Etitiological Relationship between Hyperlipidemia and Acute Pancreatitis

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Abstract

Hyperlipidemia is a kind of pancreatitis caused by high triglyceride levels in the blood. The morbidity and mortality of this disease continue to increase worldwide, and it has become one of the most common gastrointestinal diseases in developed countries worldwide. Although many studies have been conducted, the pathogenesis still cannot be defined. Many studies have shown that this may be related to the triglyceride decomposition products free fatty acids are the main toxic substances, which can directly damage pancreatic acinar cells and vascular endothelial cells, causing tissue ischemia and acidic environment. Therefore, this paper focuses on the correlation of triglycerides and their decomposition products in plasma and provides evidence on the pathogenesis of AP and the disease progression of AP. Finally, the future potential to prevent and treat acute pancreatitis by some new drugs to reduce plasma triglycerides is summarized.

Keywords

1. Introduction

Acute pancreatitis (acute pancreatitis, AP) has become one of the most common gastrointestinal diseases in developed countries in the world, with a high mortality rate and no specific treatment methods. AP refers to a disease in which the pancreas self-digest, leading to pancreatic tissue damage, which leads to dysfunction of glands, organs and systems. Due to changes in lifestyle and dietary habits, risk factors such as population growth, smoking, changing drinking patterns, and rising obesity rate all lead to a significant increase in the incidence of

AP [1]. Among them, hypertriglyceridemia (HTG) is a rare but recognized cause that is more likely to lead to higher morbidity, recurrence risk and serious complications, and these probability increase year by year. According to the latest research data in China, the proportion of patients with HTG-AP has increased to 34.0%. Experts believe that high CRP, hypocalcaemia, and low albumin are the risk factors for severe HTG-AP [2]. Some scholars have proposed that the etiology of HTG can be roughly divided into two categories: primary and secondary. And that primary and secondary interactions can cause very severe HTG. In a multicenter prospective study, HTG-AP was the fourth most common cause of AP worldwide, and patients with primary HTG-AP were about 10 years younger than those with other causes, and were mostly male, or about 2/3. In addition, the proportion of obese patients (BMI values) is also higher than that of patients with other etiologies, which may be associated with their frequent alcohol consumption. First we know that both chylomicron and VLDL are the main carriers of TG, and alcohol leads to increased VLDL synthesis in the liver and suppresses the activity of lipoprotein lipase, which leads to reduced chylomicron breakdown, and then increased TG levels, leading to the occurrence of HTG-AP [3]. Severe HTG is common in familial chylomicronemia (FCS), primary hypertriglyceridemia and mixed hypertriglyceridemia, called type Fredrickson I, IV and V, respectively, which also includes the involvement of complex genetic inheritance. Secondary factors associated with HTG include obesity, alcohol abuse, diabetes mellitus, hypothyroidism, oestrogen, and retinoic acid [4]. However, the exact mechanisms and biological pathways of HTG involvement in AP are not fully elucidated, and there are no standardized treatment guidelines. Therefore, a deeper understanding of the mechanisms associated between HTG and AP is needed, as well as further exploring the current treatment of AP and promising future therapeutic prospects.

2. A Study on the Pathogenesis of HTG and AP

2.1. TG/FFA and HTG-AP

Although the pathogenesis of HTG-AP is not completely understood, numerous studies have shown that TG and its products play an important role in the process of HTG-AP. Many experiments have been conducted to propose some theories about the pathogenesis of HTG-AP. Triglycerides (TG) have a crucial role in storing excess energy, which is stored as a TG for excessive nutrients (say, carbohydrates, protein, fat) [5]. Tracking TG levels early disease (especially within 24 hours without intervention) facilitates assessment of disease severity [6]. Furthermore, it has been proposed that the odds of developing SAP are significantly increased at 48 h TG levels > 5.6 mmol/L after admission, so that TG can predict AP severity to some extent and may be related to the progression of SAP [7]. The severe hypertriglyceridemia (sHTG) was defined as TG 880 mg/dl [8], While the standard mentioned in the US literature is that TG 500 mg/dl only meet the sHTG diagnostic criteria [9]. Although a high-fat diet (HFD) increases

