Editorial Commentary

Antioxidant therapy in chronic pancreatitis—promises and pitfalls

Kwang Hyun Ko[1], Jeong Min An[2], Mi Seo Son[2], Jae Bock Chung[3], Ki Baik Hahm[1,2]

[1]Digestive Disease Center, CHA University Bundang Medical Center, Seongnam, Korea; [2]Cancer Prevention Research Center, CHA Bio Complex, Pangyo, Korea; [3]Department of Gastroenterology, National Health Insurance Service Ilsan Hospital, Ilsan, Korea

Correspondence to: Ki Baik Hahm. Professor of Medicine, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam, Korea.
Email: hahmkb@cha.ac.kr.

Provenance: This is an invited article commissioned by the Section Editor Dr. Jia Zhu (Shenyang Pharmaceutical University, Shenyang, China).

Comment on: Singh N, Ahuja V, Sachdev V, *et al.* Antioxidants for pancreatic functions in chronic pancreatitis: A double-blind randomized placebo-controlled pilot study. J Clin Gastroenterol 2019. [Epub ahead of print].

Submitted Apr 11, 2019. Accepted for publication May 17, 2019.
doi: 10.21037/atm.2019.05.46
View this article at: http://dx.doi.org/10.21037/atm.2019.05.46

Chronic pancreatitis (CP) is a progressive, inflammatory disease of the pancreas, in which pathogenesis, oxidative stress led to progressive fibrosis accompanied with pancreatic functional insufficiency and intractable pain, and miserably impended the risk of pancreatic cancer (1,2). In this matter of oxidative stress relevant to CP, Singh *et al.* (3) published the results after randomized controlled trial (RCT) that though antioxidants supplementation increased blood levels of antioxidant in CP, they had no addition benefit over on endocrine and exocrine functions, markers of fibrosis, inflammation, nutritional status, pain, and quality of life (3). In a similar study investigating the efficacy and adverse effects of antioxidant therapy in acute pancreatitis (AP), CP and post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) by Gooshe *et al.* (4) through meta-analysis, there is some evidence to support the efficacy of antioxidant therapy only in AP, whereas its effect on CP and PEP is still controversial. Stimulated with these findings, in this editorial, the assessment of antioxidants in CP was done to put promises and pitfalls of antioxidant therapy in CP.

Antioxidant to tackle the progression to CP

As evidence of promises, our group have published two related papers, one was that novel antioxidant ameliorated the fibrosis and inflammation of cerulein-induced CP (5) and the other was that antioxidative phytoceuticals ameliorated AP (6) and the conclusion was that despite the promise of studies evaluating the effects of antioxidants/phytoceuticals in pancreatitis, translation to the clinic has still far been disappointing. However, it is expected that continued research will provide solid evidence to justify the usefulness of antioxidative phytoceuticals in the treatment of pancreatitis. Though multiple publications have shown some phytoceuticals or antioxidative agent exerted anticipatory results to lessen the progression to CP by virture of their anti-inflammatory and anti-oxidative actions, still overall outcome was still under expectation in clinic (7,8). We speculated that like other disease model, gap exists between the results from experimental animals and human, difference in heart rate, surface area, and exposure time, etc.

Antioxidants to improve pain in CP

As the first study to document long-term outcome of patients with CP treated with antioxidant therapy, Rupasinghe and Sinwardena (9) followed up for up to 10 years in 30 patients with CP with micronutrient antioxidant therapy. Their result was proven to be insufficient except relief of pain. However, the additional evaluation by same research group concluded that antioxidant therapy did not reduce pain in CP caused by alcohol, The ANTICIPATE study concluded that the administration of antioxidants to patients with painful CP of predominantly alcoholic origin does neither reduce pain nor improve quality of life, despite only mild improvement in pain in other type of CP (10). Talukdar *et al.* (11) found the combination of antioxidant and pregabalin rather than

antioxidant alone significantly ameliorated pain recurrence after ductal clearance in CP. Conclusively, since there is no specific therapy for CP and in spite of incomplete evidence, micronutrient antioxidant therapy for relieving painful CP has been recommended for more than 30 years. Cai *et al.* (12) did do meta-analysis to investigate the safety and efficacy of antioxidant therapy for pain relief in patients with CP. Randomized controlled trials showed that nine RCTs involving 390 patients were included, after which strong evidence was obtained that antioxidant therapy seems to be a safe and effective therapy for pain relief in CP patients. Recent advancement in drug formulation of antioxidants, mitochondria-targeted antioxidant SkQ1 treatment significantly showed an analgesic effect (13).

