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Review

Hypertriglyceridemia-Associated Pancreatitis: New Concepts and Potential Mechanisms

Signe E.J. Hansen,[a,b,c] Anette Varbo,[a,b] Børge G. Nordestgaard,[a,b,c] and Anne Langsted [a,b,c,*]

BACKGROUND: Triglycerides are a major source of energy, while high plasma triglycerides are a risk factor for various diseases and premature death. Severely elevated plasma triglycerides are a well-established cause of acute pancreatitis with high mortality, likely due to the presence of elevated levels of chylomicrons and large very low-density lipoproteins in plasma. As markedly elevated levels of these very large lipoproteins are not generally found in mild to moderate hypertriglyceridemia, this was previously not regarded as a cause or marker of increased risk of acute pancreatitis. However, mild to moderate hypertriglyceridemia may identify individuals who at a later timepoint develop severe hypertriglyceridemia and acute pancreatitis.

CONTENT: We describe measurement of plasma triglycerides and studies on plasma triglycerides and risk of acute pancreatitis. Further, we summarize current European and American guidelines for the prevention of acute pancreatitis and, finally, the potential for future prevention of acute pancreatitis through lowering of plasma triglycerides.

SUMMARY: Recent observational and genetic studies indicate that mild to moderate hypertriglyceridemia is causally related to increased risk of acute pancreatitis, most likely as a marker of future severe hypertriglyceridemia. Current guidelines do not mention individuals with mild to moderate hypertriglyceridemia, even though newer evidence suggests an unmet medical need. Treatment could include plasma triglyceride-lowering therapy targeting the pathway for lipoprotein lipase as the main triglyceride degrading enzyme in plasma. Angiopoietin-like 3 and apolipoproteinC-III are inhibitors of lipoprotein lipase, and blocking of these 2 inhibitors is showing promising results in relation to marked triglyceride-lowering and could perhaps be used to prevent acute pancreatitis in the future.

Introduction

Hypertriglyceridemia is associated with high morbidity and mortality, mainly due to its association with diseases such as ischemic heart disease, stroke, and cancer (1, 2). In Western countries, 25%–33% of the adult population has hypertriglyceridemia (>1.7 mmol/L; >150 mg/dL), and over the past decades incidence has been rising concordantly with the obesity pandemic (3). Indeed, as plasma triglycerides are highly positively correlated to body mass index, individuals with hypertriglyceridemia are more likely to live with overweight and obesity (4).

The incidence of acute pancreatitis has also been increasing, and it is now one of the most common admission diagnoses in gastroenterology emergency departments in the United States, with yearly direct costs of $2.8 billion (5). The estimated global incidence and mortality for acute pancreatitis is 34 cases and 2 deaths per 100 000 person-years, with geographical differences and the highest rates in the United States (6).

Currently, treatment options for hypertriglyceridemia and acute pancreatitis are limited, and it is important to prevent both conditions to reduce morbidity, mortality, and hospitals costs. In this review we discuss the interplay between plasma triglycerides and acute pancreatitis.

Plasma Triglycerides

Triglycerides are hydrophobic fat molecules packed into and transported by lipoproteins in plasma. The synthesis of triglycerides is mainly regulated by the enzymes monoacylglycerol acyltransferase and diacylglycerol transferase. Monoacylglycerol acyltransferase facilitates addition of a fatty acid to monoacylglycerol while diacylglycerol transferase facilitates the addition of a fatty acid to diacylglycerol, resulting in the formation of triglycerides.

Triglycerides enter the circulation in chylomicrons that are very large lipoprotein particles uniquely

[a]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; [b]The Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark; [c]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
*Address correspondence to this author at: Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Borgmester Ib Juuls Vej 73, 2730 Herlev, Denmark. E-mail anne.langsted.01@regionh.dk.
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containing apolipoprotein (apo)B48. Chylomicrons are assembled in the intestine after fat absorption from food, whereafter they bypass the liver and enter the circulation via the lymph through the thoracic duct, thereby reaching body tissues that are capable of utilizing free fatty acids (FFA) from lipoprotein lipase facilitated triglyceride hydrolysis, either as energy source in muscles or for storage in fat tissue. Subsequently, the remainder of the particle is cleared from the circulation by the liver as a chylomicron remnant. The remaining triglycerides, as well as newly synthesized triglycerides together with cholesterol, are later resecreted into the circulation by the liver in apoB100 containing very low-density lipoprotein particles. Triglycerides in these particles are again hydrolyzed by lipoprotein lipase with liberation of FFA, thereby producing smaller very low-density lipoprotein remnants, intermediate-density lipoproteins, and finally low-density lipoproteins (LDL) (Supplemental Fig. 1), the endpoint particle that is removed from the circulation by the liver or other tissues (7).