oxidative stress and enhances inflammation in the body [10]. However, one study showed that TG did not induce AP only when TG was hydrolyzed by lipase to FFA (free fatty acids) and in the presence of Ca at sufficient high concentrations of unsaturated fatty acids^{2+} Concentrations will continue to rise, as well as trypsin activation and cell damage, and eventually AP occurs [11]. Perhaps, this would suggest that TG has no intrinsic toxicity to the pancreas, and can cause lipotoxicity when TG is decomposed into FFAs by pancreatic lipase. Another study demonstrated that exposure to free fatty acids resulted in intracellular Ca^{2+} Concentrations increase, thereby inducing ER stress, and hyperlipidemia can prolong ER stress, leading to acinar cell deregulation and aggravating AP [12]. HTG-induced up-regulation of miR-153 could exacerbate the inflammatory response and metaplastic process of acinar-duct by targeted inhibition of TRAF 3, so increasing AP severity and delaying repair of pancreatic tissue. However, SREBP1c can inhibit miR-153, thus preventing AP and promoting tissue repair. When this signal is dysregulated, it can cause severe AP and impaired tissue repair [13]. Glycosylphosphatidylinositol-anchored high-density lipid egg-binding protein 1 (GPIHBP1) is a glycolipid-anchored protein of capillary endothelial cells that can transport lipoprotein lipase (LPL) to the capillary lumen and stabilize LPL. Functional loss of GPIHBP1 can lead to retention of LPL in the capillary lumen space, leading to HTG. And autoantibodies to GPIHBP1 were found to be common in the serum of HTG-AP patients and were an independent risk factor for AP recurrence [14].

2.2. Ca^{2+} and the HTG-AP

A retrospective single-center study has long since identified serum Ca in patients with HTG-AP^{2+} Low level, which is one of the main risk factors of severe AP [15]. Moreover, it have also demonstrated that Ca in HTG-AP^{2+} Toxicity is critical for the short-term, localized Ca^{2+} The peak may be converted to long-term intracellular cytosolic Ca^{2+} Elevated, leading to intracellular trypsin activation [16]. In cases of excessive fat content, FAE-induced ATP depletion is prevented by plasma Ca^{2+} The-ATP enzyme-mediated Ca^{2+} Squeeze as well as Ca^{2+} The refilling of the ER stores by the-ATP enzyme, resulting in Ca^{2+} Concentrations continued to increase, when Ca^{2+} Into the cytoplasm will further aggravate the mitochondrial Ca^{2+} Overloading and dysfunction, forming a vicious cycle that ultimately leads to cell death [17]. It was shown that fatty acid ethyl esters can cause pancreatic cell-free Ca mediated by the inositol triphosphate receptor channel^{2+} Concentrations and Ca^{2+} The increased oscillation of the activation current, and the decreased ATP synthesis, contributes to the development of AP [18]. According to Navina *et al.*, unsaturated FFAs can induce elevated Ca^{2+} concentrations in acinar cells and inhibit mitochondrial complexes I and V, leading to their dysfunction, and these pathological processes eventually induce mitochondrial swelling and necrosis, acinar cell necrosis, and tissue inflammation [19]. It is well known that PA (palmitic acid) is the most common saturated

fatty acid in human [20], It can promote protein kinase activation, Ca^{2+} overload, ER stress, increase of ROS, and enhanced signaling of TLR 4 to lead to inflammation generation [21] [22]. So, many experiments through the use of PA induction to establish mouse AP model, we know that PMCA (plasma membrane calcium ATP enzyme) is the only calcium ion efflux pathway, in the mouse model, although the mitochondrial function is impaired, but using insulin pretreatment can effectively eliminate POA induced ATP depletion during cell stress, which is enough to maintain the function of PMCA and partially prevent Ca^{2+} cytotoxic harmful effect overload, reduce the damage of pancreatic acinar cells. Furthermore, insulin enhances the glycolytic ATP supply, thereby maintaining PMCA activity, helping to prevent the overload and subsequent self-sustained tissue damage of cytotoxic calcium during AP, and these studies provide convincing evidence of a direct protective effect of insulin on acinar cells [23] [24].

