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Exploring the Ketogenic Diet's Role in Acute Pancreatitis

Aemen Kamran[1]*, Rabeya Farid[2], Muhammad Khizer Molani[1], Sbahat Fatima[3] and Mohammed Mahmmoud Fadelallah Eljack[4]

[1]*Dow Medical College, Dow University of Health Sciences, Pakistan*

[2]*Department of Medicine, Jinnah Sindh Medical University, Pakistan*

[3]*Karachi Medical and Dental College, Pakistan*

[4]*Community Department, University of Bakhtalruda, Sudan*

***Corresponding author:** Aemen Kamran, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

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ABSTRACT

Background: Ketogenic diets (KDs) are high-fat, low-carbohydrate, and low-calorie diets that benefit weight control, metabolic disorders, and neurological disorders such as epilepsy. Hypertriglyceridemia (HTG) is an uncommon but well-established cause of acute pancreatitis (AP). This narrative review explores the link between KD and AP, focusing on the hyperlipidemic pathways involved.

Methods: Case studies and cohort studies were selected by searching PubMed, Cochrane Trials, and Google Scholar. A total of 12 articles were identified for inclusion in this review. Results: Individuals with KD, especially those with accompanying predisposing factors such as obesity, type 2 diabetes, and genetic predispositions, are at increased risk of developing HTG and subsequent AP. Further research is required to better understand the mechanisms linking KD to AP and to refine dietary recommendations for patients on this diet.

Conclusion: A balanced approach, thorough monitoring, and personalized nutritional plans are essential to maximize the benefits of a KD while minimizing its adverse effects.

Keywords: Ketogenic Diet; Acute Pancreatitis; Low-Carbohydrate Diet; Hypertriglyceridemia; High-Fat Diet

Introduction

Ketogenic diets (KDs) are high-fat (55%-90%), low-carbohydrate (5%-10%), and balanced-protein (30%-35%) diets characterized by low caloric intake. They are known to have beneficial effects on weight control, glycemic management, polycystic ovarian syndrome, and neurological disorders such as epilepsy [1-5]. Although the exact mode of action is not completely understood, KD is thought to have antiseizure effects by stabilizing multiple inhibitory neurotransmitters [6]. The classic ketogenic diet consists of one gram of protein per kilogram of body weight, 10–15 g of carbohydrates per day, and the remaining calories are derived from fat [7]. A KD is a high-fat diet that induces a state of ketosis, where the utilization of ketone bodies is the main energy source. While studies have reported that KD is strongly associated with body weight control in overweight individuals [8-10], other evidence has shown an association between KD and a deteriorated lipid profile [11,12]. Acute pancreatitis (AP) is a disorder of inflammation of the pancreas, and the pathogenesis and causes of AP have been extensively researched, with alcohol and gallstones being the most common. Hypertriglyceridemia (HTG) remains an uncommon but well-established cause of AP. Although the exact mechanism is not understood, most studies suggest that the metabolism of excessive triglycerides (TGs) by pancreatic lipase to free fatty acids (FFAs) leads to pancreatic cell injury and ischemia. AP can be diagnosed by the presentation of characteristic symptoms such as abdominal pain and elevated pancreatic enzyme levels [13].

The most common adverse effects of KD include hypoglycemia, vomiting, metabolic acidosis, constipation, nephrolithiasis, electrolyte imbalance, anemia and leukopenia, and acute pancreatitis [14]. Given the high-fat content of KD patients, there is an emerging concern about the association between acute pancreatitis and KD. This review aimed to explore the link between KD and AP, focusing on the

hyperlipidemic pathways involved. By examining the current literature, case studies, and clinical evidence, this review seeks to provide a comprehensive understanding of the potential risks associated with KD, particularly concerning lipid metabolism and pancreatic health.

The Ketogenic Diet – A Dietary Treatment for Epilepsy

The first modern use of starvation as a treatment for epilepsy was recorded in Paris in 1911. Over the next decade, different variations of a low-calorie diet were demonstrated to be effective in decreasing the severity and frequency of seizures. In 1925, the Mayo Clinic introduced the ratio of macronutrients to be consumed to induce ketosis: 1 g of protein per kilogram of body weight in children, 10–15 g of carbohydrates per day, and the remainder of the calories in fat [15]. A 1972 Johns Hopkins Hospital textbook stated that 52% of epileptic children on the KD had complete control of seizures and 27% had improved control [16]. Given the dawn of modern anti-epileptic drugs, the use of the KD decreased drastically. However, since the early 2000s, the KD has gained popularity for managing refractory seizures [17]. Over the decades, many variations of the classic ketogenic diet have emerged, as seen in Figure 1 and Table 1.

