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Medical Therapy for Chronic Pancreatitis: Antioxidants

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Introduction

The medical treatment of chronic pancreatitis includes nutritional assessment and targeted supplementation, avoidance of potential environmental toxins (alcohol and tobacco), replacement of pancreatic enzymes, management of associated diabetes, monitoring for complications, and control of abdominal pain. In many patients, pain is the dominant clinical feature and the most difficult to treat. The effectiveness of medical therapies to relieve or reduce pain is limited. These potential therapies for pain include abstinence from alcohol and tobacco (if applicable), oral analgesics, adjunctive agents (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRI], serotonin–norepinephrine reuptake inhibitors [SNRI], gabapentoids), and antioxidants. Antioxidants are attractive as a potential therapy, given the contribution of oxidant stress and reactive oxygen species to acinar cell injury, pancreatic fibrosis and possibly pain; and by the finding that some patients with chronic pancreatitis have deficiencies in antioxidants such as vitamins C and E, methionine, or selenium.

Pain and Oxidative Stress

The mechanisms of pain in chronic pancreatitis are varied, and include ischemia, direct toxicity (alcohol and its metabolites, tobacco), increased pressure within the gland or duct, associated complications (pseudocyst, secondary malignancy), and neurotoxic mechanisms involving inflammatory cells, nociceptive neurotransmitters, nerve cell injury, and neural remodeling. Chronic pain of any type also produces changes in central neural signaling and processing, which produces a neuropathic pain with features of hyperalgesia (exaggerated pain in response to normal stimuli) and allodynia (pain in response to normal physiologic processes). This centrally sensitized neuropathic pain may persist despite treatment of the underlying cause (e.g., continued pain after total pancreatectomy), and severely limits the effectiveness of therapies for chronic pain syndromes.

Oxidative stress is implicated as a potential mechanism of pain in chronic pancreatitis, and has been documented in some patients with chronic pancreatitis. Deficiencies in baseline antioxidant levels [1,2], increases in antioxidant catalytic enzymes [2,3], and elevations in markers of oxidant-driven lipid peroxidation have been noted [2–5]. Most of these studies include patients with advanced chronic pancreatitis (due to alcohol or tobacco), as well as patients with tropical pancreatitis. These patients, particularly if they are malnourished, may be prone to preexisting deficiencies in antioxidant capacity. In addition, the proportions of patients who smoke vary from study to study, and smoking is a potent inducer of oxidative stress. Thus the presence of smoking or of malnutrition could be important confounders in assessing the pathologic contribution of antioxidants to chronic pancreatitis in general and pain in particular. These studies did not directly correlate the level of antioxidants with the severity (or even presence) of abdominal pain. Replacement or supplementation with antioxidants might change the micronutrient and antioxidant milieu in patients who are deficient, and remediate oxidative stress. This could potentially reduce pain, or could have other beneficial effects in protecting the remaining pancreas from additional damage. The precise mechanism by which a change in oxidative stress could reduce pain is not known. In addition to the treatment of pain in chronic pancreatitis, there has been interest in using antioxidants to treat acute pancreatitis,

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prevent relapses of acute pancreatitis, and prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [6], but these topics are not reviewed in this chapter.

Clinical Studies of Antioxidants for Pain

A number of randomized trials have assessed the efficacy of various antioxidants in reducing the pain of chronic pancreatitis but have reached different conclusions on the overall effect, and on the magnitude of pain relief. They include the use of single antioxidant agents (e.g., allopurinol or curcumin) as well as mixtures of antioxidants (usually vitamins E and C, methionine, selenium, and β-carotene). These randomized studies have been the subject of several meta-analyses [6–10] and a Cochrane systematic review [11]. Interpreting the results is made more difficult by the various types of antioxidant agents and mixtures utilized, and by the various methods of measuring pain. In addition, the studies comprise patients with a wide variety of etiologies, are often small, may only exist in abstract form, and include a mixture of both chronic pancreatitis and relapsing acute pancreatitis. This chapter will focus on studies using mixtures of antioxidants.

An early and widely quoted study by Uden et al. recruited 23 patients with both acute relapsing and chronic pancreatitis in a blinded crossover study [12]. The patients were provided a mixture of selenium, β-carotene, vitamin C, vitamin E, and methionine (or matching placebo) for 10 weeks. Only 20 patients followed the protocol, including 15 patients with chronic pancreatitis. Patients on active therapy reported less background pain, and fewer exacerbations of pain. A trial by Kirk et al. [13] recruited 36 patients with painful chronic pancreatitis into a placebo-controlled crossover trial of a similar mixture of antioxidants. This trial reported on the 19 patients who completed both periods of treatment, and noted improved quality of life. Data from the pain diaries used to assess pain were not analyzed because they were not consistently completed, although there was improvement in pain based on a single question from the quality of life (QOL) instrument. Both of these studies had large numbers of dropouts, and did not employ a washout period between treatments. A washout may be particularly important, as those receiving antioxidants may exhibit improved levels of antioxidants in the subsequent placebo period.