2.3. ER Stress

Endoplasmic reticulum (ER) is a multifunctional organelle involved in protein synthesis, folding and quality control. Because the acinar cells have a very rich ER network, the function and homeostasis of ER are highly susceptible to various external factors. ER stress is a key process leading to cell death, an adaptive process, and is an early event mediated by calcium signaling, and also leads to the activation of NF-κB signaling [25], Is a pathophysiological concept explaining AP at the cellular and biological level. Several studies have shown that ER stress is responsible for lipid-induced inflammatory response, causing ER stress in excess lipids, and shown that PA can inhibit cell proliferation and induce ER-related apoptosis [26]. In the HTG rat model established by PA, it was found that activation of ER stress and inflammatory response occurred during PA-induced acinar cell damage, and that ER stress was mediated by the inflammatory response through two transcription factors, C/EBP α and C/EBP β [27]. It is worth noting that the high fat diet itself can cause visceral, fat, muscle tissue, such as ER stress triggers the unfolded protein response (UPR), UPR signal transduction depends on highly coordinated response, involving three parallel signal branches, including inositol demand enzyme 1 α (IRE 1 α), double-stranded RNA-dependent protein kinase-like endoplasmic reticulum kinase (PERK) and activating transcription factor 6 (ATF 6), the three transmembrane proteins are activated under ER stress [27] [28]. The *in vivo* and *in vitro* experiments also proved that HTG not only strengthens AP, but also enhances the degree of ER stress, so lipid metabolism disorder may promote ER stress, thus promoting pancreatic damage. The classical pathway involved in lipid metabolism and inflammatory response is the sXBP 1 signaling pathway of IRE 1 α splicing [29], Quercetin (QE) can inhibit ER stress by reducing IRE 1 α and reduce inflammation. In PA-induced pancreatic injury, the CCAAT enhancer binding proteins C/EBP α and C/EBP β were found involved in HTG-associated AP and respon-

sible for the inflammatory response caused by ER [27].

2.4. Microcirculatory Disorders

The pathological process of pancreatic microcirculation disorder in HTG-AP patients is very complex, mainly including the secretion of vasoactive factors, increased vascular permeability, ischemia/reperfusion, intravascular coagulation, and leukocyte adhesion. Nitric oxide (NO) in promoting vasodilation, inhibit leukocyte adhesion, promote vascular smooth muscle proliferation and platelet aggregation plays a vital role, when HTG, then the early vascular disease is the decrease of endothelial endogenous NO, characterized by microvascular dysfunction, experimental data show that this process involves arginase activity [30]. When HTG-AP occurs, platelet-neutrophil complex formation, a key component of the local inflammatory response, in addition, activated platelets induce TXB 2 secretion, and TXB 2, as a powerful vasoconstrictor, can cause severe pancreatic tissue ischemic necrosis and worsen the inflammatory response [31]. Although the exact mechanism by which HTG causes AP is not completely cleared, HTG decomposes into FFA and chylomicrons, which increase plasma viscosity and may trigger organ inflammation [32] [33]. And elevated plasma viscosity can lead to pancreatic capillary obstruction and pancreatic ischemia, leading to acidosis of acinar cells. While acidosis may increase cathepsin B activation and promote local thrombosis, thromboembolism, and trypsinogen activation, pathological mechanisms that also exacerbate inflammation [33]. In addition, FFA can be used as a surfactant supplement to promote the formation of detergent micelles. Excessive clumps of micelles can also cause vascular obstruction, leading to vascular ischemia, which easily leads to thromboembolism and reperfusion injury, which in turn further enhances the toxicity of FFA and aggravates the acidic environment and acidosis [34]. It is noteworthy that FFA can also act directly on the pancreatic vasculature, causing direct destruction by increasing the permeability to the vascular endothelium, causing intravascular coagulation, especially in pancreatitis disease [35]. The P38 mitogen-activated protein kinase (MAPK) pathway activates phospholipase A2, which promotes the release of arachidonic acid from membrane phospholipids. The next step is the release of the vasoconstrictor thromboxane A2 (TXA 2) and the vasodilator prostaglandin (PGI 2), where the imbalance of TXA 2/PGI 2 imbalance can lead to excessive capillary constriction and aggravate pancreatic microcirculation disorders [36].

2.5. Autophagy

In HTG-AP progression, ER stress is closely associated with autophagy disruption. Autophagy is a general term for several pathways, and the formation of autophagosomes comes from various donor membranes, including the endoplasmic reticulum (ER), the Golgi apparatus, or the plasma membrane. The process begins with the formation of a detached membrane/phagophore, followed by