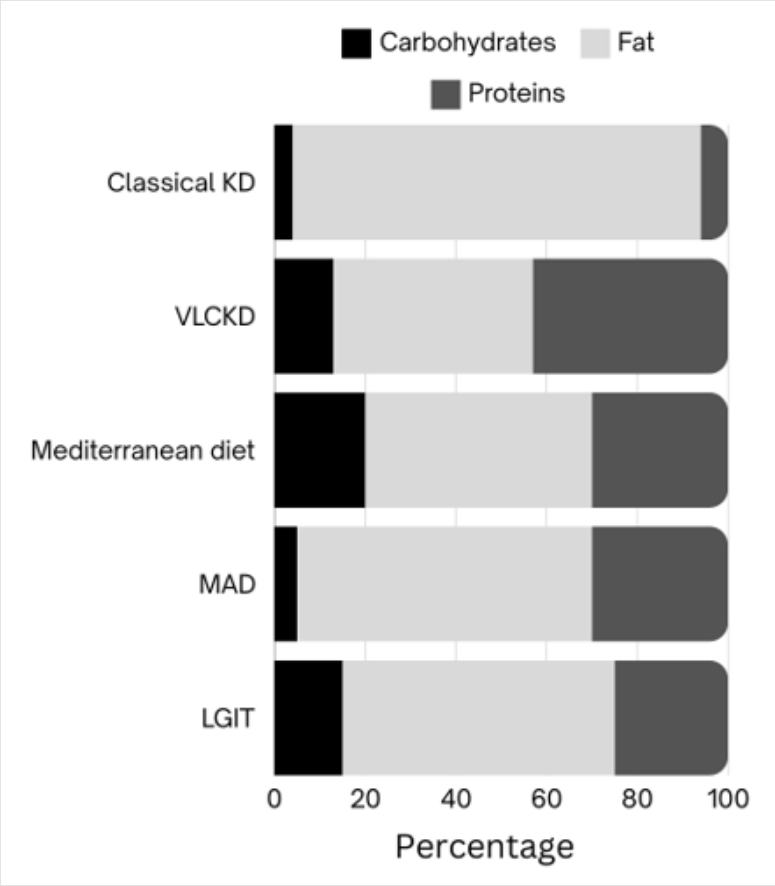

Figure 1: Variations on the ketogenic diet.

Table 1: Proportions of nutrients in the variants of the ketogenic diet.

Diet	Fat	Carbohydrates	Proteins
Classic KD	90%	4%	6%
VLCKD	44%	13%	43%
MAD	65%	5%	30%
LGIT	60%	15%	25%
Mediterranean diet	50%	20%	30%

The diets vary in their composition of free fatty acids (FFAs). The classic KD (fat = 90%, protein = 6%, carbohydrate = 4%) has a 4:1 ratio of grams of fat to grams of carbohydrates and protein. The very low energy KD (VLCKD) (fat = 44%, protein = 43%, carbohydrates = 13%) restricts daily calories to <800 kcal/d. The modified KD, or Mediterranean diet (fat = 50%, protein = 30%, carbohydrate = 20%) emphasizes lean meats and plant-based fats. The modified Atkins diet (MAD) (fat = 65%, protein = 30%, carbohydrate = 5%) does not restrict calories and allows for a greater proportion of proteins [18].

The medium-chain triglyceride (MCT) diet derives 30% of its energy from MCT oil and 30% from long-chain fats, while the proportions of proteins and carbohydrates are greater than in a classic KD [19]. The Mediterranean and MCT diets must be supplemented with external vitamins and minerals. The low glycemic index treatment (LGIT) (fat = 60%, protein = 25%, carbohydrate = 15%) encourages eating low glycemic index foods along with a high fat intake. It produces a lower level of ketosis and is usually preferred in adolescents and adults, as compared to the classic KD, which is preferred in ages <2 years [20].

