MEDS Clinical Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2024.050304
ISSN 2616-1907 Vol. 5 Num. 3

Advances in the diagnosis and treatment of liver injury in acute pancreatitis

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Keywords: Acute pancreatitis liver injury, diagnosis, treatment

Abstract: Acute pancreatitis, as a common acute abdominal disease, has a rapid onset and rapid development, and if not properly diagnosed and treated, it can easily lead to systemic inflammatory response syndrome and multi-organ dysfunction. In recent years, many studies have shown that liver damage is often combined with AP (Acute Pancreatitis) in the course of its development, and the degree of liver damage is closely related to the disease progression and severity of AP and affects its prognosis. Therefore, the diagnosis and treatment of LIAAP (Liver Injury Associated Acute Pancreatitis) is of great clinical significance for the comprehensive evaluation of patients' conditions and therapeutic effects. In this paper, we briefly review the progress of diagnosis and treatment of liver injury caused by acute pancreatitis.

Acute pancreatitis refers to the abnormal activation of pancreatic enzymes due to various factors, thus producing digestive effects on the pancreas itself and its surrounding neighboring organs and tissues, and then causing an acute abdominal disease characterized by local inflammatory changes in the pancreas, which may be accompanied by damage to the liver, lungs, kidneys, intestines and other organs. The mortality rate of severe acute pancreatitis is between 15-35%.[1] . The mortality rate of SAP(Severe Acute Pancreatitis) patients associated with hepatic failure is as high as 83 percent[2] and about 5% of these SAP patients will also have fulminant liver failure[1] The liver can be damaged as a result of AP. Liver damage can be a marker for the beginning of the process of multiple organ damage complicating AP. About 70% of patients with AP will have concomitant liver injury, and the percentage of SAP with concomitant liver injury is as high as 88.9%, and about 20% of patients with AP will develop SAP.[3] AP can cause liver injury, and at the same time liver injury can exacerbate the severity of AP[4] AP can cause liver injury and liver injury can exacerbate the severity of AP. The severity of liver injury in patients is positively correlated with the progression of AP. LIAAP and AP are closely related and interact with each other, and in patients with LIAAP, effective treatment of liver injury can improve the prognosis of AP.

1. Damage mechanism

1.1 Anatomical factors

Due to the close anatomical relationship between the pancreas and the liver, the portal venous system collects blood from the pancreas, and the liver becomes the first stop for blood returning from the pancreas, which leads to the fact that when pancreatitis occurs, all kinds of pathogenic factors are able to pass through the portal venous system, the hepatoduodenal ligament, and the Gleason's sheath and other structures to reach the liver first.[5]At the same time, the relationship between the liver and the pancreas is complex and intertwined with the lymphatic and nervous systems. In an animal experiment, by cutting off the large visceral nerves bilaterally, NF-κB, an inflammatory pathway, was inhibited, thus reducing the liver injury in pancreatitis.[6] In an animal experiment, by cutting off the large nerves bilaterally in animals, it was possible to inhibit NF-κB, an inflammatory pathway, and thus reduce liver injury in pancreatitis.