extended closure to form mature autophagosomes. These steps are mediated by the hierarchical recruitment of autophagy-associated protein (ATG) complexes. When autophagy is blocked, cells accumulate in cells, and mitochondrial damage also impairs autophagy. This suggests that mitochondria and autophagy are cross-regulated to maintain homeostasis in pancreatic exocrine secretion [37]. MPTP opening is mediated by endotoxin-induced release of inosiol triphosphate and ryanodine receptor calcium channels, resulting in reduced ATP production, impaired calcium clearance, zymogen activation, defective autophagy, etc. MPTP opening inhibition by triggering defective autophagy when MPTP opens can preserve the ATP supply and improve the autophagy efficiency [38]. But, we must know that effective autophagy eliminates misfolded, removes aggregated proteins, reduces damaged cells, suppresses inflammation, and helps cells to adapt to a stressful environment. In HFD fed rats, researchers found that effective autophagy was blocked, ER stress was enhanced in pancreatic tissue, and autophagic flux was impaired, all of which suggested that autophagy does exist during the progression of HTG-AP, and significant remission of stress response was observed when the corresponding inhibitors were used [39].

2.6. Oxidative Stress

A high-fat diet (HFD) usually increases oxidative stress and promotes an inflammatory internal environment in the body. Oxidative stress is mainly due to the large amount of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and these active substances can cause damage to cell membrane, DNA and protein, leading to cell dysfunction. Toll-like receptor 4 (TLR 4) is widely expressed in pancreatic tissue and plays an important role in the development of AP. By establishing a healthy diet rats (SCD) and HFD rat AP model, comparing the results between the two models, it is not difficult to find that HFD rats significantly higher than SCD rats and showed more serious tissue damage, also observed pancreatic malondialdehyde (MDA) and lipid peroxidation (LPO) levels, as well as pancreatic superoxide dismutase (SOD) activity and glutathione (GSH) content also decreased, the infiltration of inflammatory cells is much higher than the SCD group. In addition, HFD was found to significantly increase the expression of TLR 4 and necrotrophic regulatory markers (RIP 3), aggravating the activation of NF-κB P65 and TNF-α expression in rat pancreas [10], These lines of evidence suggest that oxidative stress and inflammatory damage occur in HTG-AP. The imbalance between oxidants and antioxidants can lead to an increase in the generation of free radicals, namely oxidative stress, which can recruit inflammatory cells to trigger inflammatory responses and exacerbate pancreatic damage [40]. Another study also fed rats with HFD diet and showed increased Nox expression in various tissues, along with oxidative stress and tissue damage [41]. Because Nox is an important enzyme in the body that promotes the generation of oxygen free radicals, changes in its activity are very important for the levels of tissues and even in the human body. In addition, mito-

chondria are one of the main sources of ROS production, and their inner membrane components approach the sites of free radicals, so they are highly vulnerable to oxidative stress damage, which eventually leads to depolarization of mitochondrial membranes and impaired ATP generation, aggravating disease severity [42].

2.7. Chemokines and Inflammatory Factors

HTG-AP has been shown to be caused by the chemokine and inflammatory factor cascade. In the murine HP model, the expression and levels of IL-1 β and TNF-α were significantly increased in peripheral blood, while the anti-inflammatory factor IL-10 levels decreased, in this study, cathepsin S (CTSS) was known to be present in macrophages, FFA stimulation of macrophage-derived CTSS induced pyroptosis, and high levels of FFA promoted M1 polarization in macrophages, leading to the deterioration of pancreatitis associated with HP [43]. When acutely exposed to overloaded PA, primary exocrine pancreatic cells express a proinflammatory state by increasing the levels of transcripts for TNF-α, TGF-β, IL-6 cytokines, and pancreatic lipase protein levels [44]. In addition, besides activating NF (κB and AP-1 pathways in acinar cells, the activation of the transcriptional activity of STAT 3 may also be critical to the signaling mechanism of inflammatory mediators in acinar cells under stress conditions [45]. High concentrations of FFA can upregulate the expression levels of various PKC subtypes, including PKC-α, PKC-δ, PKC-ε, and non-typical PKC-ζ, which regulate the expression of inflammatory mediators and promote the release of zymogen granules from acinar cells, aggravate inflammation. The study also found that the activity of PKC was directly proportional to the degree of pancreatic impairment, which proved the close relationship between PKC and HTG-AP [11]. FFA promotes the progression of HTG-AP by increasing inflammatory mediators.

