Chapter 3

Do Elderly Patients with Acute Pancreatitis Need a Special Treatment Strategy?

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1. Introduction

Acute pancreatitis(AP) in spite of thousands of experimental and clinical studies remains a disease with significant impact in many countries being one of the most common gastrointestinal diseases requiring hospital admission in the United States[1]. Although the overall mortality in AP patients is about 5% in severe AP is increasing up to 25 [2] mainly in elderly people [3]

The aging process is believed to influence the course and outcome of AP. Indeed, AP in elderly patients is associated with high morbidity and mortality [4]. Although Frey at al [5] have related the presence of comorbidities in elderly patients to their increased mortality, others consider advanced age to be an independent prognostic factor in AP [6].

The mechanisms underlying the increased severity of AP in elderly patients are not completely understood. Possibilities include the presence of a proinflammatory status in older people [7] or organ-specific alterations that may contribute to increased systemic inflammation in AP. The lungs are particularly affected in AP, releasing a second wave of inflammatory mediators that may increase systemic inflammation in older patients [8].

2. Aging and systemic inflammation

Cytokine production in elderly patients with sepsis is higher than in young people [9]. We have observed that old people sometimes have a smooth initial postoperative course, followed

by an increased inflammatory response that may have catastrophic outcomes. Delayed explosive levels of interleukin (IL)-6 have been observed in elderly patients after surgery [10].

A recent report also demonstrated that the production of tumor necrosis factor (TNF)-α, IL-1β or IL-6 in the lung cells of older subjects after exposure to lipopolysaccharide occurs relatively late, but remain sustained when compared to lung cells from young subjects [11]. Monocyte activation and hypercytokinemia have also been observed in elderly patients after surgical procedures [12] and *in vitro* studies have demonstrated that mitogen-stimulated peripheral mononuclear cells from the elderly produce higher levels of TNF-α, IL-6, and IL-1 when compared to young subjects [13]. All these findings support the concept that aging affects the immune system and promotes inflammation that is also associated with metabolic dysfunctions [14].

3. Molecular mechanisms of the proinflammatory status related to aging

The molecular mechanisms involved in the proinflammatory condition of aged people are still poorly understood, but inflammatory genes dysregulation may be involved in the process.

The potential role of the poly(ADPribose) polymerase-1 gene in inflammation and in the aging process has been reported [15].

Higher splenic expression of toll-like receptor-4 and CD14 were also demonstrated in older animals with sepsis when compared with young animals [16]. In this report, an increased 2A adrenergic receptor and phosphodiesterase in older animals was also found. It was concluded that in old animals the proinflammatory status is related to the innate immune response and to the upregulation of the adrenergic autonomic nervous system that also may contribute to the increased proinflammatory cytokine production [16].

Besides the proinflammatory condition in aging animals with acute pancreatitis, an increase in plasma concentration of plasminogen activator inhibitor-1, a primary inhibitor of the fibrinolytic system, has been shown in experimental pancreatitis resulting in increased extra pancreatic thrombosis [17].

We are currently evaluating the differential gene expression in older patients with sepsis compared to young patients. Recently, the important role of adipose triglyceride lipase (ATGL) activity in the increased inflammatory status related to the aging process has been reported [18]. Reduction of ATGL in aging animals is related to the increased inflammatory status in these animals [18]. However, the mechanism by which ATGL modulates the production of inflammatory mediators is still unknown.

4. Acute pancreatitis in the elderly population

The mortality rate in elderly patients is significantly higher than in younger patients(21.3 % vs 5.9%) [6].Recent clinical study also reported that elderly patients with severe acute

pancreatitis have significant higher mortality rates than younger patients (17.0% vs 5.3%) [20].We have observed similar findings in our own experience. Although no differences in local complications in acute pancreatitis between young and elderly people have been observed, the increased mortality that occurs with aging is related to increased rates of organ failure [19–21].

The mechanisms underlying this increased distant organ failure and mortality associated with aging is not completely understood. However, possible explanations include the increased inflammatory response, worsened organ response to injury, or increased bacterial translocation with increased systemic injury.

Recently, it was reported that there is a loss of pancreatitis-associated proteins with aging. These are a group of innate pancreatic proteins with a protective effect, that are induced in the process of AP and that are related to the increased severity of acute pancreatitis in the aging population [22].

However in elderly patients with AP, there is a similar occurrence of local complications associated with a significant increase in multiple organ failure when compared to young patients [20].

It is well established that older patients are more susceptible to infections in surgical procedures, probably related to an exaggerated inflammatory response after surgery that can be attributed to the proinflammatory status of older people [23].

It is conceivable that in surgical procedures and in acute pancreatitis, bacterial translocations due to increased intestinal damage may be the underlying process that increases distant organ failure. Intestinal fatty acid binding protein (IFABP) is a 15-kd protein located at the tips of intestinal mucosal villi usually undetected in plasma circulation. Recently it has been shown that IFABP is a specific marker of gut epithelial dysfunction in clinical cases of acute pancreatitis and a useful marker of the severity of the disease [24]. In our laboratory we also demonstrated in an experimental model of acute pancreatitis that plasma levels of IFABP are correlated with bacterial translocation (unpublished data).

In fact we have demonstrated increased intestinal damage, evaluated by plasma levels of ileal fatty acid binding protein in an experimental model of acute pancreatitis in aging animals when compared to young animals. This increased intestinal damage was followed by increased bacterial translocation and pancreatic infection in old animals (unpublished data; Figs 1, 2 and 3).

