Progress in Pathogenesis of Pancreatitis with Acute Kidney Injury

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DOI: 10.32629/jcmr.v5i1.1795

Abstract: Acute pancreatitis (AP) is a common gastrointestinal disease. About 20% of patients with acute pancreatitis develop severe acute pancreatitis, often with multiple organ dysfunction and poor prognosis. In the process, about 10% of patients develop acute renal injury (AKI). Acute renal injury (AKI) is a major complication of severe pancreatitis with a case fatality rate of up to 75%. AP associated AKI (AP-AKI) has both common and significant differences from other AKIs associated with intensive care. Although its pathogenesis is not clear, systemic and regional inflammatory responses play a key role. Early detection, early and effective support and pathogen treatment can significantly improve the results.

***Keywords*:** acute kidney injury, acute severe pancreatitis, pathogenesis

1. Introduction

Acute pancreatitis (AP) is a common gastrointestinal disease. About 20% of patients with acute pancreatitis develop severe acute pancreatitis, often with multiple organ dysfunction and poor prognosis.[1, 2] In the process, about 10% of patients develop acute renal injury (AKI). Acute renal injury (AKI) is a major complication of severe pancreatitis with a case fatality rate of up to 75%.[3]

AP associated AKI (AP-AKI) has both common and significant differences from other AKIs associated with intensive care. Although its pathogenesis is not clear, systemic and regional inflammatory responses play a key role. Early detection, early and effective support and pathogen treatment can significantly improve the results.[4]

2. Epidemiological characteristics

About 7% to 20% of patients report acute kidney damage. In some critically ill patients, the incidence may rise to 50 percent, significantly increasing patient mortality[5, 6]. The exact incidence of AKI in patients with acute pancreatitis has not been documented. Although the existing studies are mostly small sample, retrospective study. However, there is a lack of prospective studies on AKI.

Studies have shown that patients with acute pancreatitis associated with AKI have between 25% and 75% mortality. Elderly, male, sepsis, respiratory failure, ICU, and chronic kidney disease are risk factors for AKI.[7]

3. Pathogenesis

Because of clinical difficulties in accessing the pancreas for direct intervention studies or biopsies. At present, the pathophysiology of SAP-induced AKI has been studied mainly through animal models.[8, 9] According to the existing relevant studies, we know that AKI and SAP have similar pathophysiological mechanisms. acute kidney injury (AKI) occurs in patients with severe acute pancreatitis (SAP) by multiple pathways. Clinically, AKI can be classified as prerenal, renal, and retrorenal. [10]Due to the complexity of SAP, the pathogenesis of SAP-related AKI includes prerenal, renal and postrenal, and its specific pathogenesis includes intestinal barrier injury, systemic inflammatory response, hypoxemia, pancreatic and pancreatic amylase release, intraperitoneal high pressure and hypovolemia, which lead to direct renal tubular injury or renal hemodynamic changes. Other factors such as endotoxins and reactive oxygen species also play an important role in the pathophysiology of SAP-associated AKI. [11]The pathogenesis of metanephric injury in SAP is not well understood, so there is no effective treatment for AKI. Therefore, it is very important to explore the pathogenesis of SAP-induced AKI, which may be helpful to reduce the mortality of patients and improve the related prognosis. The following is a summary of the pathogenesis of SAP-induced AKI based on existing relevant studies.

3.1 Intestinal barrier dysfunction

The intestinal mucosal barrier is an important immune defense system and initiator of multiple organ failure (MODS). [12, 13]Intestinal mucosal injury is closely related to the release of inflammatory mediators and SIRS caused by endotoxin translocation. Intestinal mucosal barrier is the key link of SAP distal organ damage. In SAP, the inflammatory factor TNF - α

(TNF - α) is overexpressed, causing damage to the intestinal mucosal barrier, which in turn causes the intestinal mucosal immune response[14]. Secondly, patients with severe acute pancreatitis (SAP) are prone to endotoxemia caused by gram-negative bacteria, which is closely related to the occurrence, development and complications of SAP multiple organ failure. Previous studies have shown that endotoxin can cause renal failure by activating ETs, which constricts renal blood vessels and reduces renal blood flow.[11] [15]

3.2 Hypovolemia

In the early stage of acute pancreatitis, low blood volume is an important factor leading to AKI. This study was the first to document the presence of pancreatitis in dogs with experimental acute pancreatitis, a 40% reduction in GFR and a 26% reduction in plasma volume after 4 hours of bile infusion. Renal biopsy showed no significant morphological changes, but plasma supplementation could prevent the decrease of GFR. However, 24 hours later, renal failure is no longer able to expand the volume. These results were reproduced by injecting trypsin,chymotrypsin, elastase and PLA2 into dogs.[16]The researchers speculate that the release of these enzymes may be responsible for the increased permeability of blood vessels, while protein-rich body fluids leak into the stroma, resulting in low blood volume. In canine models, ascites accumulate rapidly, increase the specific volume of blood and decrease arterial pressure, indicating a decrease in blood volume[17].