While the role of the KD in abating seizures is still under investigation, here is what is known. The KD works against seizures through a combination of metabolic shifts, neuroprotective mechanisms, modulation of ion channels, reduction of oxidative stress, alteration of neurotransmitter levels, and increased mitochondrial density. The shift in energy production to fats produces ketone bodies (KBs), reducing neuronal excitability. KBs also alter ion channels and slow down spontaneous neuronal firing. Increased acetyl-CoA production due to ketosis confers neuroprotection via myelin synthesis. The KD leads to an initial increase in reactive oxygen species (ROS) due to heightened mitochondrial activity; the body adapts to this change and in response triggers mitochondrial biogenesis in the brain and glutathione production, both necessary cellular infrastructure to prevent seizures. The KD also enhances inhibitory effects in the brain via adenosine receptors [21,22]. Evidence also suggests that by decreasing aspartate levels, KBs lead to the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) [22]. Another hypothesis suggests that, on the KD, the brain utilizes KBs for energy, instead of glucose. This reduces energy levels, thus also reducing excitatory neuronal activity that causes seizures [21,22]. As we will explore later, KD alters the gut microbiome. Gut microbiota is known to affect the activity of a myriad of neurotransmitters. The increase in Akkermansia and Parabacteroides species increases GABA in the brain, providing protection against seizures [23].

Methods – Literature Search

We undertook a narrative literature review of peer-reviewed articles to identify, appraise, and analyze research conducted on acute pancreatitis and dyslipidemia due to KD. The structure of our review follows Ferrari's [24] 2015 paper. Studies were selected by searching PubMed, Cochrane Trials, and Google Scholar. The following search string was found to yield the most relevant results: "pancreatitis" AND "ketogenic." Reference lists of the included papers were also searched. We included papers that described patients with classic symptoms of acute pancreatitis, as described by Szatmary in 2022 [25]. We did not limit or filter our search by comorbidities to gain a better understanding of the relationship between low-carbohydrate/high-fat diets and acute pancreatitis due to hyperlipidemia. Only fully available research texts were included, and any letters, commentaries, or literature reviews were excluded. Papers focusing only on animal studies and staff perspectives were also excluded. A total of 4,340 articles were identified in our initial search. After reviewing the titles and full texts, origin, duplication, and excluded texts, 12 articles were identified for inclusion in this review. One researcher read these papers and completed a spreadsheet presenting the main details of each article.

Results

Patient Demographics and Reasons for Initiating KD

The patients with outcomes of interest ranged in age from 4.2 years to 70 years. All but two of the case studies [26,27] described male patients. The most common reasons for initiating KD were refractory epilepsy [26,28-32], dyslipidemia [33,34], obesity [33,35], and diabetes [28,34,36]. Other reasons included hypertension [34,27] and gout [34]. In total, 14 patients were found to have acute pancreatitis in our review. Notably, none of the studies reported which classical category of KD the participants adhered to. The duration of KD adherence before acute pancreatitis development ranged from 3 weeks to 15 months. One case study [33] did not report the duration of KD adherence, and the patients in Almodallal, et al. [35] study had varied adherence periods.

Overview of the Case Studies and Cohort Studies

Seven articles were case studies [26-28,33,34,36,37]. The majority of patients in these case studies presented with body mass indices (BMIs) in the obese range (36-41 kg/m^2). Additionally, three patients [26,34,37] exhibited abnormal liver function enzymes. All patients who developed acute pancreatitis discontinued the KD following diagnosis and hospitalization, with one case of fatality reported [28]. Specific patient history revealed that one individual had a history of fibrate use [33], two were on insulin therapy [28,36], and one was on multiple medications, including valsartan, amlodipine, fibrate, and chlordiazepoxide [37]. In contrast, patients described in the studies by Stewart, et al. [26], Choi, et al. [34], and Shanti, et al. [27] were not on any medications. The findings of the case studies have been summarized in Table 2. Four articles involved retrospective cohorts [29-31,35], and one involved a prospective cohort [32]. These studies primarily focused on evaluating the efficacy of a KD in alleviating symptoms of refractory epilepsy; consequently, comprehensive data on the development of acute pancreatitis are lacking. Among the 445 patients included in all cohort studies, only 7 (1.6%) developed acute pancreatitis. Additionally, at least 61 patients (13.7%) developed HTG. Notably, Mackay, et al. [31] and Almodallal, et al. [35] reported unspecified dyslipidemia instead of specific HTG. The findings of these cohorts are summarized in Table 3.

