Antioxidant Supplementation in Chronic Pancreatitis: Current Evidence An Overview

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Chronic pancreatitis is a complex disease, with a 4-fold increase in mortality and has a colossal personal, social and economic impact. Pain is its debilitating manifestation that remains a serious medical challenge with limited treatment options. Great efforts have been focused on investigating the mechanisms of chronic pain with the main objective being to find the ways to improve quality of life in patients. There is evidence suggesting that oxidative stress is one of the factors responsible for pancreatic inflammation, which results in pain. The interest has been directed to the nutrients possessing antioxidant and anti-inflammatory properties in attempt to diminish oxidative pancreatic damage and improve the debilitating manifestations. This review will focus on the accumulated evidence and recent progress in understanding the role of the nutritional components in the management of chronic pancreatitis.

INTRODUCTION

Chronic pancreatitis significantly decreases quality of life in affected individuals mainly because of debilitation and compromised ability to work and perform activities of daily living secondary to chronic pain.1 Most patients develop pain along the course of the disease, and only few become pain-free. The exact mechanism of pain is unclear. One of the existing theories considers oxidative stress as a cause of chronic inflammation leading to destruction of pancreatic tissue.2 There is emerging evidence that the neuronal damage caused by the chronic inflammatory process leads to “neurogenic inflammation.”3 The resultant “neural remodeling”4 can be responsible for the generation and progression of pain. Stimulation of pancreatic stellate cells by oxidative stress eventually causes pancreatic fibrosis, which could contribute to chronic pain.3 The oxidant-antioxidant imbalance can facilitate formation of calcifications in the pancreas.6 The derangements in the antioxidant protection may be aggravated by concomitant diabetes mellitus7 and may progress from chronic pancreatitis to pancreatic cancer.8 Thus, prevention of oxidative stress could be a reasonable target for the inflammatory suppression, reduction of neuronal damage and management of pain.

Vitamins, Microelements, Amino Acids

A potential tool to confront the oxidative process is to enforce antioxidant protection. Deficiency of antioxidants, including selenium, vitamin E, carotenoids and vitamin A9, along with elevated level of oxidative stress markers10 have been documented in chronic pancreatitis. Malabsorption of fat-soluble vitamins in advanced disease is a well-known fact and can contribute to the discovered low level of vitamin A and E. Patients suffering from chronic pancreatitis also have decreased oral intake of antioxidants as a result of diminished food intake due to pain.11 Dietary counseling plays an important role in achieving optimal goals in nutritional status12, along with directed dietary supplementation with commercially available products.

Effects of supplementation with antioxidants have been studied, and in experimental chronic pancreatitis, both vitamins E and C were shown to suppress oxidative stress when utilized individually, and vitamin E was...
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...able reduce pancreatic fibrosis.\(^{13,14}\)

Human studies on chronic pancreatitis have analyzed the effect of the antioxidant complex, consisting of vitamins A, C, E, methionine and selenium. Studies by Uden et al.\(^{15}\) and Bhardwaj et al.\(^{16}\) demonstrated successful suppression of oxidative stress as a result of administration of antioxidant complex. Decrease in pain and improvement of quality of life were found to be beneficial effects of antioxidant supplementation in at least 5 studies (Table 1). Despite the accumulated evidence, antioxidants are underutilized as a part of the management of chronic pancreatitis. Their effectiveness may vary depending on the etiology of pancreatitis, being higher in non-alcoholic types.\(^{17}\) No significant adverse effects have been reported with administration of antioxidant complex for up to 12 months.\(^{18}\)

Further nutritional analysis in chronic pancreatitis discovered deficiency of certain amino acids, such as essential and aromatic,\(^{23,24}\) sulphur containing and branched chain,\(^{25,24}\) while levels of others were unaffected or only slightly decreased.\(^{23,24}\) Although the significance of selective alteration in amino acid levels is not clear, it could be related to nutritional deficiencies and involvement in the oxidative process. Reduction in the level of taurine in chronic pancreatitis was described by Schrader et al.\(^{26}\) An experimental trial on rats demonstrated that taurine was able to play a role in the oxidative process via inhibition of pancreatic fibrosis and suppression of oxidative stress.\(^{27}\) Although informative, further studies are necessary to define the role of selective amino acids deficiency in chronic pancreatitis.