3.3 Release of molecular patterns associated with damage

SAP can induce apoptosis of acinar cells. Studies have shown that DAMPs (DAMPs) are involved in many diseases[18-20]. In addition, HMGB1 (high mobility groupbox-1), nucleosomes, autologous DNA and ATP (triphosphatase, triphosphate, triphosphate) have been shown to be closely related to the development of SAP. Blocking HMGB1 can significantly reduce the damage of severe acute pancreatitis and its related organs. [21, 22] The course of acute pancreatitis may cause vascular damage with endothelial dysfunction, coagulation activation and inflammatory response.[23]

In SAP, excess trypsin and inflammatory mediators are released from the pancreas into the systemic circulation. Plasma trypsin and kallikrein activate renin to renin, increasing angiotensin II, increasing renal vascular resistance, decreasing effective renal blood flow, and decreasing GFR. [17]At the same time, excessive release of trypsin and inflammatory mediators can lead to heart, lung, kidney and other systemic vascular injury. Vascular endothelial injury triggers clotting cascade reaction, which mainly includes tissue factor exposure, prothrombin activation, thrombin production and fibrin formation.[24]

3.4 Complications of abdominal compartment syndrome

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are often found in critical surgical patients [18]. Elevated intra-abdominal pressure can have adverse cardiovascular, lung and kidney effects. IAH is defined as a sharp rise in intra-abdominal pressure resulting in adverse physiological outcomes, and its diagnosis is primarily through intra-abdominal pressure monitoring. [25, 26]Systemic inflammation and vascular permeability increase during SAP, leading to intraperitoneal and retroperitoneal inflammatory fluid exudation and thus IAH. Persistent Intra-abdominal hypertension (IAH) can cause a lack of blood supply to the organs, affect renal blood flow and renal perfusion, and further impair the function of glomeruli and renal tubules. Further studies showed that the activated.[27] renin-angiotensin system (RAS) increased significantly, renal resistance increased and glomerular filtration decreased in SAP patients with hypotension and hypovolemia.[28, 29]

3.5 Inflammatory mediator and cytokine

Inflammatory cell infiltration and excessive release of inflammatory mediators are the key links of renal damage in SAP. The systemic inflammatory response syndrome (SIRS) in the first 1-2 weeks and compensatory anti-inflammatory response syndrome (CARS) in the second 1-2 weeks are prone to AKI[19, 30]. Over-production of inflammatory mediators, such as TNF -α, platelet activating factor (PAF), chemokines, and interleukin (IL), also play an important role in the pathogenesis of AKI. Platelet activating factor (PAF) and PAF -like phospholipid (PAF-LPL) mediated synchronous iron death can promote the occurrence and development of AKI. [11] At the same time, the overexpression of TNF - α during the development and progression of SAP can up-regulate PAF by living cytokine cascade reaction, further leading to glomerular injury and renal fibrosis. [31, 32]

4. Conclusion

In this paper, the mechanism of renal damage after severe acute pancreatitis (SAP) was reviewed. But the mechanism of its action is not clear. This project will provide a new idea for the prevention and treatment of renal injury after SAP.