In plasma, triglycerides are liberated from lipoproteins by the highly regulated lipoprotein lipase (LPL). The lipolytic function of LPL is facilitated by apo C-II as an essential cofactor and is further enhanced by apo A-V, while apo C-I, apo C-III, ANGPTL3, and angiopoietin-like 4/angiopoietin-like 8 inhibit its function. LPL cleaves triglycerides into monoacylglycerol and FFA at the luminal site. FFA are transported into cells and are either oxidized in mitochondria in skeletal and heart muscle to produce ATP or stored in lipid droplets in adipose tissue to provide potent fuel storage. Compared to glycogen, FFA contain several times the amount of energy per unit stored mass (8).

The distribution of nonfasting plasma triglycerides in the Danish general population is shown in Fig. 1. Concentrations of plasma triglycerides are a consequence of an interplay between (*a*) dietary intake, (*b*) hepatic secretion, (*c*) LPL function, and (*d*) hepatic uptake or, in other words, between production, lipolysis, and clearance (9) and can further be influenced by genetics. Disturbances in either of these functions can lead to hypertriglyceridemia, often considered as plasma triglycerides >1.7 mmol/L (150 mg/dL) in the fasting state and >2 mmol/L (177 mg/dL) in the nonfasting state. The optimal concentration of plasma triglycerides is likely to be <1.2 mmol/L (100 mg/dL). Hypertriglyceridemia is further classified into mild to moderate (1.7–5.6 mmol/L; 150–500 mg/dL), severe (5.6–10 mmol/L; 500–880 mg/dL), and extreme (>10 mmol/L; 880 mg/dL) (9).

Primary and secondary causes of hypertriglyceridemia are listed in Table 1. In the clinical situation, it is important to first exclude and potentially treat secondary causes before diagnosis and interventions for hypertriglyceridemia due to primary causes are considered. Extreme high concentrations of plasma triglycerides are rare and mainly seen in individuals with monogenic disorders such as familial chylomicronemia syndrome, in the more common multifactorial chylomicronemia syndrome, or in severely

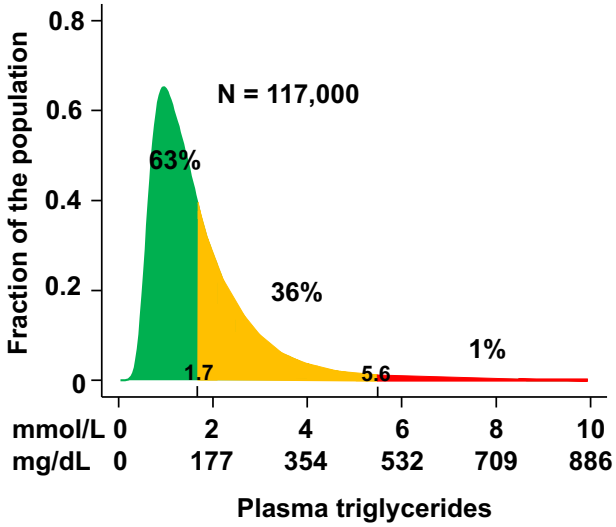


Fig. 1. Distribution of nonfasting plasma triglycerides in the Danish general population. 1.7 mmol/L marks upper normal level. Above 5.6 mmol/L indicates severe hypertriglyceridemia. To convert mmol/L to mg/dL, multiply by 88.6. Based on individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study combined.

Table 1. Possible causes of hypertriglyceridemia.

Primary
Genetic syndromes (monogenic) presenting as chylomicronemia/extreme hypertriglyceridemia
Genetic syndromes (polygenic) with moderate hypertriglyceridemia
Secondary
Central obesity
Diabetes (poorly controlled, mainly type 2)
Renal diseases/nephrotic syndrome
Pregnancy
Autoimmune disorders
Hypothyroidism
Alcohol excess
High fat diet
Medication
Metabolic syndrome
Paraproteinaemia

Based on data from Hegele et al. (10).

uncontrolled diabetes as a result of interaction with genetic factors, while mild to moderate hypertriglyceridemia is more likely due to a combination of polygenic and environmental factors (10). Both mild to moderate and severe hypertriglyceridemia are polygenic traits and share identical profiles of common single-nucleotide polymorphisms and rare heterozygous pathogenic variants (Supplemental Table 1), except that the burden of common and rare variants is greater in severe hypertriglyceridemia. Insulin resistance, as seen in individuals with obesity, the metabolic syndrome, and/or type 2 diabetes, is associated with hypertriglyceridemia as it leads to (*a*) higher secretion of apoB48-particles from the intestines, (*b*) higher production and secretion of apoB100-particles from the liver, (*c*) reduced peripheral lipolysis (reduced LPL function), and (*d*) release of FFA from adipocytes into the circulation (providing a substrate for de novo lipogenesis in the liver) (9). Prolonged hypertriglyceridemia is harmful for various tissues in the body, with the greatest health concerns for individuals with hypertriglyceridemia being atherosclerotic cardiovascular disease (ASCVD) and pancreatitis.

