

Role of antioxidants and oxidative stress in the evolution of acute pancreatitis (Review)

VLAD PĂDUREANU^{1*}, DAN NICOLAE FLORESCU^{2*}, RODICA PĂDUREANU³, ALICE ELENA GHENEA⁴, DAN IONUȚ GHEONEA² and CARMEN NICOLETA OANCEA⁵

Departments of ¹Internal Medicine and ²Gastroenterology, University of Medicine and Pharmacy of Craiova, 200349 Craiova; ³Department of Internal Medicine, Emergency Clinical County Hospital of Craiova, 200642 Craiova; Departments of ⁴Bacteriology-Virology-Parasitology and ⁵Analytical Chemistry, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania

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Abstract. Acute pancreatitis (AP) is a severe disease with a high prevalence and 3 to 15% mortality worldwide, which can represent an important challenge for the physician. Oxidative stress and antioxidants are involved in AP progression. The mechanisms responsible for the onset and progression of AP are still poorly understood. Previous studies have highlighted the important contribution of antioxidants and oxidative stress in AP. The existence of a relationship between oxidative stress and antioxidants in AP is unquestionable, although a more accurate understanding of the mechanistic pathways involved is required to create a solid basis for potential prevention or treatment strategies. Further investigation is needed to clarify the role of antioxidant status and the severity of AP and to determine the association between oxidative stress and pancreatic enzyme activities. Antioxidant therapy may represent an interesting option for the management of patients with AP, although additional information about the effectiveness of this potential treatment is required.

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1. Introduction

Acute pancreatitis (AP) is a severe disease which can represent an important challenge for the physician, especially gastroenterologists and surgeons, and has an incidence of 4.6-100/100,000 persons in Europe (1). AP aetiology includes mainly gallstones and excessive alcohol consumption. The mortality varies from ~3% for AP cases with interstitial (oedematous) pancreatitis (1) to 15% for cases with important pancreatic necrosis (2). An international consensus managed to complete a full revision of the Atlanta Classification and definitions (3). This classification identifies two types of the disease, interstitial oedematous pancreatitis and necrotising pancreatitis (3). Inflammation, edema and necrosis of pancreatic tissue are major pathophysiologic processes (4,5). Obstruction of the pancreatic bile duct, pancreatic ischemia, as well as activation of inflammatory cytokines and pancreatic proteases represent the main causes reported in AP (6). An intense inflammatory response (6,7) as consequence of the imbalance between anti-inflammatory mechanisms and pro-inflammatory mediators best describe AP (8,9). The underlying mechanisms of AP pathogenesis remain elusive despite significant progress in the recent years. In addition, no specific therapy exists (4,10). Oxygen radicals play an important role in the development of inflammation in many inflammatory diseases. Previous studies investigated the role of oxidative stress (OS) in AP (11,12). OS appears when there is an imbalance between the antioxidant defence systems and the production of reactive oxygen species (ROS). It is well known that ROS serve numerous important biological functions, including the regulation of redox-sensitive transcription factors, redox-sensitive signal transduction pathways as well as direct interaction with various molecules. Cell damage can be caused by increased oxidative stress either directly or by altering certain signalling pathways.

Correspondence to: Dr Rodica Pădureanu, Department of Internal Medicine, Emergency Clinical County Hospital of Craiova, 1 Tabaci Street, 200642 Craiova, Romania
E-mail: zegheanurodica@yahoo.com

Dr Alice Elena Ghenea, Department of Bacteriology-Virology-Parasitology, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rares Street, 200349 Craiova, Romania
E-mail: gaman_alice@yahoo.com

*Contributed equally

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For example, in biliary pancreatitis, exposure to biliary acid can cause damage of the pancreatic acinar cells, hence promoting cell apoptosis, but not necrosis (13). Oxygen free radicals have been shown to mediate an important step in the initiation of AP in *in vivo* models (11,14).