Table 2: Summary of case reports.

	Stewart, et al. [26]	Buse, et al. [33]	Mori, et al. [28]	Choi, et al. [34]	Chan, et al. [36]	Sikaroudi, et al. [37]	Shanti, et al. [27]
Demographic	9 yo female	42 yo male	5 yo male	35 yo male	19 yo male	48 yo male	47 yo female
Reason (s) for initiation of a KD	Defects in glucose transport protein leading to seizures	20-year history of hypertriglyceridemia	MEHMO syndrome refractory to antiepileptics	Hypertension	Type 2 diabetes mellitus	Family history of hyperlipidemia	Hypertension
	kidney stones			Gout			Depression
				Type 2 diabetes mellitus			Hypothyroidism
				Dyslipidemia			
MEDICATION HISTORY	N/A	gemfibrozil	insulin	N/A	insulin	fenofibrate	N/A
						valsartan	
						amlodipine	
						chlordiazepoxide	
Duration of KD before symptoms appeared	8 years	N/A	5.25 years	3 weeks	3 months	45 days	24 days
SERUM AMYLASE U/L	2810	114	196	N/A	25389	10150	3500
SERUM LIPASE U/L	N/A	530	N/A	2283	2195	140	19500
WBC COUNT WBC/mm3	N/A	12800	N/A	15400	N/A	N/A	16100
SERUM TRIGLYCERIDE mg/dL	N/A	>1000	6500 at age 49 months	222.3	6021	7891	normal
			NA at the time of admission				
BMI kg/m2	N/A	36	obese	obese	41	36.7	N/A
SERUM GLUCOSE mg/dL	N/A	N/A	444	167.4	319	699	N/A
OUTCOME	N/A	discharge after 13 days	death after 5 days of admission	discharge after 2 days	discharge after 8 weeks	discharge after 10 weeks	discharge after 2 months

Table 3: Summary of cohorts.

	Kang, et al. [29]	Lyczkowski, et al. [30]	Mackay, et al. [31]	Almodallal, et al. [35]	Sofou, et al. [32]
MEAN AGE	5.4 years	6.52 years	6.1 years	70 years	4.2 years
Reason (s) for initiation of a KD	refractory epilepsy	refractory epilepsy	refractory epilepsy	obesity	Pyruvate dehydrogenase complex deficiency
				diabetes control	
MEDICATION HISTORY	N/A	N/A	N/A	N/A	N/A
Duration of KD before symptoms appeared	12 months	4 months	9 months	varied	15 months
Number of patients who developed pancreatitis (%)	1 (0.8)	2 (2.8)	1 (4)	2 (1)	1 (7.7)
Number of patients who developed HTG (%)	46 (35.6)	15 (21.1)	N/A	N/A	N/A
OUTCOME	71.7% of hypertriglyceridemia cases resolved spontaneously, while 1 patient discontinued KD treatment	AP patients discontinued	Early cessation of the ketogenic diet	N/A	AP patients discontinued
	AP patient discontinued				

Laboratory Values and Reporting Inconsistencies

The reported laboratory values were inconsistent across the studies. Serum amylase levels, where reported, were significantly elevated, ranging from 114 U/L to 25,000 U/L (normal range: 30-110 U/L). Notably, Choi, et al. [34] did not report serum amylase levels. Serum lipase levels, also elevated, ranged from 140 U/L to 19,500 U/L (normal range: 10-140 U/L), with omissions reported by Stewart, et al. [26] and Mori, et al. [28]. Three studies [36,27,31] reported white blood cell (WBC) counts, which varied from 12,800 WBC/mm^3 to 16,000 WBC/mm^3. Regarding serum triglyceride levels, all case reports except one [26] provided data. Of these, one patient [27] reported normal triglyceride levels, while others showed HTG ranging from 220 mg/dL to 7900 mg/dL. Serum glucose levels were reported in four case reports [28,34,36,37], with values ranging from 165 mg/dL to 700 mg/dL. Management of all aforementioned cases is discussed later.