Measurements of Triglycerides

Biological variation within (CV_I%) and between (CV_G%) individuals for plasma triglycerides is 20% and 40%, respectively. CV_I% is usually high in individuals with high plasma triglycerides, and these individuals may experience large differences between fasting and post prandial triglyceride concentrations. A meal high in saturated fat can lead to transient triglyceride increases of 50% or greater (11). Two triglyceride measurements in the same individual should differ by at least 56% to be a clinically significant change (12); however, a change of less than 56% can sometimes be clinically significant, depending on the absolute magnitude of change and the clinical scenario. Preanalytical factors influencing triglyceride concentrations include time of day, body posture, menstrual cycle, pregnancy, meals, smoking, age, and inflammation (11). Nonfasting blood sampling for lipids is endorsed worldwide by UK, Canadian, Brazilian, Asian, European, and American guidelines (13). The difference between fasting and nonfasting lipids is found to be clinically insignificant, and the use of nonfasting sampling is more convenient for patients, clinicians, and laboratories alike. Importantly, most people in affluent countries are in the nonfasting state most of the time and only fasting in the morning before breakfast. Therefore, nonfasting concentrations better reflect the person's usual triglyceride concentration and potential risk of diseases caused by elevated plasma triglycerides. If a nonfasting sample is >4.5 mmol/L (400 mg/dL), some laboratories will recommend a fasting sample; however, in 2022 in Denmark, for Copenhagen hospitals this option is no longer available (13).

Triglyceride concentrations can be measured in both plasma and serum easily and with high precision [for example, CV_A%:1.80 (95% confidence interval [CI], 1.41–1.55) Advia 2400 (12)] by commonly used laboratory assays based on enzymatic hydrolysis of triglycerides to FFAs and glycerol. The formed glycerol is further oxidized by glycerol oxidase in the presence of oxygen, forming glyceraldehyde and hydrogen peroxide. The amount of glyceraldehyde or hydrogen peroxide formed in this reaction, or oxygen uptake, is proportional to the amount of triglyceride in the sample (14). Most assays dilute samples for further measurement when triglycerides are initially >10 mmol/L (880 mg/dL), adding a little extra imprecision to results above this concentration. As it is solely the glycerol-content, which is decisive of the measured triglyceride concentration, falsely elevated triglyceride measurements (pseudohypertriglyceridemia) can be found in individuals with hyperglycerolemia, a rare genetic disease caused by glycerol kinase deficiency. Special assays "blanking" the content of free glycerol in a sample ensuring that only glycerol liberated from triglycerides is being measured can be performed to unmask suspected pseudohypertriglyceridemia (11). This could be appropriate in individuals with persistent hypertriglyceridemia despite triglyceride-lowering treatment.

Acute Pancreatitis

The clinical manifestations of acute pancreatitis are constant abdominal pain often radiating to the back, nausea, vomiting, fever, and general malaise. According to the Atlanta criteria, 2 of the following 3 criteria need to be present for the diagnosis: (*a*) abdominal pain compatible with acute pancreatitis, (*b*) serum amylase and/or lipase ≥3 times the upper normal limit, and (*c*) abdominal cross-sectional imaging findings suggestive of acute pancreatitis (15). Most cases of acute pancreatitis are mild and self-limiting; however, approximately 20% develop severe disease, defined by persistent organ failure for >48 h, with a mortality rate of approximately 20% to 50% (16). No curative treatment exists, so supportive resuscitation with fluid, oral/enteral nutrition (or in some cases avoidance of oral nutrition), pain relief, and observation for known complications such as pancreatic and/or peripancreatic oedema, sterile or infected necrosis, and pseudocysts is standard care (17). Disease severity is commonly defined using the revised Atlanta Classification (18). Many tools have been created in the attempt to predict severity; however, close monitoring of organ function and identification of the presence of a systemic inflammatory response syndrome seem just as effective (15). Long-term exocrine insufficiency is seen in approximately 35% (19), and endocrine insufficiency in about 20% (20), of patients after a first episode of acute pancreatitis, and repeated episodes can lead to chronic pancreatitis and exocrine and endocrine insufficiency.