Depletion of ROS leads to low ATP production and favours necrosis, and increased ROS favours apoptosis. In AP, OS appears to play a dual role (13,14). Excessive production of free radicals has numerous negative effects, although they are also synthesized during normal metabolism (14) and serve many physiological roles, such as in the respiratory chain, during phagocytosis, for prostaglandin synthesis and in cytochrome P450 metabolism. Because AP results in increased synthesis of ROS, this phenomenon may be associated with a protective response (14). Thiol-based redox couples, such as reduced glutathione/glutathione disulfide, cysteine/cystine, thioredoxin-reduced/thioredoxin-oxidized form independent signaling networks that selectively regulate developmental events and are closely linked to changes in intracellular redox potentials (15). In human clinical trials, OS in AP is not entirely defined, and whether increased OS might contribute to disease progression from AP to chronic pancreatitis (CP) (16) remains unknown.

Severe AP is associated with poor antioxidant status (AOS) and with significant mortality (16). Xenobiotics are detoxified in the liver (17). Increased exposure to xenobiotics, including nicotine, alcohol and petrochemical fumes, lead to increased OS (18), and pancreatic acinar cells can be exposed to the harmful effects of these free radicals (19). Increased OS can cause cell damage either directly by destroying the cell membrane, or via toxicity from free radical peroxidation products, or via altered signalling pathways, including redox regulation of genes (20,21). Paraoxonase-1 (PON-1) is an esterase associated with high-density lipoprotein cholesterol (HDL-C), which has the ability to prevent or limit lipid peroxidation (22). Previous studies have reported that PON-1 serum levels are diminished in diabetes, cardiovascular diseases and AP, which is correlated with an increase in OS (22-24). The evaluation of total oxidant status, total AOS and ischemia-modified albumin (IMA) are tests used for the evaluation of increased OS. The production of IMA seems to be associated with the production of ROS (25).

The aim of this review was to identify the role of oxidative stress and antioxidants in patients with AP.

2. Methods

In the present review, we performed a literature search in Pubmed and Scopus databases by using 'acute pancreatitis', in combination with 'oxidative stress' and 'antioxidants' between 1990 and 2020. We included relevant articles and reviews regarding the implication of oxidative stress and antioxidants in the development of AP. Exclusion criteria were as follows: Studies written in other languages than English, letters to the editor, conference presentations, editorials, comments, opinions and articles without free access.

3. Antioxidants and oxidative stress

The mechanisms of AP pathogenesis remain to be fully understood, although the implication of oxidative stress and

inflammatory stress is already known. It is considered that increased oxidative stress cannot lead to pancreatitis by itself (12). Free radicals are thought to play a major role in the development of edema in AP, as prophylactic treatment with antioxidants appears to reduce the formation of pancreatic edema (26). However, the role of free radicals in the pathogenesis of pancreatic necrosis is not yet confirmed (26). In addition, free radicals do not appear to have only negative effects on the pancreas, as previous studies suggested that nitric oxide (NO) radical may even protect the pancreas (14,26,27).

The most frequently used biomarker of oxidative stress in the body is malondialdehyde (MDA), which is one of the final products of polyunsaturated fatty acids peroxidation in the cells, while the main markers of antioxidant defence mechanisms of the body are the activity of the superoxide dismutase (SOD2) and the total antioxidant capacity (TAC), which evaluates the amount of free radical scavengers (16,24,28,29). Additional markers that can be used for assessing the AOS is glutathione peroxidase (GPx) activity, while 4-HNE represent another marker of increased OS in the body (16). Plasma level of MDA is a useful additional marker to appreciate the severity of an episode of AP in the very early stages (30). It has been demonstrated that iron may be one of the factors involved in oxidative damage of tissues. In a previous study, Chand *et al* (31) demonstrated that the interaction between ferritin, hepcidin, interleukin-6 and lipopolysaccharide binding protein can highlight the chronic hyperglycaemia, with some implication in the development of new-onset diabetes after AP. Previous studies suggested that one cause of oxidative stress may be a moderate increase in iron levels in the body (32). Kiziler *et al* (27) demonstrated that in the early stages of AP, there is a positive correlation between iron concentration and MDA level, suggesting that high iron levels and increased oxidative stress might together cause cellular damage. Norberg *et al* (33) demonstrated that normal OS controls the synthesis of regulator of calcineurin 1, and this gene might be considered as a marker for the diagnosis of AP. Increased ROS synthesis leads to mitochondria depolarization, decrease ATP production and apoptosis, thus preservation of mitochondrial function is involved in the enhancement of Ca²⁺ clearance and may decrease the outcome and severity of AP (34).