1.2 Molecular mechanisms

In current studies, the molecular mechanism of LIAAP is generally categorized into six major aspects: pancreatic enzyme-mediated, intestinal endotoxin, cytokines, inflammatory mediators, oxidative stress, and microcirculatory disorders. During AP, the pancreas releases large amounts of trypsin, elastase, lipase, cytochrome P450, and lysophosphatidylcholine to directly damage the liver through the portal system; pancreatic elastase induces cytokine production by KCs through the activation of the nuclear transcription factor-κB (NF-κB) pathway; and the production of cytokines by TNF-α, NLRP-3, and structural domain-like receptor proteins (SDRPs) is mediated by the pancreas. structural domain-like receptor protein), IL-1β (interleukin-1β), IL-6 (interleukin-6), IL-8(interleukin-8), IL-12(interleukin-12), IL-17(interleukin-17), IL-18(interleukin-18), IL-23(interleukin-23), MIF (macrophage inhibitory factor for cell wandering), MCP-1 (monocyte chemotactic protein-1), ICAM-1, (intercellular adhesion molecule), MIP-2 (macrophage inflammatory protein-2); Oxygen free radicals (OFR), nitric oxide (NO), and hepatocyte high mobility group protein (1HMGB1) enhance extracellular signal-regulated kinase (ERK) activity by promoting the polarization of Kupffer cells into M1 macrophages; activate MAPK, PI3K/AKT, JAK/STAT, and monocyte/macrophage-expressed TLR,P38- MAPK,NF-κB, TXNIP/NLRP-3 and other signaling pathways enhance the release of extracellular signal-regulated kinase (ERK) and C-reactive protein (CRP) in the inflammatory response, which further produces more cytokines, and enhances the ability of T lymphocytes and NK cells. In this way, a "waterfall inflammatory cascade reaction" exacerbates liver damage and even triggers systemic inflammatory response syndrome (SIRS).[7-13] In addition, after ischemia and damage of intestinal mucosa in AP, especially in the case of parenteral nutrition, the intestinal mucosa atrophies and the intestinal barrier is weakened, which leads to endotoxemia caused by displacement of bacteria and endotoxin in the intestinal tract and aggravates the damage of organs and tissues remote from the AP, and the transmission of endotoxin through the portal system, which is especially obvious in the damage of the liver.

1.3 Other factors

In recent years, the new hotspots about the associated factors of LIAAP mainly focus on two points: pancreatitis-associated ascites, and microcirculation disorder. Pancreatitis-associated ascites produced in some AP can stimulate the secretion of TNF-α, IL-6, IL-8, ICAM-1 to aggravate liver injury, and is closely related to MODS. In the disease process of AP, the imbalance between the release of ET (plasma endothelin) and NO (nitric oxide) causes the constriction of microvessels.

And ischemic injury of vascular endothelial cells ultimately leads to the obstruction of venous return and the slowing down of circulatory blood flow.Then causes hepatic microcirculation disorders[14]. Since liver cells are more sensitive to ischemia and hypoxia than other cells. Microcirculatory disorders are more likely to aggravate the degree of liver injury.

2. Diagnosis

2.1 Laboratory diagnosis

2.1.1 Liver-related biochemical indicators

In AP, liver-related biochemical indexes such as serum total bilirubin (TBil), albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and glutamyltranspeptidase (GGT) change with the condition, and the degree of alteration of liver function will affect the degree of development and prognosis of AP. Among them, the level of TBil reflects the ability of liver cells to metabolize bilirubin. When liver cells are damaged, the liver's ability to metabolize bilirubin decreases and the level of bilirubin in the blood rises. Beyond a certain range, patients with AP become jaundiced. ALB is synthesized by the liver and reflects the liver's synthesis function. When there is a lot of damage to hepatocytes, ALB levels may decrease. ALB is an independent prognostic factor for MODS and can predict MODS in AP.[15] TBil and ALB are independent risk factors for SAP and can predict hospital mortality in SAP.[16] ALT and AST also reflect the severity of liver injury, but transaminases decrease when there is massive hepatocellular damage and death and liver failure progresses, so elevated transaminases do not accurately reflect the extent and prognosis of liver injury.[17] ALP and GGT mainly reflect whether there is cholestasis or obstruction in liver injury.

2.1.2 Coagulation-related indicators

Prothrombin time (PT) is a common indicator to evaluate the function of exogenous coagulation system. When LIAAP occurs, it can cause the synthesis and bioactivity of coagulation factors I, II, V, VII, and X to be affected, resulting in the prolongation of PT. Changes in the coagulation and fibrinolytic marker system represented by PT are good predictors of disease progression and prognosis in patients with AP.[18] The changes in coagulation and fibrinolytic marker system represented by PT are good predictors of disease progression and prognosis in AP patients.

2.1.3 Other indicators

Neutrophil-to-lymphocyte ratio (NLR) and platelet count-to-lymphocyte ratio (PLR), as new inflammatory indicators, reflect the level of intrinsic and adaptive immunity.[19] Elevated NLR and PLR are also risk factors for SAP, and the predictive value of NLR is better than that of PLR. Combined testing of the two is more effective for the diagnosis of LIAAP and the evaluation of the progression and prognosis of AP.

