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MINIREVIEWS

Pancreatic injury in patients with septic shock: A literature review

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Abstract

Sepsis and septic shock are life threatening condition associated with high mortality rate in critically-ill patients. This high mortality is mainly related to the inadequacy between oxygen delivery and cellular demand leading to the onset of multiorgan dysfunction. Whether this multiorgan failure affect the pancreas is not fully investigated. In fact, pancreatic injury may occur because of ischemia, overwhelming inflammatory response, oxidative stress, cellular apoptosis and/or metabolic derangement. Increased serum amylase and/or lipase levels are common in patients with septic shock. However, imaging test rarely reveal significant pancreatic damage. Whether pancreatic dysfunction does affect the prognosis of patients with septic shock or not is still a matter of debate. In fact, only few studies with limited sample size assessed the clinical relevance of the pancreatic injury in this group of patients. In this review, we aimed to describe the epidemiology and the physiopathology of pancreatic injury in septic shock patients, to clarify whether it requires specific management and to assess its prognostic value. Our main finding is that pancreatic injury does not significantly affect the outcome in septic shock patients. Hence, increased serum pancreatic enzymes without clinical features of acute pancreatitis do not require further imaging investigations and specific therapeutic intervention.

Key words: Septic shock; Pancreas; Lipase; Amylase; Prognosis

Core tip: Pancreatic injury is common in septic shock patients. Tissue hypoperfusion is the main leading cause of pancreatic insult. Other factors such as oxidative stress

and cellular apoptosis have been reported to enhance the pancreatic damage. The clinical relevance of increased level of pancreatic enzymes is not well established. In fact, hyperamylasemia and/or hyperlipasemia are not associated with higher mortality. Moreover, most of the imaging investigations do not show significant morphological changes of the pancreas. Hence, disturbed serum pancreatic enzymes without clinical evidence of acute pancreatitis should not trigger any specific therapy.

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INTRODUCTION

Severe sepsis and septic shock are common life-threatening conditions in critically-ill patients[1-3]. Despite recent therapeutic advances and the establishment of internationally accepted guidelines regarding the management of patients suffering from septic shock, the overall mortality in these patients ranges from 30% to 60%[2,4,5]. This high mortality is usually associated with the onset of multiple organ dysfunction. In fact, a few studies have reported that the worsening of organ function as well as the increase in the number of the failing organs is significantly associated with poor outcome in both adult and pediatric patients[6,7]. Accordingly, it has been reported that the onset of acute kidney injury is associated with a significant rise in the intensive care unit (ICU) mortality up to 50%-70% and that the highest mortality has been in patients with a high score on the severity of illness scale and/or in those who require renal replacement therapy[2,8-10]. Similarly, hypoxic liver injury in patients with septic shock has been reported to be associated with a mortality as high as 50%[11,12]. Experimental and clinical studies also suggest that gut ischemia is one of the hallmarks of septic shock[13-15]. However, whether pancreatic exocrine function is also impaired in septic shock patients has not been fully investigated. Moreover, there is still debate regarding the optimum modality for management of pancreatic insult as well as its prognostic value.

The aim of this review is to describe the epidemiology and the physiopathology of pancreatic injury in septic shock patients, to clarify whether it requires specific management and to assess its prognostic value.

RESEARCH

A systematic literature search was conducted through Pubmed by using the following Medical Subheadings terms: Septic shock, sepsis, lipase, amylases and acute pancreatitis. Different Boolean operator combinations (AND/OR) were attempted. Overall, 97 articles were selected for this review. We didn't proceed to any language restriction and only the studies published between 1996 and 2016 were considered.

EPIDEMIOLOGY OF PANCREATIC INJURY IN SEPTIC SHOCK

The incidence of pancreatic injury in critically-ill patients is extremely variable according to the used definition. High levels of amylase levels have been reported in 32% to 79% of patients admitted in medical or surgical ICUs[16-19]. However, most of these studies have concluded that this elevation is not always due to pancreatic insults[16-18]. In fact, the proportion of non-pancreatic isoamylase in patients with hyperamylasemia has been reported to range from 30% to 74% of the total serum amylase[16,18]. Hence, other markers have been used to assess the exocrine pancreatic dysfunction in critically-ill patients. Lipase is one such marker which is more specific for the diagnosis of pancreatitis[20]. Similar to hyperamylasemia, increased lipase serum level is also common in critically-ill patients. In fact, Manjuck *et al*[21] reported that hyperlipasemia is found in 40% of the patients requiring ICU admission. Similarly, Denz *et al*[19] reported increased serum lipase levels in 57% of critically-ill patients. Recent guidelines have highlighted that the rise of one or both of these two enzymes should be higher than three times the upper limit of normal range to be considered as a useful criterion for acute pancreatitis[22]. However, only a limited number of patients admitted to the ICU with a diagnosis other than pancreatitis fulfill this definition[23] and/or have significant morphological changes in pancreatic anatomy on imaging tests[19,21]. Only a few studies have focused on the exocrine pancreatic dysfunction in the subgroup of critically-ill patients with septic shock[23-25]. Hence, epidemiological data regarding the pancreatic function impairment in this group of patient is lacking.

