Primerjava konzervativnega zdravljenja in terapevtske plazmafereze pri zdravljenju hipertrigliceridemičnega akutnega pankreatitisa

A comparison of conservative therapy and therapeutic plasma exchange in the treatment of hypertriglyceridemic acute pancreatitis

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Izvleček

Hipertrigliceridemični akutni pankreatitis (HTGP) je podtip akutnega pankreatitisa, ki nastane kot posledica izrazito povišanih serumskih trigliceridov. Najpogosteje se ta pojavlja pri mlajših moških z metabolnimi dejavniki tveganja. Možnosti zdravljenja vključujejo konzervativen pristop, ki obsega post, nadomeščanje tekočin, analgezijo in zdravljenje z inzulinom ali z ali brez nizkomolekularnega heparina, ali pa bolj invazivno metodo terapevtske plazmafereze. Ta pregledni članek obravnava patofiziologijo in klinične značilnosti akutnega HTGP, ter tudi primerja obe terapevtski strategiji s poudarkom na ključnih raziskavah in trenutnih dokazih na tem področju.

Abstract

Hypertriglyceridemic acute pancreatitis (HTGP) is a subtype of acute pancreatitis that is a result of markedly elevated serum triglycerides. HTGP most commonly occurs in younger men with metabolic risk factors. Treatment options include a conservative approach (fasting, fluid replacement, analgesia, and insulin therapy with or without low-molecular-weight heparin) or the more invasive method (therapeutic plasma exchange). This review article discusses the pathophysiology and clinical features of acute HTGP and compares the two therapeutic strategies with an emphasis on key studies and existing evidence.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the pancreas that is clinically manifested by characteristic symptoms, elevated lipase and amylase levels, and structural changes of the pancreas noted on imaging studies (1). The incidence of AP is increasing by 2%–5% annually in the United States and most of Europe, especially in the United Kingdom, Ireland, Denmark, Finland, Germany, Italy and Spain. The global incidence of AP ranges from 3–73 cases per 100,000 population per year. Differences in the incidence of AP between countries are most likely due to the regional variation in the prevalence of risk factors. AP affects men slightly more frequently (1, 2). The clinical presentation of AP typically involves sudden-onset, severe pain radiating from the epigastric or periumbilical region to the back, chest, and/or beneath the left costal margin (3). Initially, the pain is dull and mild but pain reaches a peak within 15–30 min. Pain is sometimes relieved by curling the legs towards their torso. Nausea, vomiting, and signs of peritonitis may also occur. The abdomen may be tense with clinical signs of a paralytic ileus (1). In patients with biliary pancreatitis, jaundice, and symptoms, suggest acute cholangitis. In more severe forms of pancreatitis, signs of shock, such as hypotension, may also occur (2). Less commonly, Cullen's sign (periumbilical ecchymosis), Gray-Turner's sign (ecchymosis of the flanks), both of which indicate an advanced form of necrotizing pancreatitis, and Fox's sign (ecchymosis off the upper medial thigh, often following the course of the inguinal ligament) have been reported (4).

Two of the following three criteria are required for diagnosis: characteristic pain; an increase in serum lipase/amylase levels to at least three times the upper limit; and characteristic findings of the pancreas on ultrasound, computed tomography (CT) or contrast-enhanced MRI (2, 4). Upon admission or diagnosis, it is advisable to determine the serum lactate level, which is a sign of severe AP with the development of shock (5-7). Pancreatic edema, cysts, signs of inflammation, and calcifications can be visualized by imaging studies (1, 4). The cause of AP is excessive alcohol consumption (25–35% of patients) or the presence of gallstones (30–60% of patients). The third most frequent cause of AP is hypertriglyceridemia (HTG), which is due to changes in lifestyle, dietary habits, and the increased prevalence of obesity (1, 2). Other causes of AP, such as toxins, metabolic causes, infections, injuries, medications (e.g. salicylates), congenital anomalies, autoimmune disorders, or genetic diseases, are rare. Approximately one-fifth of AP cases are classified as idiopathic acute pancreatitis [IAP] (1, 2).

The complications of AP are classified as local or systemic in accordance with the 2012 Atlantic classification (Table 1). The definition of complications is important for the classification of pancreatitis severity; the modified Marshall score can be used to identify systemic complications (4, 5, 7, 8).

HYPERTRIGLYCERIDEMIC ACUTE PANCREATITIS

Definition, epidemiology, and risk factors

Hypertriglyceridemic acute pancreatitis (HTGP) is a subtype of AP in which elevated triglycerides (TG) the cause of inflammation (8-11). The incidence of HTGP is increasing, coinciding with urbanization, a Western diet (higher proportion of fat, meat, and processed foods), reduced physical activity, and an increased prevalence of obesity, diabetes, and metabolic syndrome (10, 12).