2.2 Diagnostic imaging

2.2.1 Radiation

It is well known that the severity index score (CTSI) of AP by MSCT (multislice CT) is an important reference index in the current diagnosis and treatment of AP, and CT examination is one

of the most simple, effective, and intuitive means of examining and evaluating the condition of AP. However, the imaging characteristics of early LIAAP only include mild reduction of liver density, which lacks certain specificity. In recent years, perfusion CT (hereinafter referred to as pCT) imaging, as an emerging non-invasive modality, has been widely used to examine and assess the blood perfusion of organs and tissues.[20] pCT has a high potential for the assessment of hepatic blood flow, providing information on hepatic microcirculation and quantitatively evaluating changes in hepatic hemodynamics.[21] Because the hepatic microcirculatory disturbances in LIAAP lead to altered hepatic blood concerns, timely pCT, especially within 24 hours after the onset of AP, can be used to predict the trend and severity of disease progression through the abnormalities in hepatic perfusion.[21] . In addition, it has been shown that an imaging histology correlation model based on hepatic pCT texture analysis has potential value in the assessment of early LIAAP, and can provide a new auxiliary examination tool for clinical assessment, prediction of prognosis and guidance of individualized targeted treatment in patients with AP.

2.2.2 Magnetic Resonance

Fatty liver and AP also interact, and Wu D[22] The results of this study suggest that patients with nonalcoholic fatty liver disease (NAFLD) are at higher risk of progressing to SIRS and MODS after the onset of AP. MR severity index (MRSI) by magnetic resonance imaging (MRI) is an effective way to characterize hepatic fat signals in patients with LIAAP. xiao B[23] It was found that the fat in the liver of AP patients decreased with the improvement of the disease and increased with the aggravation of the disease. Meanwhile, MRSI and serum triglyceride levels were correlated with the level of fat signal in LIAAP, and the MRSI score is also very important for the assessment of disease progression, prognosis, and follow-up evaluation of patients with LIAAP with fatty liver, which suggests that magnetic resonance imaging has a broad prospect for the diagnosis of pancreatitis and its related complications in the future.

3. Treatment

3.1 Hepatoprotective drug therapy

An animal experiment[24] showed that 5-aminoimidazole-4-carboxyamide ribonucleotide (AICAR), a cytosolic permeable nucleotide and also an activator of adenosine monophosphate protein kinase (AMPK), can directly increase AMPK phosphorylation, and the activation of AMPK further promotes the accumulation of nuclear factor red lineage 2-associated factor (2 Nrf2), and inhibits nod-like receptor protein 3 (NLRP3) inflammatory vesicle activation, thereby partially mediating the antioxidant effects of LIAAP by effectively inhibiting liver oxidative stress and inflammation in rats.Shi Q et al.) activation of inflammatory vesicles, thereby partially mediating the antioxidant effects of hepatocytes and attenuating LIAAP in rats by effectively inhibiting hepatic oxidative stress and inflammation.Shi Q et al.[25] found that hydrogen-rich salt (HRS) could attenuate the degree of LIAAP in rats by inhibiting the phosphorylation of JNK and p38-MAPK and reducing oxygen radical-mediated apoptosis in liver cells, while inhibiting the activation of NF-κB and reducing the inflammatory response of hepatocytes in two ways. In the study of Qi Y[26] et al, lipid nanoparticles (LNPs) were modified with glycyrrhizic acid (GA) and polyprenylphosphatidylcholine (PPC) to form GA/PPC-modified LNPs, and these modified nanolipid particles were able to improve the stability of small fragment interfering ribonucleic acid (siRNA), thereby enhancing gene silencing, while decreasing inflammation, and ultimately attenuating LIAAP in rats. Magnesium isoglycyrrhizinate (MgIg), a commonly used hepatoprotective drug, binds more readily to steroid hormone receptors on hepatocytes and

enhances the integrity and stability of hepatocyte cell membranes, thereby reducing inflammatory responses.[27] Fang M et al.[28] In an animal experiment, Fang M et al. showed that MgIg could block the activation of NF-κB/NLRP3 inflammatory vesicles, reduce hepatic oxidative stress and pro-inflammatory cytokine production, inhibit the production of oxygen free radicals by neutrophils and inhibit oxidative stress in hepatocytes, thus reducing liver injury.[29]Lv P[30] et al. used thalidomide prophylactically in rats and confirmed its protective effect on the progression of LIAAP.Zhang H et al.[31] showed that ethyl pyruvate (EP) significantly reduced the infiltration of inflammatory cells in the liver by regulating high mobility group protein B1 (HMGB1) and inhibiting the activation of NF-JB, thereby suppressing the expression of cytokines such as TNF-α, IL-1β in early stage. In an animal study, growth inhibitors inhibited the secretion and activation of pancreatic elastase, inhibited the expression of Toll receptors and NF-κB, and reduced the inflammatory response, thereby decreasing the hepatic injury in hemorrhagic pancreatitis.