References

[1] Kes, P., et al., Acute renal failure complicating severe acute pancreatitis. Ren Fail, 1996. 18(4): p. 621-8.
[2] Lankisch, P.G., M. Apte, and P.A. Banks, Acute pancreatitis. Lancet, 2015. 386(9988): p. 85-96.
[3] Lin, H.Y., et al., Acute renal failure in severe pancreatitis: A population-based study. Ups J Med Sci, 2011. 116(2): p. 155-9.
[4] Scurt, F.G., et al., [Acute kidney injury following acute pancreatitis (AP-AKI): Definition, Pathophysiology, Diagnosis and Therapy]. Z Gastroenterol, 2020. 58(12): p. 1241-1266.
[5] Halonen, K.I., et al., Severe acute pancreatitis: prognostic factors in 270 consecutive patients. Pancreas, 2000. 21(3): p. 266-71.
[6] Compañy, L., et al., Factors predicting mortality in severe acute pancreatitis. Pancreatology, 2003. 3(2): p. 144-8.
[7] Devani, K., et al., Acute pancreatitis: Trends in outcomes and the role of acute kidney injury in mortality- A propensity-matched analysis. Pancreatology, 2018. 18(8): p. 870-877.
[8] Schepers, N.J., et al., Early management of acute pancreatitis. Best Pract Res Clin Gastroenterol, 2013. 27(5): p. 727-43.
[9] Dumnicka, P., et al., The Interplay between Inflammation, Coagulation and Endothelial Injury in the Early Phase of Acute Pancreatitis: Clinical Implications. Int J Mol Sci, 2017. 18(2).
[10] Cuthbertson, C.M. and C. Christophi, Disturbances of the microcirculation in acute pancreatitis. Br J Surg, 2006. 93(5): p. 518-30.
[11] Zhang, X.P., L. Wang, and Y.F. Zhou, The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. Dig Dis Sci, 2008. 53(2): p. 297-306.
[12] Sharma, B., et al., Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. J Clin Gastroenterol, 2011. 45(5): p. 442-8.
[13] Salvo Romero, E., et al., The intestinal barrier function and its involvement in digestive disease. Rev Esp Enferm Dig, 2015. 107(11): p. 686-96.
[14] Clark, E.C., et al., Glutamine deprivation facilitates tumour necrosis factor induced bacterial translocation in Caco-2 cells by depletion of enterocyte fuel substrate. Gut, 2003. 52(2): p. 224-30.
[15] Raina, R., et al., The Role of Endothelin and Endothelin Antagonists in Chronic Kidney Disease. Kidney Dis (Basel), 2020. 6(1): p. 22-34.
[16] Levy, M., R. Geller, and S. Hymovitch, Renal failure in dogs with experimental acute pancreatitis: role of hypovolemia. Am J Physiol, 1986. 251(6 Pt 2): p. F969-77.
[17] Satake, K., et al., Renal function in experimentally induced acute pancreatitis in dogs: how it is affected by the nephrotoxic substance in pancreatic exudate from ascitic fluid. Jpn J Surg, 1991. 21(1): p. 88-95.
[18] Baker, K.S., et al., Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood, 2007. 109(4): p. 1765-72.
[19] Hotchkiss, R.S. and I.E. Karl, The pathophysiology and treatment of sepsis. N Engl J Med, 2003. 348(2): p. 138-50.
[20] Pohlman, T.H., et al., An endothelial cell surface factor(s) induced in vitro by lipopolysaccharide, interleukin 1, and tumor necrosis factor-alpha increases neutrophil adherence by a CDw18-dependent mechanism. J Immunol, 1986. 136(12): p. 4548-53.
[21] McDonald, B. and P. Kubes, Innate Immune Cell Trafficking and Function During Sterile Inflammation of the Liver. Gastroenterology, 2016. 151(6): p. 1087-1095.
[22] Habtezion, A., A.S. Gukovskaya, and S.J. Pandol, Acute Pancreatitis: A Multifaceted Set of Organelle and Cellular Interactions. Gastroenterology, 2019. 156(7): p. 1941-1950.
[23] Hoque, R., et al., Sterile inflammatory response in acute pancreatitis. Pancreas, 2012. 41(3): p. 353-7.
[24] Tran, D.D., et al., Acute renal failure in patients with acute pancreatitis: prevalence, risk factors, and outcome. Nephrol Dial Transplant, 1993. 8(10): p. 1079-84.
[25] Ye, B., et al., Aggressive Resuscitation Is Associated with the Development of Acute Kidney Injury in Acute Pancreatitis. Dig Dis Sci, 2019. 64(2): p. 544-552.
[26] Kopitkó, C., L. Medve, and T. Gondos, The value of combined hemodynamic, respiratory and intra-abdominal pressure monitoring in predicting acute kidney injury after major intraabdominal surgeries. Ren Fail, 2019. 41(1): p. 150-158.
[27] De Waele, J.J., Intra-abdominal hypertension and abdominal compartment syndrome. Curr Opin Crit Care, 2022. 28(6): p. 695-701.
[28] Thabet, F.C. and J.C. Ejike, Intra-abdominal hypertension and abdominal compartment syndrome in pediatrics. A review. J Crit Care, 2017. 41: p. 275-282.
[29] Cheatham, M.L., Abdominal compartment syndrome: pathophysiology and definitions. Scand J Trauma Resusc Emerg Med, 2009. 17: p. 10.

[30] Zerem, E., Treatment of severe acute pancreatitis and its complications. World J Gastroenterol, 2014. 20(38): p. 13879-92.
[31] Sandoval, D., et al., The role of neutrophils and platelet-activating factor in mediating experimental pancreatitis. Gastroenterology, 1996. 111(4): p. 1081-91.
[32] Correa-Costa, M., et al., Activation of platelet-activating factor receptor exacerbates renal inflammation and promotes fibrosis. Lab Invest, 2014. 94(4): p. 455-66.