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Research on the clinical treatment of hypertriglyceridemia and acute pancreatitis

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Abstract: *Hypertriglyceridemia is the third most common cause of acute pancreatitis in the world [1]. In China, hypertriglyceridemia is gradually rising as the second leading cause of acute pancreatitis [2]. The disease usually occurs in patients with an underlying disorder of lipoprotein metabolisms and secondary conditions such as poorly controlled diabetes mellitus, alcohol abuse, or particular drug use. The clinical manifestations of pancreatitis caused by hypertriglyceridemia are generally similar to acute pancreatitis caused by other causes. However, patients with pancreatitis caused by hypertriglyceridemia may have a longer course of the disease and more complications [3], accompanied by a higher possibility of persistent organ failure. The initial treatment of pancreatitis due to hypertriglyceridemia is similar to that of acute pancreatitis from other causes. It includes aggressive fluid resuscitation, pain control, and nutritional support. In acute pancreatitis, timely recognition of hypertriglyceridemia is crucial in the initial and long-term management of the disease. It is also critical for preventing the recurrence of acute pancreatitis.*

Keywords: *hypertriglyceridemia; acute pancreatitis; pathogenesis; prognosis*

1. Introduction

Gallstones and chronic alcoholism remain the leading causes of AP. Hypertriglyceridemia is the world's third most common cause of acute pancreatitis, and hypertriglyceridemia is the second most common cause of acute pancreatitis in China. Hypertriglyceridemia (HTG) is an established cause of acute pancreatitis (AP). The prevalence of hypertriglyceridemia-induced pancreatitis (HTGP) has been reported as high as [4-5] 22%. However, it is generally considered to account for approximately 5% of all AP cases and 56% of AP cases during pregnancy. The clinical course of HTG-induced pancreatitis (HTGP) is highly similar to AP of other etiologies, in which HTG is the only significant clinical feature. However, HTGP is often associated with higher severity and complication rates, and early recognition of HTGP is critical for proper management and prevention of recurrence.

Hypertriglyceridemia (HTG) was a fasting serum triglyceride level above 150 mg/dL (1.7 mmol/L). The risk of developing hypertriglyceridemic pancreatitis gradually increases with increasing triglyceride levels. Triglyceride levels above 1000 mg/dL are usually required [6]; the risk is approximately 5% at levels above 1000 mg/dL and rises to 10- 20%.

An epidemiological study in China suggested that the annual hospitalization rate for HTGP increased steadily from 14.3% to 35.5% during the study period. During the same period, the proportion of gallstone-associated pancreatitis decreased yearly [7]. The rising trend of HTGP in China is thought to be related to changes in the lifestyle and behavior of the Chinese population, as well as an increase in the incidence of metabolic syndrome and an increase in caloric intake.

2. Etiology

The etiology of HTGP can be divided into two categories: primary (hereditary) and secondary lipoprotein metabolism diseases [8,14]. Primary hyperlipidemia is divided into five phenotypes, 3 of which manifested as obvious hypertriglyceridemia (types I, IV, V), and the other two phenotypes mainly manifested as hypertriglyceridemia Lipidemia, rarely associated with HTGP. Dyslipidemia type I (familial chylomicronemia syndrome) is caused by an autosomal recessive trait of lipoprotein lipase deficiency resulting in high chylomicrons. Type I dyslipidemia usually presents in infancy, and patients may have severe HTG. Pancreatitis, in this case, may appear in the absence of other exacerbating

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conditions. Type V dyslipidemia or primary mixed HTG is similar to type I in that type V dyslipidemia is associated with a high risk of acute pancreatitis and manifests as increased VLDL and chylomicrons in adulthood. Type IV dyslipidemia or familial combined hyperlipidemia is a genetic disease with isolated elevation of very low-density lipoprotein (VLDL). HTGP associated with type IV dyslipidemia usually manifests in adulthood and is induced by a secondary factor in that triglyceride levels in these patients are not elevated enough to cause HTGP without other factors.

Secondary hypertriglyceridemia occurs in various conditions, including poorly controlled diabetes, pregnancy, hypothyroidism, or after exposure to particular drug and alcohol abuse.

3. Pathogenesis

The precise pathophysiological mechanism of hypertriglyceridemia acute pancreatitis (HTGP) is still unclear. However, the most widely accepted hypothesis is that pancreatic lipase hydrolyzes excess TG leading to the accumulation of free fatty acids (FFAs) [9]. FFAs can damage acinar cells and pancreatic capillaries, resulting in local microcirculation disturbance. Ischemia, in turn, induces an acidic environment and further enhances the toxic effects of FFAs [10]. Another theory is that high concentrations of chylomicrons lead to increased viscosity of pancreatic capillaries, which leads to ischemia and acidosis of the pancreas. In addition, the pathogenesis of HTGP also involves ER stress.

4. Clinical course and natural history

The initial clinical presentation of HTGP is similar to that of AP due to other etiologies, including severe abdominal pain, nausea, and vomiting. Pancreatic necrosis, infected necrosis, organ failure, and persistent organ failure were all more frequent than patients without HTGP. Mortality and ICU length of stay was higher in HTGP patients [11]. A recent cohort study in China showed that with the increase of HTG, the mortality rate of patients and other clinical outcomes of organ failure and pancreatic necrosis increased significantly and gradually, which suggested that triglyceride levels were positively correlated with disease severity.