Summary and Recommendations

This analysis highlights the critical need for comprehensive and standardized reporting of laboratory values in case studies of patients on a ketogenic diet, particularly in the context of acute pancreatitis. Further research should include detailed monitoring of metabolic complications to better understand and mitigate the risks associated with KD therapy.

Hypertriglyceridemia and Acute Pancreatitis

The third leading cause of AP preceded by alcohol overdose, hypercalcemia, and gallstones is HTG, accounting for 1-12% of AP cases [38]. Pancreatitis secondary to HTG typically occurs due to any primary (inherited or genetic) disorder of lipid metabolism or the presence of any secondary (acquired disorders) such as after initiating KD [36]. Primary causes of HTG result from five different types of hyperlipidemia: I, II, III, IV, and V, according to the Fredrickson classification. Types I, IV, and V hyperlipidemia patients' have a relatively higher risk of developing HTG-AP. Secondary HTG occurrence is due to various conditions such as uncontrolled diabetes, pregnancy, obesity, alcohol consumption, and certain medications. It is not particularly a risk factor for AP unless accompanied by underlying dyslipidemia [39,40].

High-Risk Group

In comparison to individuals without HTG, HTG-induced pancreatitis is more prevalent in younger males than females, and middle-aged people with comorbidities such as obesity and type 2 diabetes [36,41]. Furthermore, the incidence of KD-associated pancreatitis is reported more among patients with a history of severe HTG, fatty acid oxidation disorders, refractory epilepsy with long-term classic KD, and familial hyperlipidemia [37]. Other risk factors include already present lipoprotein metabolism dysfunction, inadequately controlled diabetes, otherwise healthy patients with medication-induced secondary HTG (corticosteroids, beta-blockers, diuretics), and alcoholism [40]. Several studies have reported HTG-AP in patients on estrogen therapy, olanzapine therapy, protease inhibitors, tamoxifen, and isotretinoin [39].

Clinical Features and Diagnosis

Patients with HTG-induced pancreatitis generally exhibit symptoms such as nausea, vomiting, and intense abdominal pain, similar

to patients with acute pancreatitis originating from other etiologies [36]. The diagnosis of HTG-AP is similar to that of any other AP and requires 2 of the following 3 factors: characteristic abdominal pain, serum levels of pancreatic lipase and amylase enzymes elevated above 3 times the upper limit of normal (ULN), and characteristic radiological findings together with an elevated triglyceride level [13].

The preliminary assessment of the patient's organ function failure is necessary for monitoring and diagnosing the condition. The diagnostic work should cover several tests such as complete blood count (CBC), triglycerides, calcium, serum lactic acid levels, serum amylase, and lipase to estimate the severity or outcome of the disease [42]. Through physical examination a diagnosis of HTG-AP can be drawn, as in patients with HTG, xanthomas are observed within the skin, tendons, and subperiosteum. In the case of severe and chronic HTG, xanthomas in the dorsum of the hand, ankle, and forearm, planar xanthomas, eruptive xanthomas, hepatosplenomegaly, lipaemia retinalis, and milky plasma samples are observed [43]. A triglyceride level greater than 1000-2000 mg/dL is one of the diagnostic criteria for acute pancreatitis secondary to hypertriglyceridemia. Triglyceride (TG) levels above 1000-1999 mg/dl increase the incidence of acute pancreatitis by 10%, whereas the risk increases to 20% when TG levels exceed 2000 mg/dl [44].

Pathophysiology of HTG-Induced Acute Pancreatitis

The pathophysiology of HTG-induced AP involves the accumulation of FFAs and the subsequent initiation of the inflammatory response. According to the theory proposed by Havel in 1969, pancreatic lipase hydrolyzes excess TGs into FFAs within the pancreatic vascular bed [45]. Although TGs themselves are not directly harmful to the pancreas, their enzymatic breakdown into FFAs initiates toxicity, targeting different regions of the pancreas. As a consequence of increasing concentrations of FFAs, the free-binding capacity of albumin decreases. These unbound FFAs self-aggregate into micellar structures with detergent-like properties, which attack platelets, the vascular endothelium, and acinar cells, leading to ischemia and pancreatic injury [20]. Furthermore, an inflammatory response is triggered by elevated FFA levels, leading to acinar cell necrosis through the release of intracellular calcium and inflammatory mediators such as TNF-alpha, interleukin-6, and interleukin-10. This mechanism leads to pancreatic autodigestion and ultimately acute pancreatitis [46].