**Fish Oil And Omega-3 Fatty Acids**

Omega-3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA), have been known for their anti-inflammatory properties, and were found to be of benefit in the various states of chronic inflammation that determined its utilization in the field of cardiology\(^{28,29}\) and rheumatology.\(^{30,31}\) Inflammatory suppression was achieved after administration of omega-3 fatty acids in experimental acute pancreatitis.\(^{32,33}\) Reduction of pancreatic fibrosis in experimental chronic pancreatitis is another reported effect of omega-3 fatty acids.\(^{34}\) The described properties can be explained by the ability of omega-3 fatty acids to incorporate into the cellular membranes and inhibit metabolism of arachidonic acid. Furthermore, the synthesis of pro-inflammatory cytokines is reduced while production of omega-3-depended anti-inflammatory cytokines is increased.\(^{32,35}\) Omega-3 fatty acids are able to act as antioxidants and decrease the level of the oxidative stress markers.\(^{30}\) To our knowledge, there are no directed human studies of omega-3 fatty acids effects in chronic pancreatitis; however it can be a subject for future studies.

Dietary sources of omega-3 fatty acids include fish, in particular, salmon and trout, fish oil, and vegetable products, such as walnuts and flaxseeds.

Fish oil is considered to be a well tolerated dietary supplement, with a low frequency of adverse reactions, such as minor gastrointestinal symptoms.\(^{36}\) Omega-3 fatty acids were shown to inhibit platelet aggregation.\(^{37}\) When omega-3 fatty acids used alone, no significant increase in bleeding risk was demonstrated.\(^{38,39}\) If indication is present, patients can take omega-3 fatty acid supplements along with aspirin or warfarin and should be monitored routinely for potential bleeding events; however necessity of more frequent monitoring in this case compared to administration antiaggregants and anticoagulants alone is not clear.\(^{40}\)

Patients are often interested in decreasing the number of pills taken on a daily basis as a matter of convenience, which would make common dietary products, such as fish, a more attractive option for them compared to supplements in a pill form. Furthermore, higher efficacy to increase serum omega-3 fatty acids has been associated with consumption of fish compared to fish oil supplementation.\(^{41}\)

**Red Palm Oil**

Red palm oil is a plant edible oil of low cost used for cooking in the form of baking, frying or as a food product additive. It is produced in tropical countries, including Colombia, Malaysia, and Indonesia. Red palm oil does not undergo refining, which favors preservation of carotenoids in high concentration and makes it one of the richest available sources of carotenoids.\(^{42}\) Benefits of red palm oil include saturated and unsaturated fatty-acid content in optimal proportion, lack of trans fat, as it does not require hydrogenization, and high oxidative stability determined by a high concentration of vitamin E and carotenoids combined with a low level of lenoleic and moderate level of lenoleic fatty acids, belonging to the omega-6 group. Red palm oil acquires its antioxidant properties via high content of carotenoids and vitamin E.\(^{43}\)

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The number of studies on red palm oil in chronic pancreatitis is limited. One trial, conducted by Marotta et al, which used a daily supplementation with 40 mL of red palm oil for 2 weeks without heat processing in chronic pancreatitis and demonstrated a notable improvement of the oxidant-antioxidant balance, evidenced by a decrease in the oxidative stress markers, TNF-alpha, IL-6 (P<0.05) and superoxide anion (P<0.05). No adverse effects have been reported.44

Carotenoids, tocopherols and tocotrienols from the palm oil are “generally recognized as safe” by the United States Food and Drug Administration (FDA). Heat-processed red palm oil becomes oxidized and gains ability to cause adverse effects such as hyperlipidemia, thrombocytopenia, and tissue damage. Virgin red palm oil use has not been associated with the aforementioned adverse effects.43