The most common causes of acute pancreatitis are (*a*) gallstone disease (45%), (*b*) excessive long-term alcohol consumption (20%), and (*c*) hypertriglyceridemia (3%–10%), with alcohol consumption being more common in men than women, while in as many as 5%–25% of cases the cause remains unclear (idiopathic) (15). Hereditary, iatrogenic, medicine-induced, structural/anatomical, and infectious causes are thought to explain the remaining causes (16) (Supplemental Table 2). Early identification of disease-causing environmental exposures is crucial in the management of acute pancreatitis, and patient education in avoiding/eliminating known risk factors and recognizing early signs of pancreatitis is important since as many as 20% of individuals with a first episode of acute pancreatitis experience recurrent episodes (21). Also, the fact that acute pancreatitis is the first step in the disease continuum that may lead to chronic pancreatitis and ultimately pancreatic cancer highlights the importance of stopping disease progression (21).

Most knowledge regarding pathophysiological mechanisms of acute pancreatitis is derived from animal studies. Whether these pathways are identical in humans is not fully known, and human disease development most likely has a multifactorial dimension not easily reflected in an animal model (22). Acute pancreatitis is believed to manifest when the balance between protective factors and stressors is disturbed, indicating multiple insults might be needed to reach and exceed disease threshold. This might involve a complex interplay of (*a*) premature activation of digestive enzymes inside pancreatic tissue, (*b*) basolateral secretion of zymogens instead of via the normal apical route, (*c*) impaired ductal production of bicarbonate-rich fluid, (*d*) defective cellular cleaning mechanisms in response to acinar cell damage (impaired autophagy/lysosomal activity), (*e*) disturbed intracellular calcium-signaling, (*f*) hypoxia/ATP depletion, (*g*) enhanced inflammatory signaling activated through different pathways (lipopolysaccharide, toll-like receptor-4, nuclear factor-kappa B, and nucleotide-binding-domain, leucine-rich containing-family, pyrin-domain containing 3 inflammasome), (*h*) amplification of inflammatory responses by stellate cells inducing systemic inflammation, and (*i*) oxidative stress or damage. Genetic disposition, presence of bile acids in the pancreatic ductal system, hormonal hyperstimulation, and lifestyle mediators (e.g., alcohol, smoking, high-fat diet, and obesity) might contribute to and accelerate the process, reaching the disease threshold (23).

Hypertriglyceridemia and Acute Pancreatitis

Severe hypertriglyceridemia is an established cause of acute pancreatitis, responsible for a growing proportion of all cases, and has recently been found to cause up to about 22% of all cases of acute pancreatitis (24). In severe hypertriglyceridemia, hyperviscosity of plasma due to large lipoproteins and chylomicrons is believed to cause impaired blood flow in the pancreatic tissue, causing ischemia and tissue destruction leading to acute pancreatitis (25). Further, disease progression is enhanced by great accessibility of proinflammatory FFA in plasma and perhaps also by accumulated FFA in pancreatic tissue (26). Hypertriglyceridemia-induced acute pancreatitis and/or having elevated concentrations of plasma triglycerides at hospital admission are associated with more severe acute pancreatitis and poor prognosis (27).

As discussed earlier, the initial acute management for any patient with acute pancreatitis consists of bowel rest, intravenous hydration, and pain control. In addition, when induced by hypertriglyceridemia, insulin infusion is recommended with close monitoring of hypoglycemia. For individuals with severe pancreatitis and severe hypertriglyceridemia, more aggressive treatment in intensive care including plasmapheresis with albumin as replacement fluid is often used (28). The initial biochemical assessment of a patient in the emergency situation of acute pancreatitis will focus on

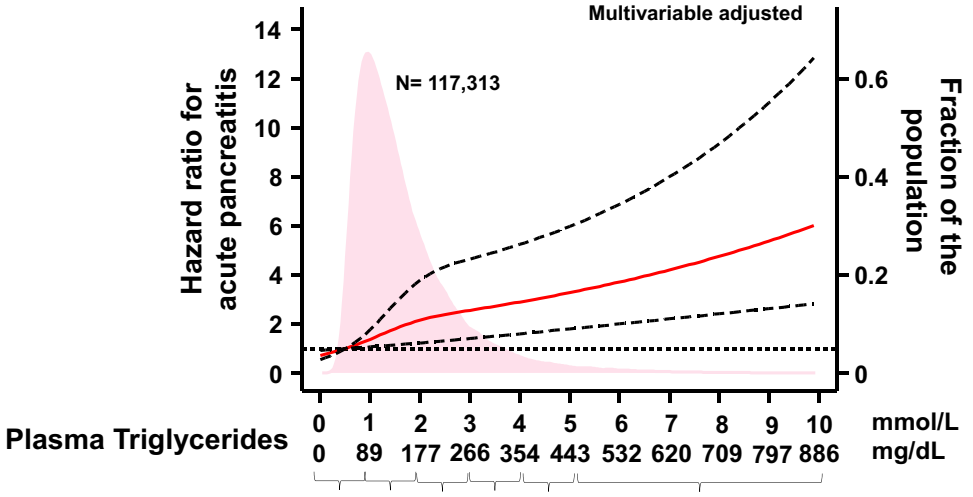
diagnosis including measurement of plasma pancreatic amylase and/or lipase as well as more general tests used in the acute setting. In the case of severe hypertriglyceridemia, tests may be affected by the presence of lipemia, making some analytes difficult to measure. These initial tests differ from the tests focusing on hypertriglyceridemia in the nonacute setting aimed at preventing future episodes of acute pancreatitis.