Antioxidants to mitigate fibrosis in CP

Pancreatic fibrosis is essential pathological compartment in CP, leading to pancreatic insufficiency and even carcinogenesis (14). A chronic oxidative stress plays a key role fibrosis noted in CP and perpetuates symptoms responsible to pain, functional derangement, and necrosis, respectively. Since pancreatic acinar as well as stellate cells (PSCs) are implicated in either oxidative stress or fibrosis, antioxidants can mitigate these pathogenesis. In a recent large RCT, it was demonstrated that antioxidant supplementation led to a significant reduction in oxidative stress related to pancreatic fibrosis (15). As RCT to document the changes of fibrosis in CP with antioxidant supplementation, Dhingra *et al.* (16) investigated the effect of antioxidant supplementation on surrogate markers of fibrosis in 61 patients with CP and found that the levels of malondialdehyde, thiobarbiturate acid-reactive substances (TBA-RS), were significantly decreased with antioxidant. As antioxidant in this study, they included ascorbic acid, β-carotene, α-tocopherol, organic selenium, and methionine, which led to significant reduction in pain through relieving pancreatic fibrosis. As antioxidant, some group administered palm oil tocotrienol rich fraction (17) and our group used *Artemisia* extracts (5). Since PSCs play a crucial role in pancreatic fibrogenesis, in which transforming growth factor-β, activin A, and connective tissue growth factor are engaged, vitamin A, vitamin E, polyphenols, taurin, peroxisome proliferator-activated receptor gamma (PPAR-γ) ligands, allopurinol, (-)-epigallocatechin-3-gallate (EGCG) from green tea, and renin-angiotensin system inhibitors are acknowledged as anticipating targets for fibrosis in CP (18). Recently, the author *et al.* extended to study the role of NADPH oxidase (NOX) inhibitor as well as Rho kinase inhibitor to relieve fibrosis in an organoid model established from tissue of CP.

Antioxidants to prevent pancreatic cancer

Very recent publication regarding the antioxidants on cancer prevention, especially pancreatic cancer, Yamagiwa *et al.* (19) showed that pancreatic cancer risk was inversely associated with total fruit intake and positively associated with total vegetable intake, especially in patients with never-smokers, stressing that antioxidant intake significantly reduced pancreatic cancer risk. As much as reactive oxygen species, excessive reactive nitrogen species (RNS) are generated in precancerous pancreas, which can induce massive DNA damage, including DNA double-strand breaks and RNS-induced DNA instability in CP (20), by which efficient suppression of RNS could be an important strategy for preventing pancreatic cancer. Conclusively, the use of antioxidants can prevent formation or progression of precancerous lesions in CP.

Promises and pitfalls—discrepancy between translational research and clinical anticipation

