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## Antioxidants as Adjunctive Therapy for Pain in Chronic Pancreatitis



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**The treatment of painful chronic pancreatitis involves the use of medical, endoscopic, and surgical therapies and is often only partially effective. Increasing evidence suggests that the use of antioxidants may have some value as an adjunct in managing this difficult to treat condition. We review the evidence of efficacy and rationale for the use of antioxidants in treating the pain of chronic pancreatitis.**

### INTRODUCTION

Chronic pancreatitis (CP) can be a challenging disease because of difficulties encountered in reaching a correct diagnosis, determining etiology and optimizing management. The prevalence of CP is reported to be between 0.4 % - 5% in developed countries. Chronic alcohol abuse has been the most common etiology of CP in such countries, although more recent studies note tobacco abuse and idiopathic cases now becoming more common. Other etiologies include metabolic (hypertriglyceridemia and hypercalcemia), ductal obstruction from tumors or strictures, environmental toxins, autoimmune, and genetic. In a small subset of patients the disease is “idiopathic.” On the contrary, in other parts of world such as India, a form of idiopathic pancreatitis called “tropical” pancreatitis has been more prevalent. The variety of etiologies causing CP has been recently

reviewed (1). The disease, regardless of its etiology, is a slowly advancing inflammatory process that eventually causes progressive fibrosis and destruction of the parenchyma. Eventually it can lead to endocrine and exocrine dysfunction with clinical manifestations such as diabetes mellitus and malabsorption; chronic abdominal pain is a hallmark feature. The focus of this article will be on pain management with an emphasis on the role of antioxidant therapy.

CP appears to evolve from acute pancreatitis. In many patients, the acute pancreatitis episode may resolve and not progress (2). However, if the offending agent is not removed, patients can progress to recurrent acute pancreatitis and over time CP may ensue. The reasons that some patients progress from acute to chronic pancreatitis and others do not are unknown. The clinical presentation of CP is quite variable and a linear progression from acute to recurrent acute on to chronic pancreatitis is not always the case. Patients may present with intermittent episodes of severe pain, which may be enough to require hospitalization. Gradually, these episodes may occur with increased frequency until the patient is symptomatic on a daily basis. Other patients may remain relatively asymptomatic for years

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and not present until quite late in the course of the disease. Unfortunately, the factors for such variation in presentation are not well understood.

Abdominal pain is the most troublesome symptom for patients with CP. The pain is described usually in the epigastric region and is often made worse by eating. Approximately half of the patients describe the pain as radiating to the back. When the pain is severe, it is often accompanied with nausea and vomiting. Reduced oral intake due to pain, coupled with malabsorption as well as hyperglycemia, can lead to marked malnutrition, subsequent weight loss and cachexia in severe cases. Interestingly, it may not be the severity of pain, but rather the presence of daily continuous pain, even if of lesser severity, which most affects patients' quality of life.

The diagnosis of CP is usually made with imaging studies. Patients can be diagnosed with cross sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) showing pancreatic calcifications, pancreatic atrophy, and/or a dilated pancreatic duct. In some patients with early or "small-duct" CP, such imaging may be normal (no dilation of pancreatic duct and no calcifications) and the diagnosis may be much more difficult. In such patients, more sensitive structural testing such as endoscopic ultrasound (EUS) or functional testing with secretin stimulation may be necessary for diagnosis.

### **Pain in Chronic Pancreatitis**

The mechanisms of pain in CP are not well understood. However, multiple factors are hypothesized including increased ductal and parenchymal pressure from strictures/stones, oxidative injury from free radicals, recurrent ischemia, neuropathic (both peripheral nerve injury due to gland inflammation and a heightened central nervous component of pain due to hypersensitivity of pain perception), and hormonal (increased cholecystokinin production from duodenum leading to increased pancreatic stimulation). Finally, complications of CP, such as pancreatic cancer or pseudocysts, may be additional sources of pain. In the case of pseudocysts in particular, obstruction/compression of adjacent structures such as the stomach, duodenum or bile duct can also contribute to pain. Since the causes of pain are multifactorial, the management can be quite challenging. Furthermore, due to variability in patient presentation, management must

be individualized. Although it is not the focus of this article, the general principles of CP pain management are medical management first, followed by endoscopic or surgical management for selected patients who are failing medical therapy. As a first step, it is necessary to make sure the diagnosis of CP is correct. This is not difficult in those with advanced structural damage (such as pancreatic calcifications or a dilated pancreatic duct), but may be quite challenging in those with early or small duct CP. We often see patients in our pancreas clinics who suffer from a chronic pain syndrome and have been labeled incorrectly as having CP. Second, other complications of CP that have specific therapy should be evaluated for and treated accordingly. These might include a pancreatic pseudocyst, duodenal or biliary obstruction, a secondary pancreatic cancer, or gastroparesis due to CP.