Table 1. Effect of Antioxidants in Chronic Pancreatitis

<table>
<thead>
<tr>
<th>Authors/Year of Publication</th>
<th>Study Design</th>
<th>Number of Participants</th>
<th>Investigated Supplement with its Daily Dosing</th>
<th>Duration of Supplementation</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Uden et al15 1992           | Double-blind double-dummy cross-over | 20 | Two types of tablets:  
- 600 micrograms organic selenium,  
- 9000 i.u. beta-carotene,  
- 0.54 g vitamin C,  
- 270 i.u. vitamin E  
- 2 g methionine | 20 weeks | • Reduced level of oxidative stress markers |
| Bilton et al19 1994         | Placebo-controlled | 44 | 1. Sulfadenosyl-methionine along (2.4 g a day in divided doses)  
2. Sulfadenosyl-methionine with selenium and beta-carotin | 20 weeks | • No effect in terms of frequency of attacks; level of pain and biochemical oxidative status |
| De las Heras Castano et al18 2000 | Prospective, descriptive, open design | 12 | Antioxidant complex :  
- organic selenium  
- beta-carotene,  
- vitamin C,  
- vitamin E  
- L-methionine,  
- selenium (75 mcg)  
- Vitamin A (2,400 mcg)  
- Vitamin C (180 mg)  
- Vitamin E (30 mg)  
- Sulphadenosyl-methionine (800 mg) | 12 months | • Decreased pain intensity by visual analogue scale  
• Reduced number of hospitalizations |
| Uomo et al20 2001           | Pilot study | 3 | Complex Antox:  
- selenium (75 mcg)  
- beta-carotene (3 mg)  
- vitamins C (150 mg)  
- vitamin E (47 mg)  
- L-methionine (400 mg) | 12 months total | • Reduced number of days with pain  
• Lower analgesic requirement |
| Kirk et al21 2006           | Randomized, placebo-controlled trial | 36 | Antioxidant complex, Betamore G  
(Osper Pharmamatics, India):  
- organic selenium (600 mcg)  
- beta-carotene (9000 IU)  
- vitamin C (0.54g)  
- vitamin E (270 IU)  
- methionine (2g) | 10 weeks | • Better quality of life and pain reduction by SF-36 questionnaire |
| Bhardwaj et al16 2009       | Randomized, placebo-controlled, double blind trial | 127 | Antox (Pharma Nord, Morpeth, UK)  
- selenium  
- beta-carotene  
- vitamin C  
- vitamin E  
- methionine | 6 months | • Reduced number of days with pain  
• Lower analgesic requirement  
• Decreased level of oxidative markers and improved antioxidant status |
| Shah et al22 2010           | Prospective, single center clinical study | 137 | Antox (Pharma Nord, Morpeth, UK)  
- selenium  
- beta-carotene  
- vitamin C  
- vitamin E  
- methionine | 6 months | • Decreased pain intensity by visual analogue pain score  
• Lower analgesic requirement  
• Higher quality of life by EORTC questionnaire |
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Curcumin
Curcumin is a component of turmeric and curry powder, commonly used as a spice, which has documented anti-inflammatory and anti-oxidant properties. The ability of curcumin to suppress inflammatory response was demonstrated by Gukovski et al in experimental alcohol-induced and alcohol-unrelated pancreatitis. Masamune et al discovered suppressed activation of pancreatic stellate cells after curcumin administration. A pilot study of 20 patients by Durgaprasad et al reported that curcumin supplementation at a dose of 500 mg per day combined with 5 mg of piperine after 6 weeks of treatment lead to a decrease in lipid peroxidation and reduction oxidative stress in patients with tropical pancreatitis. However, curcumin has low bioavailability with oral intake, which can be a limiting factor in its utilization. It is “generally recognized as safe” by United States FDA. In the doses up to 12,000 mg per day, only mild side effects were reported, including diarrhea, stool discoloration, headache and rash that did not appear to be dose-related.

CONCLUSIONS
Pain is a debilitating factor in patients with chronic pancreatitis leading to significant implications regarding optimal performance of daily social activities. Available medical therapy for chronic pancreatitis is limited. The benign side effect profile of the studied antioxidant complex, consisting of vitamin A, E, C, methionine and selenium, and its potential postulated benefit makes its routine use an attractive option. Omega-3 fatty acids, red palm oil and curcumin may have a good potential as nutritional additives in chronic pancreatitis, however, knowledge of these supplements in chronic pancreatitis so far is limited to experimental and low powered studies. Well designed, randomized, higher-power studies with the objective assessment of response to therapy will assist in further recommendations regarding routine, universal use of available and not costly supplements.

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