional and metabolic abnormality in CP patients.

The indications for nutritive correction and the choice of method are defined by the malnutrition grade and existing diet status. The main purpose of nutritive correction is to guarantee a sufficient supply of macronutrients and micronutrients to reduce malnutrition, malabsorption, and other risk factors, ensuring preventive care or treatment of nutritive insufficiency. The treatment of exocrine pancreatic insufficiency begins with the diet recommendations and substitutive enzyme therapy with pancreatin medications. Approximately 80% of CP patients respond by stabilization of their nutritive status to standard complex therapy including analogesics, pancreatic enzymes, and modifications of food and lifestyle. On average, 10–15% of CP patients require nutritive correction, 5% need enteral feeding, and only 1% have indications for parenteral feeding [3,72,74-76].

The efficacy of enteral feeding as a nutritive support for pancreatitis patients has been reported in many studies [10,77,78]. Enteral feeding stimulates not only the improvement of nutritive status rates but also reduces abdominal pain. The pain relief experienced during the administration of enteral feeding in CP patients can be explained by the probable reduction of cholecystokinin (CCK) levels in the serum. High values of CCK in blood serum could be responsible for pain persistence in CP patients [79]. In other words, CP patients with a meager food intake will have minimal postprandial stimulation of pancreatic secretory activity [80] and a lower CCK secretion.

**Antioxidants**

The efficacy of antioxidant vitamin/mineral complex administration to improve life quality and relieve pancreatic pain has been actively discussed in recent years [4].

The reduction of cysteine, cysteinylglycine, glutathione [81], tocopherol, vitamin A and carotenoids, and selenium [82] in CP patients suggests a connection between antioxidant deficiency and inflammation in pancreatic tissues. Free radicals and peroxidation products can destroy cell membranes or damage cells via oxidative stress [83]. Free radicals and peroxidation products cause the degradation of mast cells with subsequent chemotaxis induction, inflammation, and pain [84]. Some studies have noted the presence of oxidative stress in patients with alcoholic and idiopathic CP [81,85-87]. One theory (2012) suggests that free radical accumulation in CP patients intensifies pancreatic injury and stimulates more intense pain [88].

The efficacy of antioxidants in reducing pancreatic pain in CP has been tested previously, but the results of different studies are inconsistent [89-95]. The first studies evaluated the effect of mono-medications with antioxidant activity of allopurinol [91,94], dimethylsulphoxide (DMSO) [91], ademetionin [93], and curcumin [95] (the active curcuma component). Many studies [89,90,92,96,97] have demonstrated an effect of pain relief with antioxidant complexes that include selenium, β-carotene, vitamin C, vitamin E, and methionine.

Kirk et al. [89] published a randomized study including 36 patients with potential CP who received either the antioxidant complex (selenium 75 mcg, β-carotene 3 mg, tocopherol 25 mg, cevitamic acid 150 mg, and methionine 400 mg) or placebo over 10 weeks. Patients with CP who received the antioxidant complex experienced a significant improvement in quality of life, pain, and physical and social functioning [89]. The largest randomized trial included 127 patients and was conducted by Bhardwaj et al [96]. Patients received antioxidant complexes containing selenium 600 mcg, cevitamic acid 540 mg, 9000 ME β-carotene, 270 ME α-tocopherol, and 2000 mg methionine or placebo. The number of days without pain was significantly increased in the treatment group (7.4 ± 6.8 days without pain [placebo] vs. 3.2 ± 4.0 days without pain[treatment] over a month; P < 0.001), diminishing the need for analogesics and decreasing the hospitalization risk compared with placebo [96].

Another recent placebo-controlled trial included 61 CP patients who received either placebo or an antioxidant complex for 3 months [63]. The authors noted not only a reduction in pancreatic pain (17/31 in the treatment group vs. 9/30 in the placebo group; p = 0.05) but also an antifibrotic effect assessed by TGF-β1 levels in the blood serum (p = 0.001) [63].

The most recent randomized controlled trial conducted in Manchester compared the efficacy of
antioxidant therapy to placebo in 70 CP patients (A.K. Siriwardena et al., ANTICIPATE study, 2012). The results did not show any substantial pain reduction or life of quality improvement [98]; this publication was highly criticized in several articles [99,100].

The study by Siriwardena et al. [98] influenced the results of the meta-analysis estimating the pain relief efficacy of antioxidants in CP patients [101]. This meta-analysis included 9 randomized trials (n = 390) and demonstrated that higher antioxidant levels in the blood ($P < 0.00001$) did not affect pain ($P = 0.67$) and led to an increase in adverse effects ($P < 0.01$) [101]. An earlier meta-analysis by Bjelakovic et al. [102] demonstrated an increase in lethality in patients taking the antioxidant complex over a mean period of 2.7 years for primary or secondary preventive treatment of heart diseases, cancer, and infectious diseases.

In summary, there might be a potential benefit of antioxidants in CP patients if the purpose is pain relief, a reduction of inflammation, and potentially antifibrotic activity. The contradictory results of the trials might be due to differences in research designs, variable antioxidant treatment durations, and the variable medications tested (monocomponent and various polycomponent complexes).

CONCLUSIONS

Deviations in nutritive status play an important role in the pathophysiology of CP and in the prognosis of this disease. The limitation of food ration without nutritional support not only results in caloric and essential nutrient insufficiency but also intensifies the primary pancreatic insufficiency.

Future research is needed that takes into account the various nutritive risks that would help the development of case management algorithms for patients with CP. Particular attention must be paid to body composition, nutrient absorption, metabolism, and micronutrient deficiency evaluation. To include nutritive correction in routine practice, controlled trials must be conducted with relevant clinical CP endpoints such as disease incidences, quality of life, physical functioning, and survival.

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