PHYSIOPATHOLOGY OF PANCREATIC INJURY IN SEPTIC SHOCK

The pathophysiology of pancreatic injury in septic shock patients is not fully understood. The most commonly accepted hypothesis is pancreatic ischemia[26,27]. However, few experimental and human studies have suggested that other mechanisms might also be involved such as cell apoptosis[28,29], increased release of nitric oxide by the endothelial cells[30], platelets activation[31], ischemia - reperfusion phenomenon[32], elevated triglyceride levels and the development of biliary sludge[33].

Pancreatic ischemia

Severe hypotension and tissue hypoperfusion are the main hallmarks of septic shock[34,35]. Experimental studies have shown that gut perfusion is severely impaired in the early stages of septic shock[14,36]. In a porcine model of septic shock caused by fecal peritonitis, Ijungdahl *et al*[14]

have reported that the oxygen consumption of the gut, including that of pancreas, is markedly increased in this condition. This is accompanied by a significant decrease in the gut intramucosal pH which occurs even before the lactate rises in the arterial blood. The pancreas is particularly sensitive to hypotension. In fact, a temporary ischemia for 40 min has been shown to be sufficient to cause significant pancreatic injury on histological examination, presenting mainly as peripheral necrosis of the lobules[37]. Several studies have suggested that the impairment of pancreatic perfusion is more pronounced in septic shock. In fact, in an experimental animal model study, Raper *et al*[26] reported that the cardiac output is increased during the hyper dynamic phase of septic shock. Concomitantly, the systemic blood flow is increased in the gallbladder and the colon whereas it is markedly decreased in the pancreas. This demonstrates that the oxygen delivery to the pancreatic cells is significantly decreased despite the considerable increase of their oxygen requirement[26].

Beside these macro-circulatory abnormalities, pancreatic injury related to septic shock can also be explained by micro-circulatory and cellular dysfunctions[38]. In fact, severe sepsis and septic shock are commonly associated with coagulation abnormalities, usually manifested as disseminated intravascular coagulation[39,40]. Several forensic studies have reported ischemic and necrotic changes in various organs. These include occlusion and fibrin deposition in small and mid-size vessels, observed in patients who die from septic shock[41]. These abnormalities are triggered mainly by an overwhelming inflammatory reaction which is orchestrated by the immune host defense in response to the endotoxinic aggression[34,39]. The expression of the tissue factor by the mononuclear, polymorphonuclear and endothelial cells activates the coagulation cascade[42,43]. Activation of platelets, down-regulation of anticoagulant pathways and reduced fibrin removal due to inhibition of fibrinolysis enhances microvascular thrombosis[39]. Experimental studies have shown that the pancreatic microcirculation is deeply disturbed in septic shock. In fact, in a model of fecal peritonitis, Hiltebrand *et al*[27] reported that the microcirculatory flow is reduced by 50% in various splanchnic organs within 240 min. The flow normalizes after fluid resuscitation in all the organs, except in the pancreas.

Although the most widely accepted hypothesis used to explain pancreatic dysfunction in patients with septic shock is pancreatic ischemia, significant pancreatic injury has also been reported in normotensive sepsis model. This suggests that other mechanisms may also be responsible for causing pancreatic ischemia[44].

Cellular apoptosis

Delayed and inappropriate management of septic shock is associated with a worse outcome due to multiple organ dysfunction syndrome (MODS)[45-48]. The main cause of MODS in this condition is the uncontrolled inflammatory storm caused by overwhelming host immune response[49]. Beside the deleterious effect of this reaction on the macrocirculation and microcirculation, as described above, the pro-inflammatory cytokines-mainly interleukine (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α - also activate the NF-κB pathway. This causes cellular self-destruction and apoptosis[50]. This has been demonstrated in the hepatocytes and the immune cells with severe Gram-negative bacterial infection[50,51]. Experimental studies have shown that the exposure of pancreatic cells to lipopolysaccharide is associated with apoptosis and increased release of TNF-α, IL-1β and IL-8. Damage to the Acinar cells consists of nuclear fragmentation, abnormal cytoplasmic vacuoles and cellular swelling[28,29,52,53]. Unlike these experimental studies, there is no evidence to suggest that apoptosis is a major cause of exocrine pancreatic dysfunction in patients suffering from septic shock. In fact, histological studies performed in patients who died from septic shock and multiorgan failure have shown that the apoptosis of acinar cells is seen only in a scattered manner[54].