Medical management consists of abstinence from alcohol and smoking, and removal of other environmental toxins or medications, which could be precipitating superimposed attacks of acute pancreatitis. Vigorous attempts at encouraging abstinence are necessary. Smoking cessation is as important as alcohol cessation, as there is now abundant evidence that smoking is equally injurious to the pancreas. A variety of medications can be utilized for pain management, including NSAIDs, pancreatic enzyme replacement, narcotics, non-narcotic analgesics (such as anti-depressants, pregabalin or gabapentin), antioxidants, and octreotide. Referral to psychiatry or pain management specialists may be necessary in some patients. For those patients who fail medical therapy, a careful evaluation of pancreatic parenchymal and ductal morphology via good quality cross-sectional imaging is imperative. In general, patients with "big-duct" disease are amenable to decompressive endoscopic or surgical therapy. The choice depends upon many factors such as patient preference, tolerability, availability, and center expertise. Options for endoscopic or surgical therapy, unfortunately, are limited in those with "small-duct" disease. A proposed algorithm (see Figure 1) for pain management was recently published by our group and is included at the end of the article (3). It is important to remember that antioxidants are only one component of an overall pain management strategy.

### **Role of Oxidative Stress**

Oxidative stress can be defined as an imbalance between pro-oxidants and antioxidants leading to free radical

formation. Despite the endogenous antioxidant system being quite efficient, increased exposure to pro-oxidants or reduced antioxidant capacity can lead to an imbalance and hence oxidative stress (4). Oxidative stress has been proposed as a potential important mechanism of pathogenesis in both acute and chronic pancreatitis. Numerous enzymatic processes result in the generation of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can oxidize a wide range of biomolecules. Moreover, they can turn on many stress-activated pathways (5). The oxidative stress can be self-perpetuating leading to recruitment of ROS-generating inflammatory cells to the pancreas, which worsen the oxidative burden leading to further injury (5). The proposed mechanisms of injury from free radicals include direct attack, lipid peroxidation, DNA modification, and enzyme degradation/inactivation (4, 5)

The mechanisms of detoxification include alteration of toxic substances to a more polar state thereby allowing for easier excretion (4). Two types of reactions exist: In Phase I metabolism, enzymes cleave the toxic molecule into products that could be more or less toxic. In Phase II an endogenous molecule is attached to the altered products thereby rendering it more polar and easier to excrete. Phase I enzymes include the CYP450 oxidase system and hydrolyzing enzymes. Phase II involves glucuronidation and glutathione conjugation (4).

Pro-oxidants that are implicated in acute and chronic pancreatitis include alcohol, tobacco, environmental and dietary toxins, certain drugs, and transition metal cations in a free state such as iron and copper. Both in-vitro and in-vivo animal studies have suggested that pro-oxidants play a role in both acute and chronic pancreatitis. The role of oxidative stress in both animal models of pancreatitis and human disease lead naturally to an interest in using antioxidants to treat the pain of CP. There are a number of substances that might be considered antioxidants. These are listed in Table 1. Studies have used different combinations and different dosages of these antioxidants.

### **Clinical Studies of Oxidative Stress and Antioxidants in Pancreatitis**

There have been a number of studies evaluating patients with both acute and chronic pancreatitis demonstrating increased levels of free radicals, oxidative stress, and reduced antioxidant capacity. These observations support the idea that supplementation with antioxidants

might have value in mitigating the damage and reducing pain. There are several studies that have been performed to determine the effect of antioxidant therapy in treating the pain associated with CP that will be discussed below.

Uden et al. performed a double-blind placebo controlled trial utilizing organic selenium, carotene, vitamin C, vitamin E, and methionine (6). In this small group of patients with chronic pain and recurrent acute pancreatitis, they found that fewer patients on antioxidant therapy had recurrent attacks compared to placebo ( $p=0.032$ ). The authors concluded that clinical improvement was noted in patients on therapy above and beyond placebo effect. Another small study by Heaney and colleagues looked at the role of antioxidant therapy in patients with recurrent acute pancreatitis from familial hypertriglyceridemia (7). They showed that in a very small group of patients, antioxidants prevented recurrent episodes, despite unchanged triglyceride levels. A more recent randomized study from India evaluated the antioxidant curcumin (from turmeric) and its effect on patients with tropical pancreatitis (8). Patients on therapy had decreased markers of oxidative stress compared to placebo. Unfortunately, no improvement of pain was seen. Another randomized, placebo-controlled cross-over study by Kirk and colleagues evaluated the efficacy of combined antioxidants (selenium,  $\beta$ -carotene, L-methionine, and vitamins C and E) in patients with CP (9). Only 19 of 36 patients completed the trial. Nevertheless, the investigators found that treatment with combination antioxidants led to significant improvements in quality of life with regards to pain, physical and social functioning, and general health perception.