A number of other crossover trials [14,15] and unblinded randomized trials [16,17] suggested benefit, although each was relatively small and had significant numbers of dropouts. Recently, larger and better designed trials have provided estimates of the potential effectiveness of antioxidants.

A large, placebo-controlled, randomized, and blinded study by Bhardwaj et al. [4] recruited 147 patients with painful chronic pancreatitis for a 6-month trial of antioxidants (600 μg selenium, 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine daily). The main outcome, reduction in number of painful days per month, was higher in the active treatment arm (10.5 ± 11.8 fewer days per month, vs. 4.4 ± 5.8 in placebo), which also corresponded to less use of analgesics. One-third of the antioxidant group became pain free during treatment, compared with 12.5% of the placebo group. The study also assessed baseline nutritional status and markers of oxidative stress and antioxidant status, and demonstrated significant improvement in these in the active treatment arm. The patients in this trial were relatively young (mean age 30) and two-thirds had idiopathic pancreatitis; with 36% being undernourished at initiation of the trial. There were a significant number of patients lost to follow-up during the trial (40/147 patients lost to follow-up at some time during the 6-month trial). The large number of dropouts is seen with most trials in chronic pancreatitis, but did create imbalances in the two groups which could have introduced bias.

The other large, randomized, blinded, placebo-controlled trial by Siriwardena et al. [18] recruited 92 patients with painful chronic pancreatitis for a 6-month trial of antioxidants (300 μg selenium, 740.4 mg [496 IU] α-tocopherol, 758 mg ascorbic acid, 2.88 g l-methionine, and 25.2 mg β-carotene daily). These dosages are higher than those in the study by Bhardwaj et al. [4]. The primary outcome was the change in pain, using a visual pain score. A variety of other pain scores were also calculated from pain diaries, as well as pain questions on QOL measures. Although the study initially planned to recruit 57 patients, a planned interim analysis by the steering committee led to an increase in sample size. Compared to the study by Bhardwaj et al., these patients were older (mean age 50), more likely to have alcohol and smoking as the etiology, not undernourished, more likely to be on chronic opioid therapy, and more likely to have undergone previous endoscopic or surgical therapy. After 6 months there was a general decrease in overall pain in both groups of around 2 points on the visual scale, but no difference between groups in these measures or in other measures using daily pain diaries, pain questionnaires, need for hospitalization, opiate use, or QOL. The level of antioxidants was significantly increased in the active treatment arm. During follow-up 22/92 patients withdrew or were lost to follow-up.

These two large randomized trials and several smaller trials have been the subject of several systematic reviews

and meta-analyses. A Cochrane review [11] analyzed 12 randomized controlled trials, of which 6 were double-blinded and placebo-controlled. They note that most trials were small and had high rates of dropout. Combining the studies, those randomized to antioxidants had less pain after 1–6 months of therapy (an average difference of 0.33 [95% CI: −0.64 to −0.02] points less on a visual analog scale of 0–10). The number of pain-free patients was not different between groups, and side-effects were more common in the antioxidant group (leading to 16% of participants stopping therapy). The data were not felt to be sufficient to be able to draw conclusions on the effect of antioxidants on analgesic use, exacerbations of pancreatitis, or QOL. It should be noted that although many of the analyzed studies used mixtures of antioxidants, the dose varied, and some studies used allopurinol or curcumin. This Cochrane review concludes that antioxidants can reduce pain slightly in patients with chronic pancreatitis, but that the clinical relevance of this slight decrease is uncertain.

Given this analysis of the existing data, it is logical to try to identify the subgroup of patients most likely to experience benefit from antioxidants. A number of expert opinion and additional meta-analyses have suggested that the response might vary with etiology of chronic pancreatitis [19,20], baseline levels of antioxidant reserve [21], adequacy of baseline nutrition, type of antioxidant [9], duration of opioid analgesia use [21], stage of disease [19], and others. Although many of these seem plausible, they remain unproven.

Antioxidants are not without risk. The randomized trials of antioxidants note a relative risk of side-effects (largely headache and gastrointestinal side-effects) approximately 5 times greater in the antioxidant group (occurring in 1 in 6 patients) [11]. In addition, mortality appears to be slightly increased in patients receiving antioxidants (vitamin E and β-carotene in particular) as part of large primary and secondary prevention trials [22], with a hazard ratio of 1.03–1.05.

Conclusions

Oxidative stress and reactive oxygen species clearly play an important role in the pathogenesis of chronic pancreatitis. Although the two best studies reach opposite conclusions, the combined analyses of all randomized controlled trials demonstrate a measurable beneficial effect of antioxidants on pain. Even though the overall magnitude of this effect is quite small and not likely to be clinically meaningful, there is the potential that a subgroup of patients might be able to be identified who are much more likely to benefit. The varied and heterogeneous mechanisms of pain and the complexity of nociceptive signaling [19,23,24] imply that no single therapy will be effective in all patients, but the specific subgroup that might respond to antioxidants is not known. Additional studies will be required to identify this cohort.

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