According to previous studies performed on experimental models of pancreatitis, increased OS is present in AP from the early stage of the disease (35,36). Increased OS is present from the beginning of AP and until the first time of patient hospitalization (37). Circulating concentrations of antioxidant vitamins, such as beta-carotene, vitamin C and vitamin E, are decreased in AP, which are inversely associated with increased C-reactive protein (CRP) levels (38). Antosiewicz *et al* (39) reported in experimental models of AP decrease in vitamin E serum level. Furthermore, the serum concentration of vitamin E might be decreased in patients with PA, and a negative correlation has been demonstrated between the minimum concentration of vitamin E and the maximum level of CRP in patients with AP, suggesting that the severity of inflammation may contribute to the vitamin E status (26). Tsai *et al* (36) reported an association between AP severity and OS. It has been demonstrated that the evolution of AP is characterised by increased lipid peroxidation and reduced glutathione levels and other sulphhydryl compounds in pancreatic tissue (40).

Patients with AP present with elevated blood levels of superoxide radicals and lipid peroxides (LPO) (41). Lipid peroxidation is most likely secondary to pancreatic inflammation but not a cause and may be associated with the intensity of the systemic inflammatory response, rather than the degree of damage to pancreatic tissue (42). Increased OS was observed in the early stages of AP (43). SOD levels and thiobarbituric acid reactive substances (TBARS) levels are significantly higher in patients with AP compared with healthy controls and AOS was demonstrated as poor (43). A favourable evolution of AP was noticed along with the improvement of AOS (43). OS markers and pancreatic enzymes can be used together to evaluate the severity of pancreatitis in AP patients. Higher plasma levels of myeloperoxidases and LPO and lower SOD activity were reported in patients with severe AP compared with those with mild AP (44,45). In the early stages of AP, the oxidant-antioxidant balance changes rapidly and is directly correlated with the clinical severity of pancreatitis (35,46).

Previous studies assessing the plasmatic concentration of free radicals in patients with AP and complicated systemic inflammatory response syndrome reported high levels of LPO and NO and decreased levels of beta-carotene, vitamin E, glutathione and reduced activity of GPx (47,48). Another study reported that free radicals can participate to the pathogenesis of AP and SIRS, and that they could play an important role in assessing the severity of AP (49). However, in AP, NO levels increase and cause the activation of the Nuclear factor-kappa B signaling pathway in the dorsal root ganglia, which further inhibits the expression of the kappa opioid receptor leading to the development of pain. Abu-Zidan *et al* (42) demonstrated that OS markers are positively correlated with the severity of pancreatitis. In addition, AP is characterized by pancreatic glutathione depletion (50,51). Rahman *et al* (51) reported that decreased concentration of glutathione is associated with increased level of its metabolite cysteinyl glycine, which might induce severe AP.

A previous study demonstrated that serum PON-1 undergoes inhibition and proteolysis during pancreatitis (52,53). In severe cases of AP, serum PON-1 activity diminishes significantly (26). In experimental AP, a decrease in PON-1 activity and serum HDL-C level were reported and were negatively correlated with low-density lipoprotein cholesterol and MDA levels, which were both significantly increased (11). Tvarijonavičiute *et al* (53) suggested that PON-1 activity is positively correlated with CRP and triglyceride levels and could be considered as a marker to assess AP severity. Yuksekdağ *et al* (54) demonstrated that the low levels of PON-1, HDL-C, SOD and TAC identified in the early stages of AP started to increase after treatment with analgesics, antibiotics and enteral/parenteral nutrition, as well as insulin dose adjustment for diabetic patients and personal medication for arterial hypertension. Furthermore, the initially elevated MDA concentrations decreased, thus suggesting that PON-1, SOD and TAC might represent potential markers to evaluate the clinical course of the disease.