While severe hypertriglyceridemia is a well-recognized cause of acute pancreatitis, mild to moderate hypertriglyceridemia has not previously been thought to cause acute pancreatitis. However, mild to moderate hypertriglyceridemia (2–5 mmol/L; 177–446 mg/dL) has recently in observational studies been associated with higher risk of acute pancreatitis (26, 29, 30) (Fig. 2), with a seemingly more pronounced association for women than for men (4). A study of 117 313 individuals (including 452 acute pancreatitis events) from the Danish general population (26) has shown that absolute numbers of acute pancreatitis cases are highest in individuals with plasma triglycerides between 1 and 3 mmol/L (89–265 mg/dL), because most individuals have plasma triglycerides in this range. In that study, the population attributable fraction was 19% (potentially prevented cases, n = 40) for individuals with plasma triglycerides of 1–1.99 mmol/L (89–176 mg/dL) including many individuals with triglycerides in the normal range, 14% (n = 13) for 2 to 2.99 mmol/L (177–265 mg/dL), 7% (n = 3) for 3 to 3.99 mmol/L (266–353 mg/dL), 6% (n = 1) for 4 to 4.99 mmol/L (354–442 mg/dL), and 11% (n = 3) for individuals with plasma triglycerides ≥5 mmol/L (443 mg/dL) (26).

Mild to moderate hypertriglyceridemia is often accompanied by obesity and other metabolic dysfunctions such as impaired glucose tolerance and hypercholesterolemia (31). In observational studies, stepwise higher body mass index above normal weight was associated with stepwise higher risk of acute pancreatitis (4, 32), and almost 30% of the association was mediated by elevated plasma triglycerides (4), while none of the other components of the metabolic syndrome were found to be mediators (4, 30). Also, evidence from studies investigating the effect of bariatric surgery reducing body weight and plasma triglycerides shows lower risk of acute pancreatitis in individuals who underwent bariatric surgery (33).

The underlying mechanism causing acute pancreatitis in individuals with mild to moderate hypertriglyceridemia is not completely understood. The most plausible mechanism is that mild to moderate hypertriglyceridemia, rather than being a direct cause of acute pancreatitis, is associated indirectly because it is a reliable marker of future severe hypertriglyceridemia, which could be the actual cause of the clinical problem. However, large lipoprotein particle size does not seem to be the sole explanation as the association between higher plasma triglycerides and risk of acute pancreatitis is more linear than sigmoid/exponential, indicating that no specific size of lipoproteins drives the association. It seems that risk of acute pancreatitis increases similarly for changes in lower triglyceride concentrations where chylomicronemia/hyperviscosity is not present as in high triglyceride concentrations with the presences of larger lipoproteins (26) (Fig. 2). It can be speculated that constant mild to moderate elevated plasma triglycerides could make the pancreas susceptible to acute pancreatitis due to (*a*) exceeded storage capacity of triglycerides in adipose tissue leading to accumulation of triglycerides elsewhere including the pancreas, where pancreatic lipase can result in liberation of cytotoxic FFA in pancreatic tissue (34); (*b*) the pancreas has a high protein production relative to its size, and energy is derived from β-oxidation of FFA—the more FFA utilized for energy production, the more cytotoxic byproducts are produced, contributing to shifting the intracellular balance toward inflammation (35); and (*c*) the pancreas is situated in the abdomen close to metabolic active adipose tissue, which may liberate cytotoxins, and is not protected from these/the environment by a fibrous capsule, meaning that an "acute pancreatitis threshold" is more easily reached when other stressors are added.