Although there have been the aforementioned clinical trials, some limitations have been small sample sizes, lack of evaluation of confounding variables, and short duration of antioxidant supplementation. The largest randomized study to date for relieving pain in CP with antioxidant therapy was published by Bhardwaj and colleagues (10). In this trial the investigators studied patients with both alcoholic and idiopathic CP. One hundred twenty-seven patients were randomized to receive either antioxidant therapy ( $n=71$ ) or placebo ( $n=56$ ) for a 6-month period. The antioxidant supplementation was a combination of 600 mcg selenium, 0.54 g ascorbic acid, 9000 IU  $\beta$  carotene, 270 IU  $\alpha$ -tocopherol and 2 g methionine daily in divided doses. The primary outcome was pain relief assessed by reduction in painful days per month as

**Table 1.** Commercially Available Antioxidants

Antioxidant	Recommended Daily dose (RDA)*	Dose used in studies**	Mechanism of Action	Adverse Effect of High doses ***	Est. Cost (\$ per U.S. month)****
Vitamin E (Alpha Tocopherol)	22.4 I.U (men and women)	270 I.U	Cell membrane stabilization by preventing oxidative stress.	High doses can cause nausea, diarrhea, stomach cramps, blurred vision, increased risk of bleeding including hemorrhagic stroke.	1.5
Vitamin C (Ascorbic Acid)	90 mg (men) 75 mg (women)	540 mg	Acts as a electron donor thus gets oxidized itself in reactions.	Nausea, diarrhea, stomach cramps, iron overload in hemochromatosis.	0.96
Beta Carotene	900 I.U (men) 700 I.U (women)	9000 I.U	Membrane stabilization by quenching singlet oxygen species and trapping peroxy radicals.	Yellow skin. Controversial evidence on increased lung cancer in current smokers.	0.96
Selenium	55 mcg (men and women)	600 mcg	Substrate for antioxidative enzymes, especially Glutathione peroxidase	Selenosis: gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability, and mild nerve damage	8.64
Methionine	12 mg/kg/day (840 mg for 70 Kg male)	2000 mg	Participates in synthesis of antioxidant proteins (Glutathione and cysteine pathways)	ataxia, hyperactivity, hemosiderosis, reduced growth, loss of appetite, and suppressed hematocrit. Increased conversion to homocysteine if taken exclusively leading to increased cardiovascular adverse effects.	21.6
Curcumin	No standard RDA	500 mg	Downregulation of COX2, lipoxygenase and iNOS pathways.	No specific adverse affect profile.	5.67

\*RDA: per Office of dietary supplements, National institute of health (<http://ods.od.nih.gov>).  
 \*\*Studies: using combination of Alpha Tocopherol, Ascorbic acid, Beta Carotene, Selenium and Methionine:  
 (1) Uden S, Schofield D, Miller PF, et al. Antioxidant therapy for recurrent pancreatitis: placebo- controlled trial. *Aliment Pharmacol Ther.* 1990;4(4):357-71.  
 (2) Bhardwaj P, Garg PK, Maulik SK et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009;136:149-59.  
 (3) Kirk GR, White JS, McKie L, et al. Combined antioxidant therapy reduces pain and improves quality of life in chronic pancreatitis. *J Gastrointest Surg.* 2006;10(4):499-503.  
 \*\*Study using Curcumin:  
 Durgaprasad S, Pai CG, Vasanthkumar, et al. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. *Indian J Med Res.* 2005;122(4):315-8.  
 \*\*\*Adverse affects not including pregnancy, not all inclusive.  
 \*\*\*\*Approximate cost calculated from commercially available agents in United States per web search  
 Total cost of combination of Alpha tocopherol, Ascorbic acid, Beta Carotene, Selenium and methionine: \$33.7 per month. Curcumin: \$5.7 per month.