Patients with HTGP are typically younger men with an average age of approximately 40 years, according to epidemiologic studies. Seasonal fluctuations in prevalence are also a characteristic of HTGP with peaks during the winter months and following the festive season due to the consumption of high-calorie foods and alcohol (10, 12).

Serum TG levels must exceed 10 mmol/l to establish a diagnosis of HTGP; clinically, a TG threshold of 11 mmol/l (>1000 mg/dl) is also frequently used. The risk of AP increases even at lower TG concentrations (10, 11).

The causes of HTG are classified as primary and secondary. Primary causes of HTG are less common and mainly involve genetic disorders of lipid metabolism, such as familial combined

Table 1: *Complications of acute pancreatitis according to the 2012 Atlanta classification. GDA – gastroduodenal artery, ARDS – acute respiratory distress syndrome, AKI – acute kidney injury, DIC – disseminated intravascular coagulation (9)*

Local complications	Interstitial edematous pancreatitis	< 4 weeks	Acute peripancreatic fluid collection
		> 4 weeks	Pancreatic pseudocyst
	Necrotizing pancreatitis	< 4 weeks	Acute necrotic fluid collection (ANC)
		> 4 weeks	Walled-off necrosis (WON)
		Infection of necrosis (ANC or WON)	
	Vascular complications	Thrombosis (splenic, portal veins) Pseudoaneurysm (GDA, splenic arteries)	
Systemic complications	ARDS and respiratory failure AKI DIC and other hemostasis impairments Electrolyte impairments (e.g. hypocalcemia)		

hyperlipidemia. Polymorphisms in genes, such as *APOE*, *LPL*, and *APOA5*, are associated with an increased risk of HTGP and a more severe course of the disease. *APOA5* and *LPL* mutations are more common in China than Western cohorts, which can explain the higher prevalence of HTGP (10, 12). Secondary causes, which are presented in Table 2, are more common than primary causes (10, 12).

Pathophysiology

HTGP occurs when the presence of chylomicrons and/or the breakdown of TG into free fatty acids (FFA) triggers lipotoxicity, local inflammation of the pancreas, and damage to distant organs (9, 11). The mechanism underlying the development of HTGP is based on the relationship between lipid metabolism, the inflammatory response, oxidative stress, and an imbalance in the gut microbiota. An excessive number of chylomicrons is formed at TG levels > 10–20 mmol/L, which increases plasma viscosity and causes microcirculatory ischemia in the pancreas. TG lipase hydrolyses triglycerides into FFA, which are toxic to acinar cells and the vascular endothelium in excess, triggering local necrosis, inflammation, and a systemic

Table 2: *Secondary causes of hypertriglyceridemia (10, 12)*

Secondary causes of hypertriglyceridemia	
A diet high in carbohydrates	Excessive alcohol consumption
Obesity	Pregnancy
Diabetes	Medications (estrogen, isotretinoin, beta-blockers)
Hypothyroidism	Acute hepatitis
Chronic renal failure	Systemic lupus erythematosus
Lipodystrophy	Ileal bypass surgery
Glycogen storage diseases	Stress
Monoclonal gammopathies	
AIDS: protease inhibitors	
Sepsis	

inflammatory response (9, 11, 13). FFA activate the NF-ϰB signaling pathway, leading to the release of pro-inflammatory cytokines, such as IL-6 and TNF-α, and consequently accelerated tissue damage and organ failure. Studies have shown that IL-6 levels in HTGP are up to 3 times higher than in AP with other etiologies (10-13). Genetic predispositions, such as mutations in the lipoprotein lipase gene, also have a significant role in the development of HTGP (10, 12). Another important factor in the development of HTGP is gut microbiota dysfunction, particularly a reduced presence of *Bacteroides uniformis*, which decreases taurine production and increases the release of IL-17 and the formation of neutrophil extracellular traps (NETs). Consequently, gut microbiota dysfunction leads to further activation of the NF-ϰB signaling pathway and additional damage to the pancreas. Taurine supplementation or colonization with B. *uniformis* represents a potential new therapeutic target. Ferroptosis, a specific form of cell death caused by lipid peroxidation and oxidative stress, is also thought to play an important role in the development of HTGP. The use of ferroptosis inhibitors, such as liproxstatin, has reduced pancreatic damage in experimental models, which also represents a promising therapeutic target (8, 10, 12). The pathophysiology of HTGP is presented in Figure 1.