In addition, related studies have shown that calcium antagonists and melatonin can also significantly reduce IL-1, IL-1, and TNF-α levels, inhibit the release of inflammatory factors and oxygen free radicals in rats, and have a protective effect on LIAAP.

3.2 Traditional Chinese Medicine (TCM)

In recent years, the treatment of traditional Chinese medicine (TCM) has gradually become a research hotspot, and rhubarb has a variety of pharmacological effects, including anti-inflammatory and antioxidant effects[32] . As a traditional medicine, it is widely used in the treatment of various acute inflammatory diseases, including SAP, due to its effects on intestinal motility, bacterial and endotoxin translocation, and anti-inflammatory activity. Rhubarb and epiphyllum soup can inhibit the release of pancreatic enzymes, protect the stability of pancreatic alveolar cells. Inhibit the expression of pJAK2 and pSTAT3 and the release of a variety of cytokines in liver tissues and KCs. Meanwhile it can effectively reduce the level of serum ALT.Which can improve the LIAAP in rats.[33] The effect of rhubarb and its active ingredient Dahuang on LIAAP in rats is summarized below. Among them, rhubarb and its active ingredient rhodopsin have been proven to protect the mucosal barrier of the digestive system, reduce the overexpression of inflammatory cytokines such as NF-κB, etc., attenuate the damage of the pancreas and its organs other than the pancreas, and curb the occurrence of MODS. In addition, Chinese medicinal preparations such as Pancreatic Cleansing Soup, Compound Chinese Medicine Pancreatic Cleansing II Granules, Gold Beneficial Bile Granules, and Ginseng and Epiphyllum Injections are able to effectively down-regulate the expression of various inflammatory factors, act on various tissues and organs in multiple pathways and directions, and effectively alleviate the damage of extra-pancreatic organs such as the liver in the process of AP development.

3.3 Other treatments

Puncture and drainage is also a common treatment measure when AP is accompanied by abdominopelvic effusion, and it has been shown that laparotomy and drainage protects patients with AP by reducing the risk of infectious necrosis and does not increase infectious-related complications in patients with AP[34]. Some animal experiments have shown that peritoneal puncture and drainage effectively inhibits the NF-κB inflammatory signaling pathway by decreasing the expression of TLR4 in hepatocytes of SAP rats, thus reducing the degree of liver injury. Therefore, for AP patients with peritoneal effusion, early treatment with peritoneal puncture and drainage can improve the liver function of patients and reduce the severity of LIAAP. On this basis, a retrospective study showed that early continuous renal replacement therapy (CRRT) combined with peritoneal puncture and drainage can significantly reduce serum AST, ALT, TBIL,

γ-GT, PCT, CRP, and IL-6 in patients with AP, reduce LIAAP and inflammatory response, decrease the incidence of MODS, and protect liver function.

4. Summary

Currently, there are more detailed studies on the etiology of LIAAP, especially cytokines and inflammatory pathways. For the diagnosis of LIAAP, new progress has been made in perfusion imaging, which is an important means for future diagnosis and research. As for its treatment, most of the studies on drugs to protect liver function remain at the level of animal experiments, and there are more studies in China than abroad, so clinical experiments need to be enhanced. Meanwhile, some Chinese medicines have obvious therapeutic effects on LIAAP, but most of them are limited to mild AP, and the molecular pharmacological studies of related tonics and formulas are very lacking, which need further in-depth study. In conclusion, LIAAP is closely related to the development of AP, and timely and effective treatment of LIAAP is very important for the control of AP and its prognosis. Early planning of therapeutic programs for LIAAP is essential in the overall treatment of AP and should not be ignored.

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