This increased bacterial translocation in older animals when compared to young ones was associated with an increased systemic damage characterized by increased pulmonary myeloperoxidase, and increased serum levels of liver enzymes, creatinine and glucose.

We also demonstrated that expression of intestinal proinflammatory cytokines genes is increased in aging animals with acute experimental pancreatitis. This increased intestinal inflammatory process may be related to the intestinal damage observed in the elderly animals.

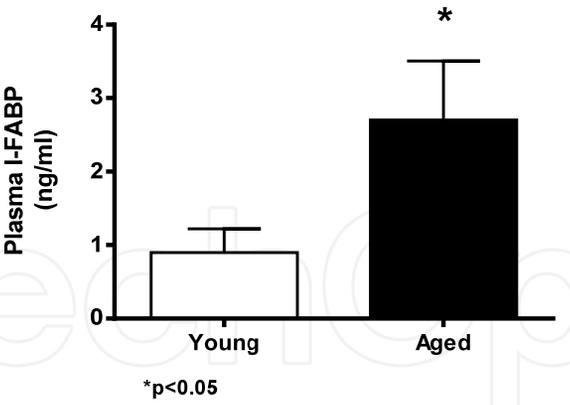

Figure 1. Plasma ileal fat acid binding protein levels.

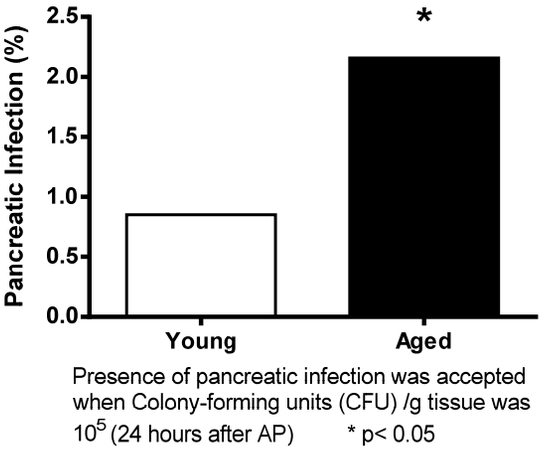

Figure 2. Pancreatic infection.

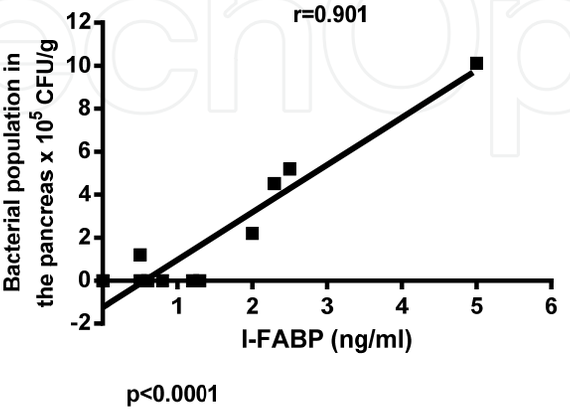

Figure 3. Correlation between plasma fat acid binding protein levels and bacterial translocation.

This concept is supported by the observation that administration of anti-platelet-activating factor reduces the bacterial translocation in a model of acute pancreatitis [25]. It is therefore possible that the reduction in the increased intestinal inflammatory process may decrease bacterial translocation and the systemic damage observed in aged patients.

Finally, we have been studying the role of antimicrobial peptides in aging. Surprisingly, we found that the production of alpha-defensin-5 is increased in the ileum of old rats when compared to young rats in an experimental model of acute pancreatitis (manuscript in preparation). This finding goes against the prevalent hypothesis that the elderly are immunosuppressed compared to the young. Antimicrobial peptides are ancient weapons of innate immunity. Despite their killing properties, a wide variety of cellular responses is affected by these molecules. Antimicrobial peptides are largely distributed in nature, being found in protozoa, prokaryotes, invertebrates, vertebrates and plants. Further research is necessary to understand the molecular pathways triggered by antimicrobial peptides during AP– whether they are produced to attack bacteria that invade the bloodstream, as a result of bacterial translocation, or are merely coordinating the innate immune response during sterile systemic inflammation.

5. Special treatment strategy

Our current knowledge indicates that we need new strategies to reduce the exaggerated inflammatory response in elderly patients with AP.

Previous reports from our group have shown that in experimental AP, peritoneal lavage [26], administration of hypertonic saline solution [27], use of platelet-activating factor antagonists [25], and administration of pentoxifylline [28] reduce the inflammatory response in acute pancreatitis in young animals. We are now investigating if these strategies are also effective in old animals.

Since bacterial translocation is increased in acute pancreatitis in aging animals with increased distant organ damage it is conceivable that different therapeutic strategies should be used in aged patients with acute pancreatitis. More liberal utilization of hemofiltration or even peritoneal lavage [26,29] may decrease the plasma level of cytokines and therefore minimize the systemic damage induced by these substances.

We agree with recent guidelines [30] that do not recommend the use of prophylactic antibiotics in patients with severe acute pancreatitis. However, in elderly patients antibiotics may not be prophylactic.

Recent experimental studies including ours (Fig 1) have demonstrated an increased bacterial infiltration in pancreatic tissues in acute pancreatitis in old animals [22].

Early antibiotic treatment in these patients may reduce the effect of increased bacterial translocation and the systemic inflammatory response may therefore decrease the age-related mortality in acute pancreatitis.

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