Treatment of hypertriglyceridemic pancreatitis

Treatment of HTGP involves fasting, pain relief, fluid replacement, and lipid-lowering therapy (9, 11). Insulin and low-molecular-weight heparin (LMWH) are indicated for the further management of HTGP because insulin and LMWH stimulate lipoprotein lipase activity and the breakdown of chylomicrons.

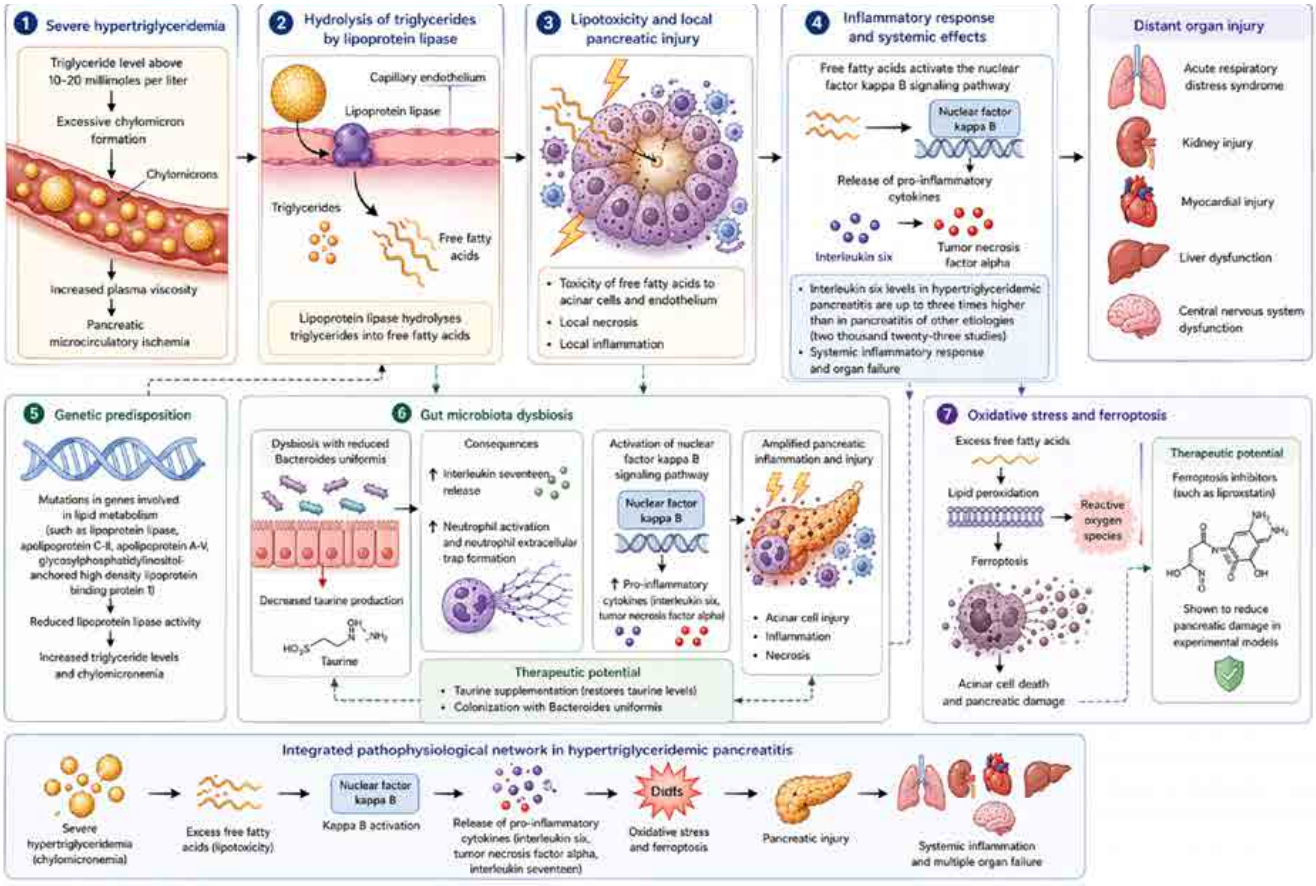

Figure 1. *Pathophysiology of hypertriglyceridemia-induced acute pancreatitis (9-13).*

However, close monitoring for hypoglycemia or bleeding is advised when insulin and LMWH are used to treat patients with HTGP (12, 14).