Other mechanisms

Other hypothesis that may explain pancreatic injury in patients suffering from septic shock.

The oxidative stress: Oxidative stress has been demonstrated in patients suffering from septic shock patients[55]. The main causes of mitochondrial dysfunction and increased release of reactive oxygen species are ischemia/reperfusion phenomenon and inflammation[55,56]. Other factors, such as the activation of the phagocytic cells and the production of nitric oxide by the endothelial cells, have been shown to aggravate the oxidative stress[57]. The cellular damage in sepsis is enhanced by the depletion of antioxidants and scavenger enzymes such as glutathione and thiamine in the plasma[56,58]. Several studies have suggested that the oxidative stress can induce pancreatic damage in septic shock[32,59].

Triglycerides: Serum triglyceride level has been reported to be significantly increased in septic shock[60,61]. Moreover, compared to those patients who survived septic shock, patients who died from it have been found to have a higher serum triglyceride level over the first 7 d of their illness[62]. Whether the high level of serum triglyceride seen in patients with septic shock is enough to induce pancreatic cell damage need to be investigated.

CLINICAL RELEVANCE OF PANCREATIC INJURY

The clinical relevance of increased amylase and/or lipase in patient with septic shock has been poorly investigated. Whether pancreatic injury is only a satellite phenomenon or a major condition affecting the prognosis of this group of patients is still a matter of debate. In fact, only a few studies, most of them with a small number of patients, have investigated pancreatic dysfunction in critically-

ill patients[19,21,23-25,44]. Pezzilli *et al*[23] have reported that amylase and lipase levels are significantly increased in patients with septic shock in comparison to a control group. However, none of the included patients met the criteria of acute pancreatitis and no significant correlation was found with mortality. These findings have been corroborated by post-mortem pancreatic tissue sample examination which has not shown significant morphological changes[24].

Available data suggest that imaging tests should not be requested for all critically-ill patients with deranged pancreatic enzymes as long as the clinical assessment does not suggest acute pancreatitis. In fact, Denz *et al*[19] reported that contrast enhanced computed tomography performed for all patients with a serum lipase level higher than 450 U/L was positive only in 35% of the patients. None of these patients had severe necrotizing pancreatitis which required specific management. However, the authors have reported that imaging abnormalities are more common in patients with increased blood levels of pancreatitis-associated protein. This raises the question: Which marker can be considered as a reliable test to assess the pancreatic dysfunction?

Even though the available data shows that the increase in the levels of pancreatic enzymes does not affect the mortality in critically-ill patients, the pancreatic dysfunction may cause malnutrition in patient with prolonged stay in intensive care units. In fact, the pancreatic secretory function is important for the digestion and absorption of fats, protein and carbohydrates[63]. In a prospective cross-sectional study of 563 critically-ill patients, Wang *et al*[64] reported that the prevalence of exocrine pancreatic insufficiency in these patients is 52.2% although only 34.9% of these patients had increased serum lipase levels and only 30.2% had increased serum amylase levels. The definition of exocrine pancreatic insufficiency in their study was based on decreased fecal elastase-1 concentration (< 200 mcg/g). The authors have also found that both shock and sepsis are independent factors which predict exocrine pancreatic insufficiency. Tribl *et al*[25] have reported similar results as they found that the concentration of amylase and chymotrypsin in the duodenal juice is significantly lower in patients with sepsis or septic shock than in healthy volunteers. Moreover, the concentration of trypsin is significantly lower in septic shock patients than sepsis patients without shock. The therapeutic implications of these findings need to be investigated by further studies.

CONCLUSION

Pancreatic injury is common in patients suffering from septic shock. Increase in levels of pancreatic enzymes does not significantly affect the outcome. Only those patients who show clinical features of acute pancreatitis need to undergo further radiological investigations. However, pancreatic dysfunction may affect the nutritional state of patients receiving enteral feeding and requiring prolonged ICU stay. Whether specific treatment should be considered to avoid malnutrition in these patients need to be investigated further.

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