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Editorial

Oxidative stress and acute pancreatitis

Acute pancreatitis (AP) is a pancreatic inflammatory condition characterized by abdominal pain and increased pancreatic enzyme levels in the blood and urine, with its diagnosis relying on these two premises. Regardless of its trigger, once active the process enters the common pathway of the local and systemic inflammatory response, and severity depends on response intensity (1).

The relevance of AP depends not only on potential complicated outcomes but also its high frequency –in our country an incidence of 15,000 new cases yearly was estimated, but it should be highlighted that 3.5-19% of cases experience no pain, and 13-42% are only diagnosed in necropsy studies (2). Clinical course is usually benign, and clinical signs and symptoms, as well as amylasemia/amylasuria levels, decrease within a few days; however, around 20% of cases develop complications both at the local and systemic levels, with pancreatic necrosis being most common and relevant (a good correlation exists between necrosis extent and patient outcome). AP-related mortality still affects around 10% of patients; half of deaths occur during the first two weeks, usually related to distributive shock and multiple organ failure syndrome; the rest occur later in the course of the disease and result from complications related to the development of pancreatic necrosis and its complications.

The pathophysiology of AP is complex and involves several inflammatory pathways. The initial trigger is the activation within the pancreatic parenchyma of various proteolytic enzymes, usually promoted by the presence of bile and duodenal contents inside pancreatic ducts. Severe forms also exhibit a disbalance in the protease-antiprotease system, which activates the complement system with release of factor C5a, which in turn stimulates macrophage and neutrophil recruitment; this further promotes intraperitoneal inflammation and cytokine activation via transcription factors such as nuclear factor kappa B (NFκB). The release of activated cytokines involves both proinflammatory (tumor necrosis factor, interleukins IL-1, IL-6 and IL-8, and platelet-activating factor) and antiinflammatory (interleukins IL-2, IL-10 and IL-11) cytokines. Other mediators involved include arachidonic acid metabolites (prostaglandins, platelet-activating factor, and leukotrienes), nitric oxide, various proteolytic and lipolytic enzymes, and reactive oxygen metabolites, which overcome the clearing capacity of endogenous antioxidant systems. The most powerful oxygen metabolite released by leukocytes is ClOH, whereas polymorphonuclear elastase is the most destructive enzyme released (3,4). Finally, acinar damage induces the expression of endothelial adhesion molecules such as VCAM-1 (vascular cell adhesion molecule), which further amplifies the inflammatory response (5) and results in a vicious circle that determines a widespread involvement of the vascular endothelium, which in turn results in vasodilation, increased capillary permeability and interstitial edema. In fact, in most serious cases the inflammatory process is similar to that of serious sepsis, which leads to mul-

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tiple organ failure and death. Furthermore, as is the case with sepsis, where genetic polymorphisms for some cytokines are associated with prognosis, the study by Rahman et al. (6) suggests that the former impact on glutathione levels in acinar cells, and may increase oxidative stress and worsen PA.

In addition, the understanding of the role oxygen metabolites play in the inflammatory process has clearly improved in recent years. Free oxygen radicals apparently regulate necrosis extent in acinar cells, the development of pancreatic edema, inflammatory cell sequestration within the pancreas, and the release of inflammation mediators from both acinar and non-acinar cells in the pancreas and lungs. Several papers show a decrease in plasma antioxidant levels (total ascorbic acid) and an increased release of lipid peroxidation byproducts both in patients with AP and experimental models. The body has a number of free oxygen radical-clearing systems, both enzymatic (superoxide dismutase, catalase, myeloperoxidase, and glutathione peroxidase) and non-enzymatic (carotenes, ascorbic acid, tocopherol) (7). Uric acid, albumin and ascorbic acid represent over 85% of the antioxidant capability of human plasma. Other elements present in a lower proportion include bilirubin, α-tocopherol, β-carotene, tryptophan, tyrosine and selenium. We may wonder which antioxidant is most relevant. The answer is dependent upon the conditions extant in a specific microenvironment at a given time, and the type of oxidative situation. Thus, the antioxidant defense system represents a complex network with interactions, synergisms, and specific actions on a given oxidant (8).

A number of studies in both animal models and human beings have analyzed the association between oxidative metabolism and pancreatic inflammation. Studies in laboratory animals suggest that pancreatic oxidative stress occurs in early stages following induction. Treatment with antioxidant agents has been seen to reduce acinar cell damage and edema in several animal models. This suggests that ongoing free oxygen radical formation reduces antioxidant defensive systems in cells. Regarding the role of bradykinin and nitric oxide, there is controversy in that on the one hand they seem to relieve pancreatic dysfunction by strengthening vascularization and its secretory capacity while on the other there is the notion that nitric oxide may enhance oxidative stress (9). Human patients with mild AP exhibit significantly higher levels of antioxidants (retinol and β-carotenes) when compared to severe cases. An inverse relationship between C-reactive protein and antioxidant levels has also been seen.

Among oxygen-derived metabolites several studies have shown that malondialdehyde (MDA), a substance derived from unsaturated fatty acid peroxidation and cell membrane oxidative breakdown, as measured by the formation of thiobarbituric acid reactive substances, is correlated to AP severity. Thus, different investigators have analyzed MDA levels in the early stages of both serious and mild acute pancreatitis with conflicting results (10-15). The measurement process is key to differentiate true MDA levels from those of other thiobarbituric acid reactive substances, as pointed out by Hernández et al. (16) in their paper published in this issue of the Spanish Journal of Gastroenterology. Researchers use a high-resolution liquid chromatography system to measure free serum MDA levels. Thus they analyze MDA levels in their series of 169 patients with early pancreatitis *versus* 20 healthy volunteers. MDA levels at 24 and 48 hours were higher in patients with mild or severe pancreatitis than in control subjects, but this difference disappears at 96 hours. On the other hand, MDA levels do not differ between patients with pancreatitis according to severity, in contrast to other papers where thiobarbituric acid levels are measured (10,12,13,17). The study results are partly as expected –patients with acute pancreatitis exhibit higher MDA levels as compared to healthy controls, similar to what would have happened should

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amylasemia be measured. However, doubt remains about the way MDA levels would behave not in healthy controls but in patients with an acute abdominal condition, including mesenteric ischemia, acute intestinal inflammation bacterial infection, etc. On the other hand, this substance measurement does not differ between more and less severe forms of acute pancreatitis, which –new studies pending– would go against a future use of MDA as a prognostic factor in these patients.

Biochemical changes during early-stage AP represent a critical fact of key significance for prognosis. Hence many authors posit the presence of a window period where all measures intended to control and modulate inflammation may improve the final result as inferred from this interesting paper by Hernández et al. (16), even though the attribution of an initial tissue damage mechanism to free oxygen radicals is difficult to establish given that patients usually delay their seeking help and are seen when these pathogenic mechanisms for acinar cell damage are already ongoing. Besides their pathophysiological involvement at process onset, they may also be generated and contribute to progression.

If oxidative stress plays a significant role in the pathophysiology of AP, particularly of severe cases, the role of antioxidant agents in the management of this disease remains to be elucidated. Several studies have attempted to demonstrate the potentially beneficial effect of antioxidant agents for AP in terms of severity, prognosis, and hospital stay, although to date no conclusive results have been obtained to support their regular use, and hence they are not included in any guidelines for the management of this condition. In these papers the use of patient inclusion criteria based on time since symptom onset, time of antioxidant treatment onset, and type of drugs used might well account for the untoward findings obtained. New multicenter studies may in the future provide more accurate information on the benefits potentially derived from their use (18-21).

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