Therapeutic plasma exchange (TPE) facilitates the rapid removal of lipids from plasma and is used in severe cases of HTGP with a baseline TG level > 1000 mg/dL (≈ 11 mmol/L). The American Association for Apheresis classifies severe HTGP as category III, the treatment of which has not been definitively shown to be effective and is used at the clinician's discretion. Despite the efficacy, TPE has not been established as the universal method of choice due to a lack of randomized prospective studies demonstrating superiority over conservative management. Complications of TPE include infections, bleeding, and complications associated with catheter insertion. Furthermore, the method is more expensive and is not available in all healthcare facilities (14). The 2025 revised International Society of Pancreatology (IAP) and European Pancreatic Club (EPC) guidelines are used in Europe and are based on systematic literature reviews and the PICO and GRADE scoring systems. The guidelines emphasize that persistent multi-organ failure (MOF) lasting > 48 h is the most significant risk factor for mortality and recommend early enteral nutrition and treatment in appropriately equipped centers for severe forms of the disease. TPE is not recommended as part of routine treatment but represents only an additional option in severe cases of HTGP where standard treatment is insufficient (13, 15).

The overall goal of treatment for HTGP is to reduce TG levels below 5.6 mmol/L because higher levels are associated with a risk of disease recurrence. Managing metabolic disorders, particularly diabetes, obesity, and alcohol consumption, which influence relapses and complications, is also crucial for long-term outcomes (9, 11).

COMPARISON OF CONSERVATIVE TREATMENT WITH THERAPEUTIC PLASMA EXCHANGE IN HYPERTRIGLYCERIDEMIC ACUTE PANCREATITIS

Comparison of mortality

The results of several cohort studies have not shown statistically significant differences in mortality between patients treated with TPE and patients treated conservatively (14-17). Although lower TG levels were often achieved more rapidly in patients undergoing TPE, this effect did not result in improved survival or a lower incidence of MOF. Fatal outcomes were limited to patients with necrotizing pancreatitis, systemic inflammatory response syndrome (SIRS), and persistent MOF independent of the method chosen to lower TG levels (15-18). It has been reported higher absolute mortality in patient groups in which TPE was used for treatment but without statistical significance, which the authors attributed primarily to the selection of clinically more severely affected patients for this type of treatment (18). In contrast, some studies have suggested a favorable outcome with early initiation of TPE in severe forms of HTGP, while late initiation was associated with a higher risk of MOF (18-20). The most important prognostic factor for outcome in HTGP is the severity of the disease and the duration of MOF, while the use of TPE does not represent an independent factor for survival (14).

Comparison of complications

Complications occur more frequently in HTGP than in AP with other etiologies and in more severe forms of AP (21). No differences were demonstrated in the incidence of systemic HTGP complications in patients treated with conservative management and TPE between the two groups in previous studies (20-22). Similarly, no differences were detected in the incidence of mortality due to systemic complications in the context of MOF (16, 22-24). Wang et al. (20) reported no differences in the rate of improvement in MOF between the groups treated with TPE and conservative management in a cohort study, despite a faster reduction in TG levels in the TPE group. Similar

conclusions were drawn in a cohort study conducted by Amin et al. (22), in which a greater reduction in TG was achieved in the first 3 d in the group treated with TPE, yet no statistically significant changes in systemic complications or mortality were noted between the two groups. Staudacher et al. (16) cited the absence of clinical evidence that a rapid reduction in TG is associated with a better clinical outcome in HTGP as one possible explanation for the comparable outcomes of both treatments, which would account for the comparable efficacy of TPE and conservative management. Shaka et al. (25) described a higher incidence of complications in patients undergoing TPE. However, this finding may be due to a preference for TPE among patients who already had a more severe form of HTGP prior to treatment or who were unresponsive to conservative management (25). Further research is needed to compare the incidence of local complications between treatment modalities.

Length of stay in the intensive care unit

The length of stay in the intensive care unit (ICU) for patients with HTGP is associated with the severity of the clinical presentation, the timeline of treatment initiation, and the presence of complications (16, 17). Most studies investigating TPE or other blood purification methods (17-20), have focused primarily on the rate of TG reduction, the inflammatory response, and the incidence of organ failure, while the length of ICU stay was not defined as an independent outcome. The results indirectly suggested that early and effective treatment may contribute to faster patient stabilization but there is no clear evidence of a reduction in the length of stay in the ICU (16, 17, 19). Krauss et al. (26, 27) reported a median ICU stay of 3 d (range, 2–16 d) in patients treated with TPE, suggesting a shorter ICU stay with timely treatment and the absence of severe complications. At the same time, Wang et al. (16,18) reported a median of 9 d