2.8. Signaling Pathway

According to previous studies showing that TRAF 6 and CAE are involved in the development of AP through activation and pyroptosis in expressing cells of the caspase-1/3 signaling pathway [46]. A recent study developed a mouse model by feeding palm oil and a high-fat diet *in vivo*, and found that the expression of TRAF 6 was significantly increased, and by downregulating TRAF 6, it could inhibit pyroptosis and relieve the severity of inflammation [47], Again verified that TRAF 6 is indeed involved in the development of HTG-AP inflammation. A hyperlipidemic environment *in vivo* leads to free fatty acid accumulation, followed by pancreatic tissue with microcirculation disorders and hypoxia/ischemia, which subsequently upregulates HIF-1 α expression [48], HIF-1 α-PPAR γ-mTORC1-mediated signaling pathway plays a key role in HLAP, with HIF-1 α up-regulation and downregulation of PPAR γ in HLAP rats, which in turn reduces the activity of mTORC1, increases autophagy, and thus aggravates the in-

flammatory response [49]. Caerulin Is a cholecystokinin (CCK) analog, which can stimulate acinar cells to secrete digestive enzymes, leading to Caerulin pancreatitis, can cause histological changes in pancreatitis after microglobulin injection, and this pathological change is associated with the induction of Leptin mRNA in the pancreas 24 hours after injection of microglobulin, Leptin mRNA has been shown to play an important role in the activation of the JAK 2/STAT 3 pathway [50]. The experiment proved that severe hemorrhagic necrotizing pancreatitis occurred in the pancreas of high-fat-fed rats, presenting with late acinar necrosis and depletion of zymogen granules. Notably, the phosphorylation of JAK 2 was elevated, but the activation of its potential downstream transcription factor STAT 3 was not further elevated under high-fat feeding. Interestingly, inhibition of JAK 2 similarly also inhibited STAT 3 activation to pancreatic inflammation and pancreatic damage, which in turn demonstrated a pathological role for the JAK 2/STAT 3 signaling pathway in Caerulin diet-induced HTG-AP [51]. P-407 is a hydrophilic triple block copolymer composed of polyoxthylene and polypropylene, and there have been reports proving that this copolymer can induce HTG with small side effects. The HTG-AP mouse model established by the combination of P-407 and I-arginine first examined the expression of B7H4 protein in animal models and found to be significantly increased, followed by JAK-2/STAT3 pathway in HTG-AP mice and Nrf 2-Keep 1 signaling as a regulator of oxidative stress, the most common inflammatory factors, IL-6, TNF-α, and IL-1 β protein [52]. Upregulation of miR-153 was observed in high-fat diet-induced mouse pancreatic tissue, and miR overexpression of miR-153 led to more severe pancreatic edema, inflammation, infiltration, and ADM structure formation, which showed that miR-153 exacerbated inflammation and acinar-to-duct metaplasia (ADM) by targeting TRAF 3. Moreover, experiments proposed that HTG-induced upregulation of miR-153 may be aggravating AP severity through targeted inhibition of TRAF 3 and delaying tissue repair, from which it can be concluded that dysregulated miR-153 signaling is responsible for more severe AP and pancreatic tissue repair in HTG mice [13]. The study demonstrated that LDH release and pyroptosis after silencing miR-192-5p and pyroptosis increased, and the expression of inflammatory factors such as IL-18, IL-1 β, GSDMD-N, IL-6 and TNF-α increased, indicating that miR-192-5p is negatively correlated with pancreatic inflammation. In experiments, it was proposed to target TXNIP by up-regulating miR-192-5p expression, inhibit NLRP 3/Caspase-1 pathway, reduce pyroptosis and inflammation of HTG-AP, and alleviate HTG [53].

2.9. Gut Microbes

The gut microbiota plays an important role in the development and development of AP. The gut microbiota not only participates in the barrier function of the gut, but also plays a key role in maintaining the microecological balance in the gut. Increased fat accumulation in the body leads to gut microbiota dysbi-

osis, increase intestinal inflammation, and alter vagal entero-brain communication [54]. Gut dysbiosis can then lead to increased intestinal permeability, triggering mucosal immune responses and chronic inflammation. Because obesity induces the expression of pro-inflammatory factors, reduces the expression of the anti-inflammatory factor IL-10, and exacerbates intestinal oxidative damage [55]. Studies have shown that the gut microbiota is closely related to the severity of AP, and some pathogenic bacteria can even become markers to predict the severity of disease. After dysregulation, the bacteria will produce the inhibition of anti-inflammatory factors, destroy the mucosal barrier, and cause adverse consequences such as hemorrhagic colitis [56].