In a Mendelian randomization study (36) including individual-level genetic data from 102 888 individuals from the Danish general population, we found that higher plasma triglycerides due to genetic variants affecting LPL function was causally associated with increased risk of acute pancreatitis; the causal risk ratio for acute pancreatitis per 1 mmol/L (89 mg/dL) higher plasma triglycerides by allele score was 1.76 (95% CI, 1.16–2.65; $P = 0.008$). Further, a genetic increase in plasma triglycerides of 0.54 mmol/L (48 mg/dL) was associated with a 1.6-fold higher risk of acute pancreatitis (36) as shown in Fig. 3, indicating that even mild to moderate lifelong elevation of plasma triglycerides could be on the causal path to acute pancreatitis most likely by predisposing to severe hypertriglyceridemia. This finding is supported by Yuan et al. (37) in a later Mendelian randomization study including summary-level data from 441 016 European descendants participating in either the FinnGen consortium or the UK BioBank. In that study, the genetic variants were chosen based on associations with plasma triglyceride concentrations from genome-wide-association-studies and not directly on protein function as in our study (36). Yuan et al. found a combined odds ratio for acute pancreatitis of 1.15 (95% CI, 1.02–1.30; $P = 0.02$) per 1 SD increase in traits associated with high plasma triglycerides, though mostly driven by the findings from the UK Biobank with an odds ratio of 1.27 (1.05–1.52; $P = 0.01$) (37).



Hazard ratio	1	1.5	2.0	2.2	4.2	7.7
95% CI	Ref.	0.9-2.5	1.1-3.6	1.0-4.7	1.6-11.5	3.0-19.8
Individuals	31,740	54,358	19,735	6,927	2,471	2,082
Events	75	209	96	35	17	20

Fig. 2. Association between plasma triglycerides and acute pancreatitis. Pink histogram depicting non-fasting plasma triglycerides in the Danish general population. Red spline depicts the hazard ratio for acute pancreatitis with 95% CI (large-dotted lines). Hazard ratio = 1 indicates no difference in hazard ratio for acute pancreatitis (small-dotted line). The Spline is based on a Cox proportional hazard regression model adjusted for age, sex, smoking, alcohol intake, lipid-lowering therapy, physical activity, diabetes, gallstones, and study. To convert mmol/L to mg/dL, multiply by 88.6. Adapted with permission from Hansen et al. (26). The table shows hazard ratios for acute pancreatitis by increasing triglycerides as a categorical parameter with 95% CIs estimated by a Cox proportional hazard regression model adjusted for age, sex, smoking, alcohol intake, lipid-lowering therapy, physical activity, diabetes, gallstones, and study, together with number of individuals and events for each group. Based on individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study combined.

Also, a Chinese study by Jin et al. (38) showed that individuals with severe hypertriglyceridemia and a history of acute pancreatitis (n = 18) presented higher frequencies of genetic variants affecting LPL (28% vs 5%), and LPL regulating genes (50% vs 20%) than individuals with severe hypertriglyceridemia not having experienced an episode of acute pancreatitis (n = 85) (38).

As mild to moderate hypertriglyceridemia recently has been found to be associated with increased risk of acute pancreatitis, and as genetics suggest that elevated plasma triglycerides per se (and not lipoprotein particle size) are causally associated with acute pancreatitis (36), many cases of acute pancreatitis with unknown origin could potentially be triggered and/or accelerated by mild to moderate hypertriglyceridemia, most likely by predisposing to severe hypertriglyceridemia. One could even speculate that both alcohol- and gallstone-induced acute pancreatitis in some cases might have plasma triglycerides as a potential intermediate/costressor in disease pathogenesis. Metabolism of alcohol leads to elevation of plasma triglycerides, and emptying and motility of the gall bladder are inhibited in individuals with hypertriglyceridemia, leaving them more prone to gallstone formation (39). Also, obesity, contrary to elevated LDL cholesterol concentrations, has been found to be causally associated with symptomatic gallstone disease (40), which potentially could be driven by high plasma triglycerides.

Inflammation, Plasma Triglycerides, and Acute Pancreatitis

High plasma triglycerides are associated with high plasma C-reactive protein (CRP) as shown in Fig. 4, while LDL cholesterol shows a negligible association with