An alternative theory regarding the mechanisms of HTG-induced acute pancreatitis involves elevated blood viscosity due to high TG levels. Increased TG concentrations can potentially result in ischemia and acidosis within pancreatic capillaries by thickening the blood and impairing microcirculation within tissues. This disruption in the pancreatic microcirculation is exacerbated by HTG-induced production of the vasoconstrictor thromboxane A2 and diminished secretion of the vasodilator prostaglandin 2. This imbalance causes excessive contraction of capillary beds, which worsens pancreatic microcirculation and contributes to the development of HTG-AP [46,47]. Significantly elevated levels of unsaturated fatty acids (UFAs), predominantly oleic (C18:1) and linoleic acid (C18:2), identify UFAs as potential biomarkers and mediators for severe AP. Moreover, diet-induced visceral fat unsaturation increases the generation of UFAs via lipolysis, which further exacerbates HTG-induced AP and results in cell injury, systemic inflammation, and organ failure. Conversely, long-chain saturated fatty acids such as palmitate reduce the production of UFAs by inhibiting the lipolysis process. Thus, despite the presence of excess adiposity, this interference reduces the severity of AP [47].

Pancreatic Injury as a Sequela of the Ketogenic Diet

A KD has promising anti-tumor effects in pancreatic cancer since the state of ketosis shifts carbon metabolism in cancer cells into the Krebs cycle [48-51]. However, the KD demonstrably increases lipopolysaccharide binding proteins (LBPs), and inflammatory cytokines such as IL-1a, IL-5, IL-12, MIP-1a, and Rantes. Dysfunction of the intestinal barrier due to the downregulation of proteins involved in maintaining tight junctions is another consequence of following a KD. This occurs primarily due to reduced levels of Bacteroidetes & short chain fatty acids, and the downregulation of the hexose monophosphate shunt. The resulting permeability of the intestinal barrier leads to gut microbiota infecting pancreatic tissue secondary to acute pancreatitis [52] – a deadly complication [53]. The variation in gut bacteria is shown in Table 4.

Table 4: Variation of gut bacteria between ketogenic and normal diets.

Predominant gut microbiome in a standard diet	Predominant gut microbiome in a KD
Bacteroidales	• Lachnospiraceae
	• Erysipelotrichales
	• Oscillospirales

Incidence and Severity of Hypertriglyceridemia in Patients on a Ketogenic Diet

Although there is limited literature discussing acute pancreatitis in direct relation to KD, there is ample evidence that KD leads to HTG. Edu et al. discovered that HTG-AP was associated with longer intensive care unit (ICU) admissions, pancreatic necrosis, acute peripancreatic fluid collection, and an overall more severe course of disease compared to severe AP from other causes [54]. As far back as 1966, epileptic children who had been on a KD for several weeks were found to have TG levels >1000 mg/dL [55]. In 1999, it was found that children on a KD for a mean of 10 months developed triglyceride levels higher than 95% of the population [56]. Long-term adherence to a KD can also alter the levels of cholesterol and lipoproteins. After 6 months on the diet, low-density lipoprotein (LDL), total cholesterol, and very low-density lipoprotein (VLDL) levels all increased well above the 95th percentile [57,58], while high-density lipoprotein (HDL) decreased significantly. This is an under reported yet key find-

ing since a high TG/HDL ratio is positively correlated with the severity of HTG-AP [59]. In fact, after 6 months, only 14% of children maintain a total TG level deemed acceptable by the National Cholesterol Education Program pediatric panel. Recent cohorts have shown that between 40% and 72% of patients develop HTG after long-term KD [60,61]. These levels can reach as high as 1900 mg/dL after 3 years of the diet [62] or even >3500 mg/dL after 9 months [63], depending upon the patients' baseline lipid profile.

Conversely, studies also suggest that long-term KD in epileptic children causes a spike in cholesterol and TGs within the first month that gradually decreases during the next 2 years of the diet. These discrepancies can be explained by the variation in the types of lipids consumed by patients. For example, the use of foods rich in monounsaturated fatty acids (MUFAs) has beneficial effects on lipid profiles and inflammatory marker levels. This is further supported by the finding that the ratio of saturated to unsaturated fats plays a role in altering the lipid profile of patients on a KD [64].