3. Therapy

Diet therapy remains the most important means of treating HTG for any cause, however, this approach is usually not enough to reduce TG levels to a safe range. In addition, due to the refractory nature of sHTG, most traditional drugs that clinically treat HTG, such as statins, fibrates, niacin, and omega-3 fatty acids, may also additionally reduce TG levels, but due to various reasons, they still can not adequately reduce TG with limited success rate [57] [58] [59]. Therefore, further understanding of the treatment options of new drugs to reduce TG is needed. Among them, apolipoprotein C-III (APO-C3) inhibitor is a promising treatment, APO-C3 is composed of 79 amino acids, mainly synthesized in the liver, can reduce lipoprotein lipase (LPL) activity, inhibit the clearance of TG particles rich in blood, promote VLDL secretion in the liver into the blood, enhance LDL under endothelial retention mechanisms such as elevated TG levels in the blood, lead to the occurrence of inflammation [60]. Volanesorsen is the second generation antisense oligonucleotide, specifically designed to reduce the mRNA level of APO-C3, it can use Watson-Crick base pair interaction to cross Volanesorsen with its cognate mRNA, induce ribonuclease H1 mediated target mRNA degradation, and then inhibit APOC3 mRNA in the nucleus to block APOC 3 protein synthesis, and then promote TG decomposition and clearance. The experimental results show that the circulating level of APOC3 is reduced by more than 90%, which is a potential drug as the treatment of HTG [61] [62]. Olezarsen Is an antisense oligonucleotide targeting hepatocytes, N-acetyl galactosamine (GalNAc) coupled to specifically bind liver APOC3 mRNA in the nucleus to block the production of APOC3 and then reduce the level of TG. Notably, Olezarsen has been shown to reduce moderately elevated TG, and its efficacy has not been established in patients with severely elevated TG, and many further studies are needed [63] [64] [65]. In an established HTG-AP animal model found that it can reduce the expression of IL-6, TNF-α, inflammatory factors and ROS levels, also down the expression of B7H4 protein, and even JAK 2/STAT 3 signaling pathway, finally reduced the inflammatory response of pancreatic tissue, interestingly also reduced ALT, AST level, also has a certain effect in improving liver function [52]. As an active ingredient in another scutellplant, bai-

calein seems to have more activity than baicalein in many aspects, such as easier absorption, stronger anti-microbial activity, inhibition of inflammatory response, anti-free radical, protecting mitochondria, etc. The study showed that the levels of AMY (serum amylase) and LDH were decreased in acinar cells after baicalein treatment, and PI staining showed the apoptosis of acinar cells after baicalein treatment. All these phenomena suggest that baicalein can reduce the pyroptosis and inflammation of acinar cells [53]. Studies have shown that excess lipids will exacerbate AP by enhancing NF-κB activation, HnRNPA2B1 overexpression suppresses PA-induced NF-κB activation and inflammation, and protects vascular endothelial cells from inflammatory damage induced by LPS through NF-downregulation of NF-κB. In addition, HnRNPA2B1 also has an anti-inflammatory role in autoimmune endocrine diseases. In conclusion, HnRNPA2B1 has an important regulatory role in preventing HTG damage to cells. Because neddylation is responsible for regulating the post-translational expression level of HnRNPA2B1, drugs targeting pharmacological inhibitors of neddylation may provide therapeutic benefit to patients with HTG-AP [66].