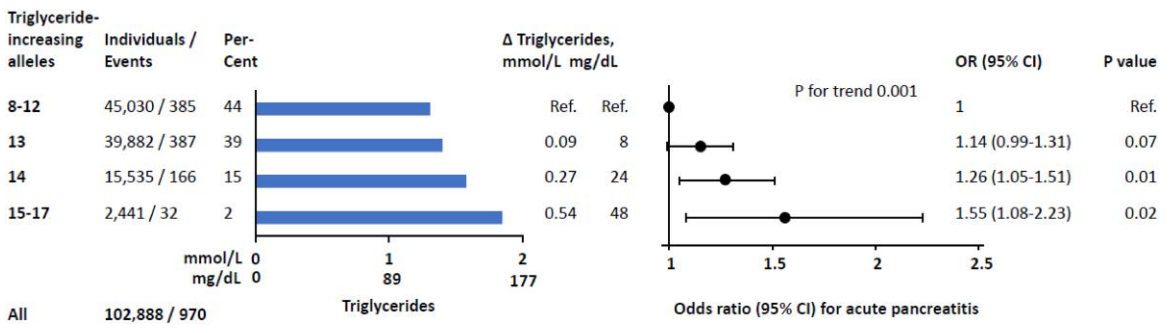


Fig. 3. Association between a genetic instrument as a proxy for plasma triglycerides and acute pancreatitis. Individuals are divided in groups based on number of plasma triglyceride-increasing alleles (unweighted allele score). Blue bars depict median nonfasting plasma triglyceride concentration. Columns in the middle show difference in concentration of triglycerides compared to the reference group. The effect plot depicts odds ratios for acute pancreatitis based on an age- and sex-adjusted logistic regression model. To convert triglycerides in mmol/L to mg/dL, multiply by 88.6. Based on individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study combined. Adapted with permission from Hansen et al. (36).

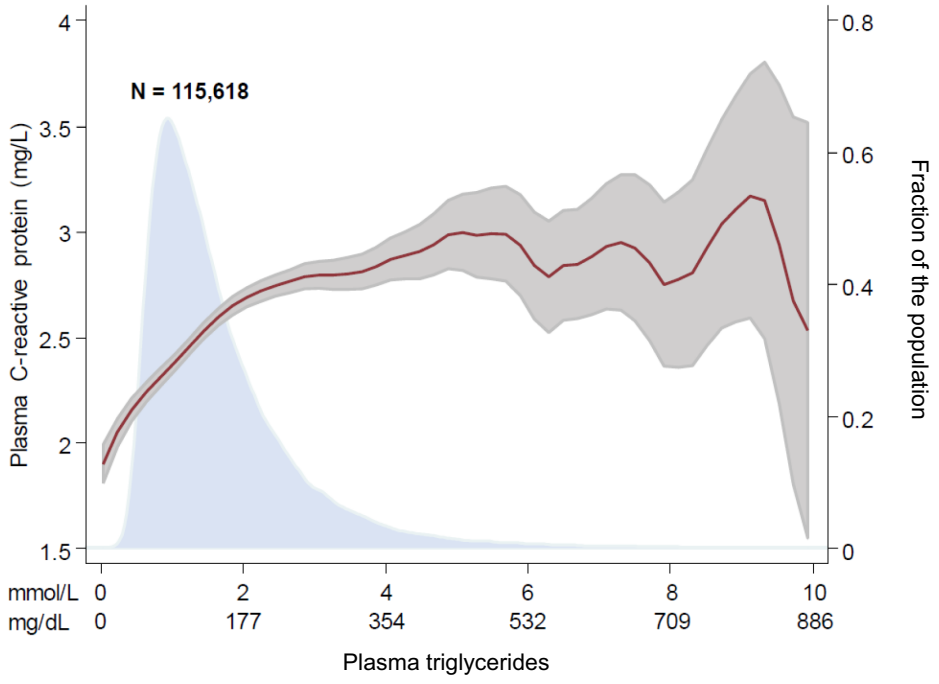


Fig. 4. Association between plasma triglycerides and C-reactive protein. The blue histogram shows distribution of nonfasting plasma triglycerides in the population. The red curve is a smoothed polynomial function and the surrounding grey area is the 95% CI. To convert triglycerides in mmol/L to mg/dL, multiply by 88.6. Based on individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study combined. Adapted with permission from Hansen et al. (26).

plasma CRP (26). CRP is an acute-phase protein produced and secreted by the liver in response to circulating upstream markers of inflammation (e.g., interleukin-6) and functions by tagging cellular debris and/or intruding organisms for recognition and removal by the complement system as part of the innate immune system (41). The inflammatory response is under normal conditions a short, strong, and efficient reply to a specific threat but is potentially harmful for the host when chronically activated, even at low intensity. Triglycerides carried in lipoproteins in plasma and stored intracellularly in lipid droplets are not proinflammatory; however, FFAs liberated by dysregulated lipase activity are (42), and saturated fatty acids are believed to directly stimulate the immune system and/or the production of endotoxins by the gut microbiota (43).

As elevated plasma triglycerides are associated with high body mass index and thus obesity (4), and as obesity implies metabolic active and proinflammatory adipose tissue, elevated plasma triglycerides are also associated with low-grade inflammation due to adipokines (44). Both adipokines and FFAs are potent activators of the nucleotide-binding domain, leucine-rich containing family, pyrin domain containing 3 inflammasome, a protease complex activating highly proinflammatory proteins (44). This pathway has been found to play a significant role in disease initiation and progression of acute pancreatitis, and both acute and chronic pancreatitis are now broadly accepted as diseases with a much larger inflammatory component than first believed (45). Supporting evidence comes from a population-based observational study of 117 313 individuals (26) in which we found that CRP >1.5 mg/L (measured by a high-sensitivity method and on a continuous scale) was associated with higher risk of acute pancreatitis. Interestingly, adjustment for inflammatory markers attenuated the risk estimates considerably in the association between elevated plasma triglycerides and increased risk of acute pancreatitis (26).