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**PAIN MANAGEMENT IN CHRONIC PANCREATITIS: ALGORITHM**

Figure 1

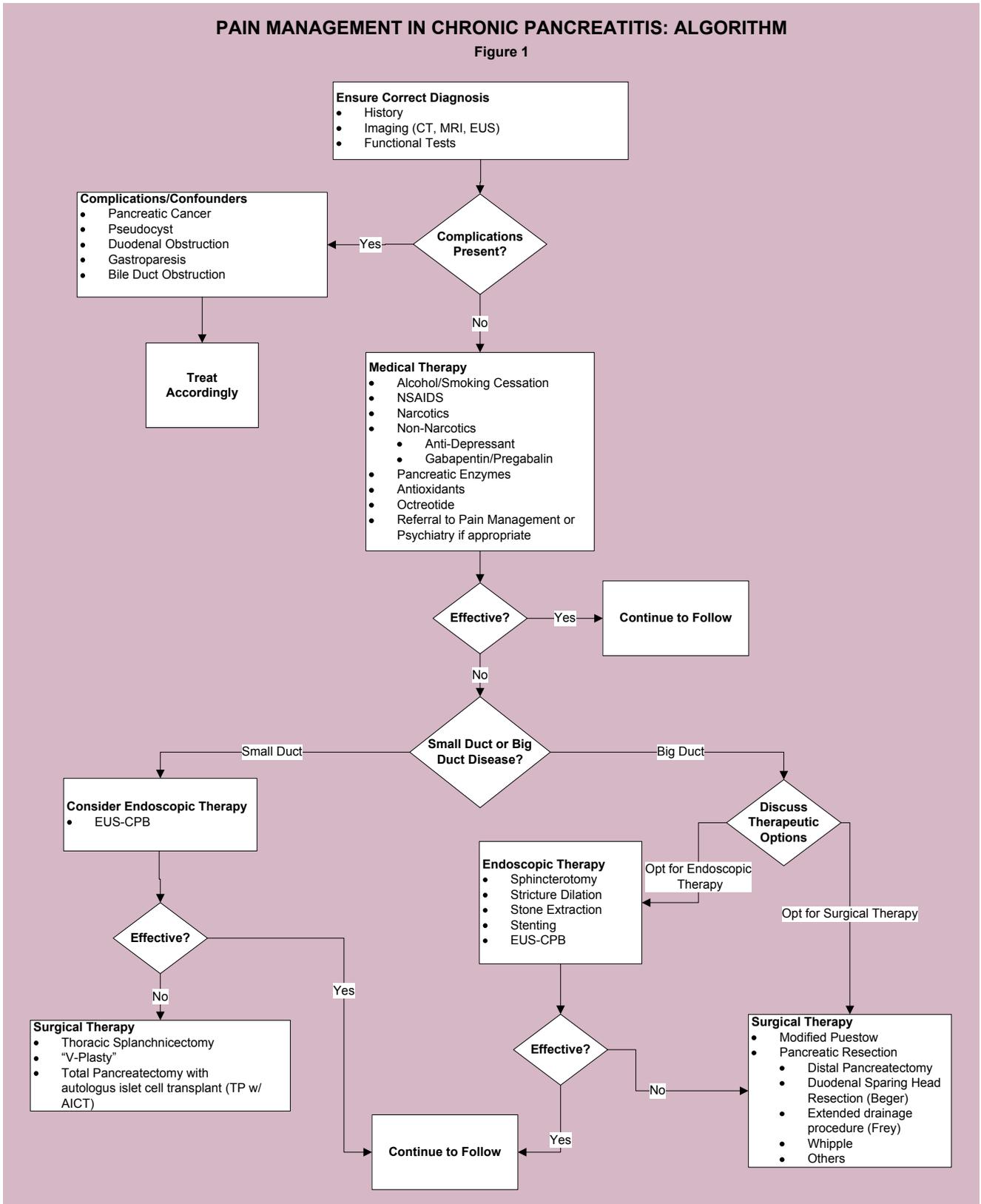


Figure 1: Proposed Algorithm for Pain Management in Chronic Pancreatitis

measured by a pain diary. The primary outcome was evaluated by a blinded clinician. Secondary outcomes evaluated were decrease in requirement for oral and parenteral analgesics, decrease in attacks leading to hospitalization, percentage of patients becoming pain free during therapy, days missed from work, and change in serum markers of oxidative stress and antioxidant levels. The results showed that reduction in painful days per month was 3.21 days in the placebo group compared to 7.37 days in the antioxidant group ( $p < 0.001$ ). Additionally, the antioxidant group had statistically significant reductions in the number of monthly analgesics required, need for hospitalization, and number of days lost from work. Interestingly, one-third of the patients in the antioxidant group became pain free compared to 12.5% of the placebo group ( $p = 0.009$ ). Patients with CP had higher levels of markers of oxidative stress and lower antioxidant levels. No adverse events were noted.