Oxidant levels may increase significantly in patients with severe AP compared with those with mild AP. AP severity is also positively correlated with the lack of an antioxidant reserve, thus leading to increased OS. An increase in OS combined with antioxidant deficiency seems to be implicated in the pathogenesis of recurrent idiopathic AP (16). It is known

that melatonin plays a role in activating antioxidant enzymes and neutralizing oxygen radicals (55-57). Previous studies that evaluated the serum melatonin in patients with AP reported that the evolution of the disease was milder in patients with increased serum melatonin levels during the 24 h following the onset of AP (58,59).

Pancreatic injury during AP is not only due to oxidants alone (40), although oxidants can affect the inflammatory response after AP onset (12). Antioxidant deficiency can affect initially the pancreatic defence mechanism and can subsequently lead to an increase in oxidants levels (41). It is believed that antioxidant levels decrease during inflammation thus leading to the development of pancreatic lesions from AP. Antioxidant blood levels are decreased during severe AP (42,43), and antioxidant supplements have been shown to prevent these decreases *in vitro* (44,45) and in patients with clinical pancreatitis (35). Previous studies demonstrated that antioxidant treatment may reduce the pain in patients with CP (16,60). Furthermore, antioxidant therapy can also ameliorate extrapancreatic complications, including peritonitis, arterial hypotension and ascites, thus improving the course of the disease (61). Although antioxidant therapy appears to have a favourable effect in CP, a previous study suggested that antioxidant agents would not bring any benefit in AP (14).

At present, antioxidants are not used in the standard treatment of patients with AP, which emphasizes the need for further studies (62). Escobar *et al* (59) reported that oxypurinol combined with pentoxifylline could decrease OS in pancreatic tissue, as oxypurinol protects glutathione from oxidation and pentoxifylline inhibits glutathione depletion. A study by Siriwardena *et al* (28) demonstrated that therapy using selenium, vitamin C and n-acetylcysteine prevents the decrease in antioxidant levels but does not seem to influence the evolution of patients with AP, the period of hospitalization and organ dysfunction. Furthermore, a study suggested that intravenous administration of antioxidants, such as n-acetylcysteine, selenium or vitamin C, to patients with AP with two or more organ dysfunctions may increase mortality. The authors suggested that systemic antioxidant weariness that is usually simultaneous with severe AP is an essential part of the regulatory mechanism that aids the activation of the anti-inflammatory cytokine response (57,58). However, another study suggested that selenium and vitamin C do not seem to have this effect, although further investigation is required (63). Uden *et al* (62) evaluated the effect of administering vitamin C, vitamin E, beta carotene, selenium and methionine on recurrent pancreatitis and demonstrated that patients receiving the antioxidant therapy did not suffer a recurrent attack during the follow-up period and suffered from less pain compared with patients receiving the placebo. Although it was reported that antioxidant therapy might have favourable effects in cases of spontaneous AP, this therapy does not appear to influence post-endoscopic retrograde cholangiopancreatography AP.

4. Conclusions

Although multiple studies have demonstrated the important role of increased OS in the pathophysiology of CP, the association between AP and OS requires further investigation, as numerous contradictory results still exist. In the literature,

there are few clinical studies about the implication of antioxidants in the mechanisms of AP. Future studies must investigate the association between increased OS and the activity of pancreatic enzymes. The inflammatory process and the severity of AP may be closely associated with oxygen-derived free radicals. Future studies are required to clarify the link between the AOS and the severity of AP. One good marker for determining the severity of the disease is the plasma level of LPO. Assessment of GPx, 4-HNE and ferric reducing ability of plasma may be considered as useful biological markers in cases of idiopathic recurrent AP.

The AOS is deficient and OS is increased in patients with idiopathic recurrent AP. In these patients, one therapeutic option may be the supplementation in antioxidants, as previous studies suggested that this therapy might prevent the development of CP. However, although this antioxidant therapy represents an exciting option for the treatment of patients with AP, further evaluation of its effectiveness is required.

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VP, DNF, RP, AEG, DIG and CNO contributed equally to the acquisition, analysis and systematization of data, manuscript writing and critical revision of it for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patients consent for publication

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Competing interests

The authors declare that they have no competing interests.

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