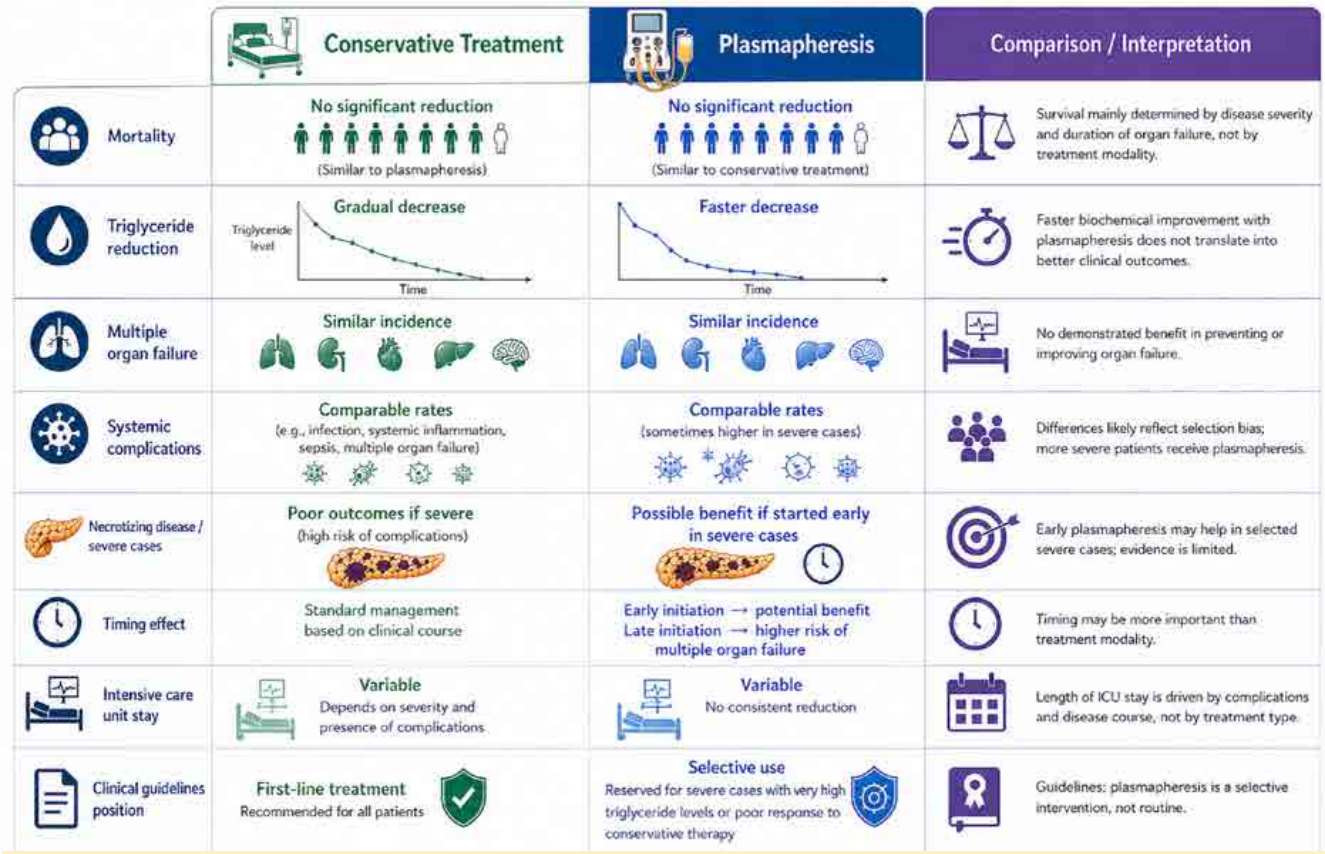

Figure 2. *Comparison between therapeutic plasma exchange (TPE) and conservative management of hypertriglyceridemic acute pancreatitis (16-20).*

with hospitalization extending to 19 d in cases of infection with multidrug-resistant microorganisms, highlighting the significant role of secondary complications. The effect of TPE on the duration of ICU hospitalization has not been demonstrated. According to existing studies, hospitalization is associated with the incidence of complications, the course of the disease, and timely treatment (16, 18). The direct comparison between both treatment approaches is presented in Figure 2.

CONCLUSION

HTGP has recently become an increasingly common cause of AP. The prognosis and course of the disease are primarily influenced by the severity of the condition and the incidence of complications, rather than a reduction in the TG level via TPE. TPE facilitates a rapid reduction in the TG level but current data do not confirm its independent effect on mortality or systemic complications, which is why the cornerstone of HTGP treatment remains a conservative approach. TPE remains a treatment option as a targeted therapy in severe forms of HTGP with very high TG levels.

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