Management

Treating HTG-AP is aimed at reducing circulating levels of TGs, specifically by using intravenous (IV) heparin and insulin [36,37,65]. Patients with refractory disease are subjected to plasmapheresis to remove TGs, lipoproteins, and inflammatory cytokines [37,65]. Plasmapheresis can also be considered during pregnancy. Surgical intervention is typically reserved for complications of acute pancreatitis, such as infected necrosis or pseudocysts, rather than as a primary treatment. Clinically, AP is an emergency. Initially, patients are stabilized with aggressive rehydration and fluid replacement [33,34,36,37,27], analgesia [33,34,27], and vasopressor therapy for shock [36]. Patients are usually kept nil per os (NPO) for a few days until painless refeeding can be established [33,34,37,27]. Additional interventions include antiemetics and prokinetics to prevent gastrointestinal upset [34,37,27], oxygen therapy via a Venturi mask, or intubation in cases of respiratory distress [36,37], and pancreatic enzyme replacement therapy [37]. Sepsis is a common consequence and must be managed with IV antibiotics [37]. Pancreatic duct disruption must be addressed by placing a pancreatic stent via endoscopic retrograde cholangiopancreatography (ERCP) [36]. Fibrates, statins, niacin, and omega-3 fatty acids can be used as adjuvant pharmacological therapies for maintaining lower levels of TGs post-hospitalization [33,36,37,66].

Counseling patients regarding healthy lifestyle changes after being discharged from the hospital is also vital; patients must maintain their ideal body weight using a low-fat diet and regular exercise [33]. Dietary strategies include a fat-restricted diet (<20 g total fat/day), a low-carbohydrate diet, and regular monitoring of TG levels [65]. Exercise plays a crucial role in preventing HTG-AP by attenuating postprandial plasma triglyceride (PPTG) elevation and reducing triglyceride-rich lipoprotein (TRL) concentrations. Studies have shown that acute exercise, regardless of timing relative to a high-fat meal, significantly decreases postprandial HTG, thus lowering the risk associated with elevated TG levels [67]. While evidence for prophylactic antibiotic use for reducing mortality is controversial and at times contradictory [68-71], butyrate supplementation proves promising in decreasing the permeability of the gut barrier, reducing pancreatic necrosis, and slowing oxidative stress in the pancreas. One hypothesis suggests that butyrate enhances tryptophan metabolism, a pathway that attenuates intestinal barrier dysfunction [46].

Risk-Reducing Strategies Against HTG-AP in KD Users

After the initial management of HTG-AP, appropriate measures consisting of both comprehensive lifestyle modification and pharmacological therapy are vital to abate the risk of recurrence. Lifestyle changes are directed at dietary adjustments achieved by adopting a diet low in saturated fat and high in omega-3 fatty acids, achieving weight loss, abstaining from alcohol, and limiting the use of refined sugar [67]. Additionally, it is crucial to manage secondary risk factors such as diabetes and avoid medications that can increase serum TG levels [72].

Monitoring Serum Triglyceride Levels

Patients with severe HTG have been reported to benefit from self-monitoring their lipid levels at home. This approach allows individuals to customize their diet according to their needs, thereby regulating TG levels and preventing severe bouts of HTG [45]. Lowering serum TG levels is the target of effective long-term therapy for HTG-AP, with levels below 500 mg/dL typically considered ideal for preventing recurrent illness. However, recent research on the risk of recurrent AP suggests that serum TG may need to be maintained at levels lower than 200 mg/dL to prevent recurrences more effectively [73].

Dietary Adjustments

A KD is an exceptionally high-fat diet that causes a considerable increase in the plasma concentrations of triglycerides and total cholesterol [46]. Several studies have shown that dietary restriction plays a crucial role in the management of HTG. Patients with excessive TG levels in the body should adhere to dietary counseling in addition to lipid-lowering treatment to manage TG within the normal range through a healthy and balanced diet [58]. A moderate-to-high-fat diet high in MUFAs is recommended by several studies, even though the ideal macronutrient balance has not yet been definitively established. Therefore, it is essential to limit the consumption of saturated fats while increasing the intake of MUFAs found in nuts and olive oil and omega-3 fatty acids present in oily fish. As highlighted by several studies, substituting 1% of energy intake from carbohydrates with fats can lower serum TG levels by 1% to 2%. Therefore, the optimal diet for individuals with HTG should consist of complex carbohydrates such as whole grains, fruits, and vegetables and should be rich in fiber [47].