Finally, an unpublished trial of 70 patients (primarily with alcoholic pancreatitis) compared an antioxidant mixture of vitamin C, vitamin E, b-carotene, selenium and methionine with placebo, noting an improvement in serum markers of oxidative stress, but no improvement in pain or quality of life (Siriwardena A, personal communication).

### Unresolved Issues with Antioxidant use in Pancreatitis

There is accumulating data from in-vitro, animal, and now human studies, that oxidative stress plays a role in the pathophysiology of acute and chronic pancreatitis. Furthermore, the antioxidant capacity of patients to respond to this oxidative stress is reduced. Although some clinical studies have shown promise in the use of antioxidant therapy, many questions remain about its use in such patients. Foremost, are the results applicable to patients with CP in the US and other parts of the world? More specifically, the study from Bhardwaj et al. included patients who were primarily young male patients (age 30.5 +/- 10.5 years), nonsmokers, with mostly idiopathic pancreatitis (10). This is quite different from the typical patient encountered in this country (11, 12). Furthermore, what is an appropriate combination of antioxidants? At what point during medical management should antioxidants be introduced and what is an optimal duration of therapy? Finally, some issues have been raised about potential side effects of antioxidants after long-term use. Some studies have

suggested increased cardiovascular risk from long term vitamin E use (13).

### CONCLUSION

Pain management in CP is frustrating and challenging for patients and physicians alike. The cornerstone of initiating management is removal of offending agents such as alcohol and tobacco. A variety of medical therapies can then be tried before resorting to endoscopic and/or surgical management. Many studies have now shown that oxidative stress is important in the pathophysiology of CP and antioxidants have an attractive potential as adjunctive therapy. The overall effectiveness of antioxidants is not known, and the best mixture of agents and dosages is not clear. At the moment, a trial of a mixture of antioxidants containing vitamin C, vitamin E, selenium, and methionine is reasonable as one component of overall medical management. However the dosage and length of therapy is unclear. Further well-designed clinical studies are needed to determine the appropriate combination of agents, time of initiation, and duration of therapy. ■

### References

1. Braganza JM, Lee SH, McCloy RF, et al. Chronic pancreatitis. *Lancet*. 2011;377(9772):1184-97.
2. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatol*. 2008;8(4-5):520-31.
3. Chauhan S, Forsmark CE. Pain management in chronic pancreatitis: A treatment algorithm. *Best Pract Res Clin Gastroenterol*. 2010;24(3):323-35.
4. Tandon RK, Garg PK. Oxidative Stress in Chronic Pancreatitis: Pathophysiological Relevance and Management. *Antioxid Redox Signal*. 2011 Sep 9. [Epub ahead of print]
5. Petrov MS. Therapeutic implications of oxidative stress in acute and chronic pancreatitis. *Curr Opin Clin Nutr Metab Care*. 2010;13(5):562-8.
6. Uden S, Schofield D, Miller PF, et al. Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. *Aliment Pharmacol Ther*. 1990;4(4):357-71.
7. Heaney AP, Sharer N, Rameh B, et al. Prevention of recurrent pancreatitis in familial lipoprotein lipase deficiency with high-dose antioxidant therapy. *J Clin Endocrinol Metab*. 1999;84(4):1203-5.
8. Durgaprasad S, Pai CG, Vasanthkumar, et al. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. *Indian J Med Res*. 2005;122(4):315-8.
9. Kirk GR, White JS, McKie L, et al. Combined antioxidant therapy reduces pain and improves quality of life in chronic pancreatitis. *J Gastrointest Surg*. 2006;10(4):499-503.
10. Bhardwaj P, Garg PK, Maulik SK, et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009;136:149-59.
11. Forsmark CE. Antioxidants for Chronic Pancreatitis. *Curr Gastroenterol Rep*. 2009;11(2):91-2.
12. Romagnuolo J. Postrandomization dropouts and other issues threaten validity of trial results of antioxidants in chronic pancreatitis. *Gastroenterology*. 2009;137(1):391-2.
13. Bjelakovic G, Nikolova D, Gluud LL, et al. Antioxidant supplements for prevention of mortality in healthy subjects and patients with various diseases. *Cochrane Database Syst Rev* 2008 Apr 16;(2):CD007176.