Thought recent publication by Singh *et al.* (3) dealing with the contributory role of antioxidant in CP was not documented in a high evidence based medicine level, there are enough rooms for anticipation of antioxidant therapy in CP. A new mechanistic definition of CP has been proposed including the recent advancement in genetic testing, elastography, and the measurement of pancreatic secretion of bicarbonate, after which the anticipation of the efficacy of antioxidants alone or combination with some combination agent like pregabalin, NSAIDs, simvastatin, and additional endoscopic intervention such as pancreatoscopy-guided intra-ductal lithotripsy is increased (21). As future anticipation, our group is now under active investigation to document the efficacy of low molecular polyphenol such as oligonol (22), oligomerized polyphenol, on CP, open rooms for higher anticipation of efficacy. With advancement of drug formulation or nanotechnology, the final achievement to benefit CP with antioxidants can be done in near future.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Tandon RK, Garg PK. Oxidative stress in chronbic pancreatitis: pathophysiological relevance and management. Antioxid Redox Signal 2011;15:2757-66.
2. Chung JB. Pancreatology. 1st edition. Seoul: Koonja Publishing, 2018:200-375.
3. Singh N, Ahuja V, Sachdev V, et al. Antioxidants for pancreatic functions in chronic pancreatitis: A double-blind randomized placebo-controlled pilot study. J Clin Gastroenterol 2019. [Epub ahead of print].
4. Gooshe M, Abdolghaffan AH, Nikfar S, et al. Antioxidant therapy in acute, chronic and post-endoscopic retrograde cholangiopancreatography pancreatitis: An updated systemic review and meta-analysis. World J Gastroenterol 2015;21:9189-208.
5. Yoo BM, Oh TY, Kim YB, et al. Novel antioxidant ameliorates the fibrosis and inflammation of cerulein-induced chronic pancreatitis in a mouse model. Pancreatology 2005;5:165-76.
6. Park JM, Lee S, Chung MK, et al. Antioxidative phytoceuticals to ameliorate pancreatitis in animal models: an answer from nature. World J Gastroenterol 2014;20:16570-81.
7. Kavitha Y, Geetha A. Anti-inflammatory and preventive activity of white mulberry root bark extract in an experimental model of pancreatitis. J Tradit Complement Med 2018;8:497-505.
8. Xia Y, Xiao HT, Liu K, et al. Resveratrol ameliorates the severity of fibrogenesis in mice with experimental chronic pancreatitis. Mol Nutr Food Res 2018;62:e1700561.
9. Rupasinghe SN, Sinwardena AK. Long-term outcome of patients with chronic pancreatitis treated with micronutrient antioxidant therapy. Hepatobiliary Pancreat Dis Int 2017;16:209-14.
10. Siriwardena AK, Mason JM, Sheen AJ, et al. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. Gastroenterology 2012;143:655-63.e1.
11. Talukdar R, Lakhtakia S, Nageshwar Reddy D, et al. Ameliorating effect of antioxidants and pregabalin combination in pain recurrence after ductal clearance in chronic pancreatitis: Results of a randomized, double-blind, placebo-controlled trial. J Gastroenterol Hepatol 2016;31:1654-62.
12. Cai GH, Huang J, Zhao Y, et al. Antioxidant Therapy for Pain Relief in Patients with Chronic Pancreatitis: Systematic Review and Meta-analysis. Pain Physician 2013;16:521-32.
13. Weniger M, Reinelt I, Neumann J, et al. The analgesic effect of the mitochondria-targeted antioxidant SkQ1 in pancreatic inflammation. Oxid Med Cell Longev 2016;2016:4650489.
14. Ozturk K, Tasci I, Yasar M, et al. Effects of rapamycin treatment on pancreatic fibrosis, cellular apoptosis and oxidative stress in experimental chronic pancreatitis model. Acta Gastroenterol Belg 2015;78:3-7.
15. Bhardwaj P, Yadav RK. Chronic pancreatitis: role of oxidative stress and antioxidants. Free Radic Res 2013;47:941-9.
16. Dhingra R, Singh N, Sachdev V, et al. Effect of antioxidant supplementation on surrogate markers of fibrosis in chronic pancreatitis: a randomized, placebo-controlled trial. Pancreas 2013;42:589-95.
17. González AM, Garcia T, Samper E, et al. Assessment of the protective effects of oral tocotrienols in arginine-like pancreatitis. Am J Physiol Gastrointest Liver Physiol 2011;301:G846-55.
18. Shimizu K. Mechanisms of pancreatic fibrosis and applications to the treatment of chronic pancreatitis. J Gastroenterol 2008;43:823-32.
19. Yamagiwa Y, Sawada N, Shimazu T, et al. Fruit and vegetable intake and pancreatic cancer risk in a population-based cohort study in Japan. Int J Cancer 2019;144:1858-66.
20. Li M, Chen Q, Ma T, et al. Targeting reactive nitrogen species suppresses hereditary pancreatic cancer. Proc Natl Acad Sci USA 2017;114:7106-11.
21. Enrique Domínguez-Muñoz J. Latest advances in chronic pancreatitis. Gastroenterol Hepatol 2016;39:87-92.
22. Kim KJ, Park JM, Lee JS, et al. Oligonol prevented the relapse of dextran sulfate sodium-ulcerative colitis through enhancing NRF2-mediated antioxidative defense mechanism. J Physiol Pharmacol 2018;69. doi: 10.26402/jpp.2018.3.03.

Cite this article as: Ko KH, An JM, Son MS, Chung JB, Hahm KB. Antioxidant therapy in chronic pancreatitis—promises and pitfalls. Ann Transl Med 2019;7(Suppl 3):S115. doi: 10.21037/atm.2019.05.46