A combination of primary genetic predisposition and secondary metabolic causes or alcoholism usually causes severe HTG [12-13]. The genetic basis of HTG is complex; HTG reaching mild to moderate levels is usually polygenic, but severe HTG, especially in younger patients, is more likely due to monogenic causes and secondary factors increase triglyceride levels when uncontrolled. Thus, HTG may be both a cause and an effect of other metabolic factors associated with acute pancreatitis, including poorly controlled diabetes, obesity, and alcohol consumption.

The risk of recurrence of acute pancreatitis is also associated with triglyceride levels [14]. It is highest when peak triglycerides are >3000 mg/dL. The prevalence of hospitalization for acute pancreatitis has increased significantly. This may be related to the increased incidence of metabolic syndrome [15]. Metabolic syndrome is associated with increased severity and mortality in acute pancreatitis. Hypertriglyceridemia may be a surrogate marker for metabolic syndrome, further contributing to the pathogenesis of increased morbidity and mortality in acute pancreatitis. The natural history of HTGP has also been shown to lead to chronic pancreatitis.

5. Management and treatment

There are no standard treatment guidelines for HTGP. Current treatment strategies include standard supportive care of acute pancreatitis (suspension of enteral intake, fluid replacement, and opioid analgesia), rapid reduction of plasma triglyceride levels, and elimination of triggers factors to reduce the likelihood of pancreatitis recurrence.

Aggressive intravenous fluid resuscitation, preferably lactated Ringer's solution, significantly reduces SIRS compared with normal saline, and mechanistic evidence may also support this finding [16]. In addition, lactated Ringer's solution contains calcium, which is associated with Unsaturated fatty acids binding and may lessen their toxic effects. Bowel rest reduces the excretion of pancreatic juice. It is an integral part of the initial treatment of patients with HTGP. Enteral nutrition also plays an essential role in providing nutritional support, preserving intestinal function, and preventing systemic inflammatory response syndrome, the most common cause of increased morbidity and mortality in patients with HTGP. Epigastric pain radiating to the back is the most common symptom leading to the diagnosis of AP.

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Therefore, adequate analgesia is essential for the initial treatment of HTGP [17]. Pethidine has emerged as one of the better alternatives for pain management in patients with HTGP. However, the safety of meperidine has changed its prescribing usage.

Insulin can be used in the emergency department for severe HTG because it is easy to initiate and is usually well tolerated by patients. Insulin reduces TG levels by enhancing the activity of lipoprotein lipase (LPL), which then hydrolyzes TG into fatty acids and glycerol and promotes the storage of fatty acids in adipocytes. Insulin can also inhibit hormone-sensitive lipase in adipocytes, a key enzyme for decomposing fat cell TG and releasing free fatty acids [18]. Insulin infusion has the most evidence of a therapeutic benefit in hypertriglyceridemia-induced acute pancreatitis. However, the evidence is inconclusive regarding its effect on mortality and long-term effects.

Heparin has also been used alone or in combination with insulin therapy, although its role is controversial [19]. Heparin initially stimulates an increase in lipoprotein lipase, which reduces triglyceride levels by converting it to free fatty acids. Treatment of severe hypertriglyceridemia with heparin is controversial because of the transient rise in LPL followed by increased degradation and depletion of plasma stores leading to LPL deficiency and the additional risk of pancreatic bed hemorrhage with heparin in acute pancreatitis.

Plasma exchange is also commonly used in treating HTG; it can quickly clear the triglycerides in the blood so that they can be reduced to below 500mg/dL more quickly. It involves removing some of the patient's blood plasma and replacing it with a colloidal solution. Plasmapheresis, although not included in the clinical guidelines themselves, recommends that plasmapheresis should be considered and is more effective only after failed insulin infusion trials or very severe HTG-AP, lactic acidosis, or worsening organ dysfunction. However, plasma exchange requires central venous access, is expensive, has the potential for infection or allergic reactions, and may not be widely available [20-21]. Studies have shown that plasma exchange as a specific treatment for HTG-AP can reduce TG concentration and may relieve symptoms (abdominal pain). However, it does not change the morbidity and mortality of AP.

Long-term management of HTGP focuses on lowering serum triglyceride levels to prevent disease relapse [22]. The optimal target triglyceride level is generally unknown, but a level of <500 mg/dL is usually the optimal target. Long-term treatment includes lifestyle changes and medications. Lifestyle changes are aimed at weight loss and restriction of sugar and dietary fat intake, as well as controlling secondary risk factors such as diabetes and avoiding medications that can raise triglyceride levels.

6. Conclusion

It is crucial for clinicians to pay close attention to hypertriglyceridemia when seeing patients meeting diagnostic criteria for AP, as early clinical recognition is essential for the treatment and prevention of future episodes. In patients with a diagnosis of acute pancreatitis (based on severe abdominal pain, elevated lipase, or imaging findings), serum triglyceride values should be determined regardless of the presence or absence of hypertriglyceridemia on test results. Patients with HTGP tend to have a more severe course of AP than patients with other pancreatitis, so initial support and adequate fluid resuscitation should begin immediately. Insulin and heparin to reduce serum TG levels has proven effective. However, caution should be exercised in the case of heparin, as depletion of LPL may have potentially adverse effects. Although plasmapheresis is one of the effective treatment options for rapidly reducing serum TG levels, it has significant side effects, and its efficacy in HTGP treatment has not been proven.

Furthermore, recent studies have shown that a rapid decrease in TG levels does not necessarily confer additional benefits on the overall outcome of treatment. As with many chronic diseases, close outpatient follow-up after hospital discharge is required to prevent the recurrence of HTGP. International consensus guidelines for the management of HTGP do not yet exist, further research is needed to guide future treatment, and the establishment of future guidelines will be necessary for the ongoing clinical management of HTGP.

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