Weight Loss

Research has revealed a significant correlation between weight loss and decreased serum TG levels. Thus, individuals dealing with HTG should consider appropriate diet plans together with lipid-lowering treatments to achieve effective reductions in TG levels [67]. Notably, a significant reduction in the serum TG level is observed when any diet plan directed toward weight loss is followed, regardless of the macronutrient composition of the diet. This is further supported by the findings that blood TG levels are lowered by 0.017 mmol/L for each kilogram of weight loss, as stated in a systematic review and meta-analysis based on 70 trials that focused solely on dietary treatments for weight loss. These data emphasize that diet-based weight management plays a crucial role in successfully reducing TG levels [47].

Gene Therapy

In individuals with HTG-AP, LPL deficiencies are the primary and conclusive cause of recurrent episodes, and recurrent AP is the most crippling and potentially fatal complication. To address this issue, routine genetic screening for mutations in key TG-regulating genes, such as LPL, APOE, APOC2, LMF1, and GPIHBP1, is recommended to identify candidates who might benefit from gene therapy [47]. A potential long-term treatment for severe HTG together with marked LPL deficiency involves the application of a viral vector containing an LPL gene directly into the muscle tissue. This gene therapy enables patients to effectively regulate postprandial chylomicronemia through a background of plasma lipolytic activity. LPL gene therapy may prove to be a valuable adjunct to other therapeutic approaches for achieving long-term control of HTG-AP [73].

Plasmapheresis

Plasmapheresis is a valuable treatment for severe hypertriglyceridemia, especially for patients who do not adhere to medications and lifestyle recommendations [46]. This therapy involves the removal of harmful antibodies, TG levels, chylomicrons, inflammatory cytokines, and other components from blood circulation, particularly by extracting and filtering a considerable amount of plasma. According to a previously conducted study, 50% to 60% of TGs are reduced in one session of plasmapheresis [47,74]. This procedure offers two significant advantages in its mechanism of action. Primarily it effectively eliminates TGs from patients' plasma, secondly, patients are simultaneously infused with lipoprotein lipase (LPL) and apolipoprotein C-II from the fresh frozen plasma of a healthy donor. Therefore, during the acute phase of AP or in the prevention of recurrence of AP, plasmapheresis is highly beneficial for lowering TG levels [75,76].

Conclusion

A ketogenic diet is known for its effectiveness in managing multiple conditions, such as refractory epilepsy, obesity, and type 2 diabetes. However, the high-fat content of KD poses a significant risk for HTG, which can lead to acute pancreatitis. This narrative review explores the link between KD and AP, emphasizing the hyperlipidemic pathways involved. Our review of case studies and cohort studies demonstrates that individuals with KD, especially those with accompanying predisposing factors such as obesity, type 2 diabetes, and genetic predispositions, are at increased risk of developing HTG and subsequent AP. The pathophysiology involves the buildup of free fatty acids FFAs and the initiation of inflammatory responses, leading to pancreatic cell injury and ischemia. The lack of consistency in reporting laboratory values across studies underscores the need for comprehensive and standardized monitoring of patients with KD, especially regarding lipid levels and genetic factors affecting lipid metabolism. Early identification and management of HTG can help prevent AP and other metabolic issues. Further research is required to better understand the mechanisms linking KD to AP and to refine dietary recommendations for patients with KD. Healthcare providers should carefully monitor lipid profiles and consider individual genetic predispositions when recommending a KD to mitigate the risks associated with this diet.

In conclusion, while a KD offers potential benefits, it also carries significant risks for lipid metabolism and pancreatic dysregulation. A balanced approach, thorough monitoring, and personalized dietary plans are essential to maximize the benefits of a KD while also minimizing its adverse effects. Healthcare professionals should prescribe restrictive diets, such as a KD, with great caution.

Conflict of Interest

The authors have no competing interests to declare.

Availability of Data and Materials

All data analyzed in this study are included in this published article.

Ethics Approval and Consent to Participate

Not applicable.

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