4. Future Outlook

In conclusion, our pathophysiology of HTG-AP is still in the initial exploration stage, although several studies have shown that HTG aggravates the severity of AP, leading to more severe outcomes, although the association between the two has been confirmed [66], But because animal models often fail to fully replicate the symptoms, signs and pathological processes of human pancreatitis, it is impossible to create an ideal HTG animal model by simply feeding a high-fat diet, and there may be some still unknown difference between animals and humans. Due to various factors (Figure 1), including high breeding costs, breeding difficulties, and lack of specific equipment and professional team, a lot of research cost and time are needed. Moreover, even animal models cultured in the same laboratory will show different results due to the presence of individual differences, which greatly affects the reproducibility and reliability of the test. Moreover, the data obtained from animal models may be difficult to directly apply to humans, which limits the widespread use of animal models. Therefore, great caution should be taken in applying the data interpretation of animal models to human diseases. Studies have shown that novel therapeutic agents found in animal models may not necessarily show the same efficacy in clinical trials, and do not reduce short-term mortality in patients [67], Future trials should include all severity of AP, reinforcing studies measuring differences between all subgroups. In animal studies, therapeutic agents are usually administered before or after AP induction, but in real clinical trials, only after symptoms appear, so animal studies have focused on elucidating the mechanism pathways of AP and pathogenesis [68]. Interestingly, HTG-AP has a complex pathophysiology, involving a wide range, including FFA, microcirculation disorders, Ca^{2+} overload, ER stress, oxidative stress, gut microbiota, etc., however, the specific impact of these factors on
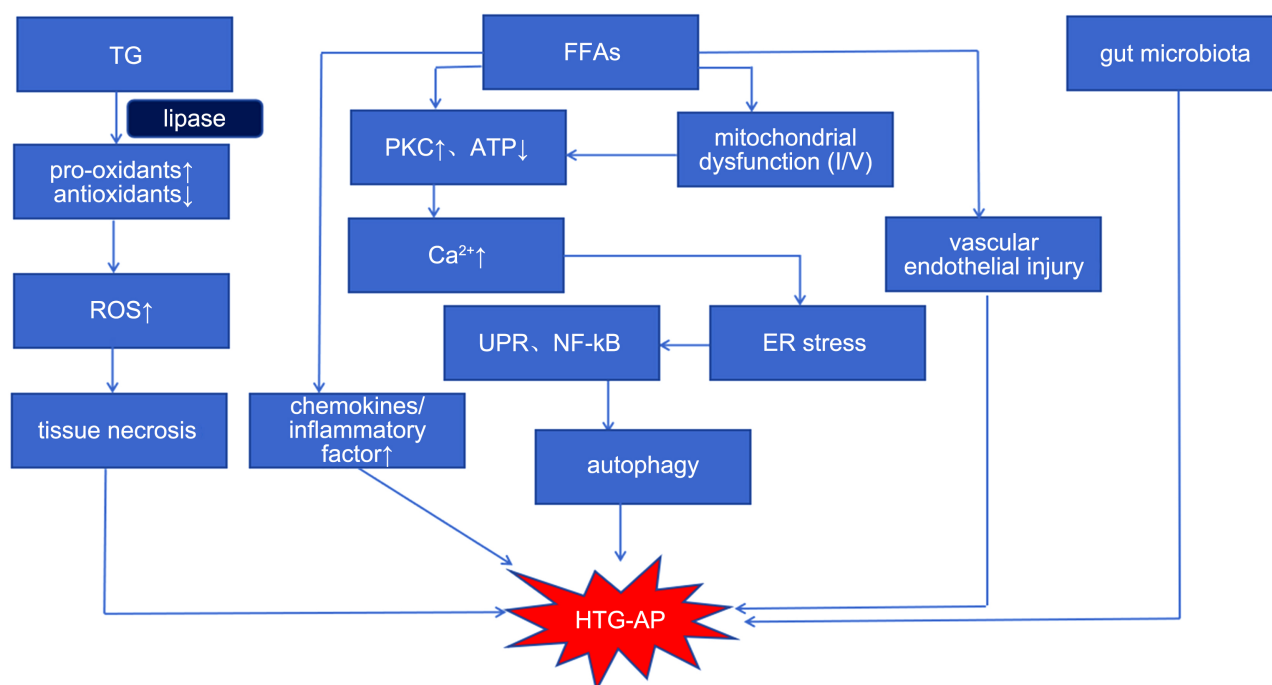
Figure 1. Mechanism of hyperlipidemic pancreatitis.

pancreatic cells, and healthy and diseased cases of complex interactions between endocrine glands and exocrine gland components, our current knowledge reserve is far from enough. But as we continue to understand HTG-AP, we can expect to develop more precise and personalized methods for diagnosis and treatment.

5. Conclusion

As a complex disease of multifactorial composition, HTG-AP has quite complex pathophysiology and involves a wide range of fields, and the existing research results can not clearly understand the intricate contents of this process. However, according to the current research project, our cognition of this disease has been greatly improved and more effective and targeted therapeutic drugs may be developed in the future. Future studies need to focus on the genetic molecular mechanisms of the disease to identify more valuable targets for therapeutic options, which requires the interdisciplinary coordination of genetics, molecular biology, and clinical research. Ultimately, if the development of more effective HTG-AP therapeutics is to be achieved, it will require continued insights into the pathophysiology of the disease. To overcome these limitations, researchers are exploring new models and research methods, how to use genetic engineering techniques to create specific human AP models, or to use *in vitro* cell models to simulate the AP environment.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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