In addition, the presence of various chronic inflammatory diseases has been found to be associated with high risk of acute pancreatitis. Chang et al. found, in a retrospective cohort study of 148 775 residents in Taiwan, that individuals with a diagnosis of rheumatoid arthritis had a hazard ratio (HR) of 1.6 (95% CI, 1.4–1.8; $P < 0.001$) for acute pancreatitis compared to individuals without rheumatoid arthritis (46). No differences in prevalence of hyperlipidemia, alcoholism, gallbladder stones, or viral hepatitis were found in individuals with or without a diagnosis of rheumatoid arthritis. The study also found that current use of oral corticosteroids was associated with a reduced risk of acute pancreatitis in patients with rheumatoid arthritis [HR: 0.8 (0.7–0.9), $P < 0.001$] (46). In line with this, a large American study of 56 183 720 individuals (518 280 with rheumatoid arthritis) confirmed the association between rheumatoid arthritis and acute pancreatitis (47). In another study, exploring the association between primary Sjogren's syndrome and risk of acute pancreatitis, Chang et al. in a cohort of 47 340 Taiwan residents found individuals with a diagnosis of primary Sjogren's syndrome to have a 1.5-fold higher risk of acute pancreatitis than individuals without [HR: 1.48 (1.03–2.12), $P = 0.03$] (48). Finally, chronic osteomyelitis, another chronic inflammatory disease, was associated with a 2-fold higher risk of acute pancreatitis [odds ratio:1.93 (1.01–3.69), no P value listed] in a study by Lai et al. of 38 390 Taiwan residents (data extracted from the same database as the 2 other Taiwan-studies mentioned earlier) (49).

Taken together, the interplay between the continuous presence of proinflammatory FFA due to mild to moderate hypertriglyceridemia and chronic low-grade inflammation in pancreatic tissue seems to be a potent enhancer of the susceptibility to acute pancreatitis. In addition, CRP concentrations are a strong predictor of disease severity and prognosis in individuals hospitalized with acute pancreatitis irrespective of the cause of pancreatitis (15).

Hypertriglyceridemia and ASCVD

Although this review focuses on risk of acute pancreatitis at elevated plasma triglyceride concentrations, it is important to mention that plasma triglycerides >1.7 mmol/L (>150 mg/dL) are also associated with increased risk of ASCVD (9), the latter roughly 10 times more common than acute pancreatitis (29). In this setting, triglycerides are mainly transported by chylomicron remnants, very low-density lipoprotein remnants, and intermediate-density lipoproteins (collectively known as remnant particles) with particle sizes capable of penetrating the endothelial layer of the arterial wall, promoting atherosclerosis due to their cholesterol content (1, 50). The FFA liberated from remnant particles after hydrolysis of triglycerides at the endothelial surface or even within the arterial intima might contribute to disease progression by enhancing inflammation and destabilizing existing plaques (1, 50). Accumulation of remnant particles in the circulation and arterial wall begins at triglyceride concentrations >1.2 mmol/L (>100 mg/dL) and increases with higher plasma triglyceride concentrations. As residence time for lipoproteins in plasma may be prolonged with higher numbers of remnant particles, small, dense LDL particles are formed, possibly making individuals even more susceptible to ASCVD (9, 51). Interestingly, elevated triglycerides within LDL particles also associate robustly with increased risk of ASCVD

(52). Currently, evidence suggests that reduction of plasma triglycerides independently does not reduce ASCVD risk, though lowering of apoB-containing particles does (53–55), indicating that plasma triglycerides are most likely a surrogate measure for the cholesterol content in all the lipoprotein particles transporting triglycerides (apoB-containing particles).

Extreme high plasma triglyceride concentrations, where mostly large-size lipoproteins are present, are not associated with risk of ASCVD as these particles are too large to penetrate the endothelial layer of the arterial wall (1, 56).

Guidelines

Guidelines from cardiovascular, lipid, and endocrinological societies globally are consistent in relation to considering hypertriglyceridemia a risk factor for ASCVD, but inconsistency is seen between societies and geographical regions regarding recommendations for plasma triglycerides in acute pancreatitis (Table 2).

In ASCVD prevention, individuals with plasma triglycerides >1.7 mmol/L (150 mg/dL), based on both European (58) and American (57) guidelines, should be encouraged to follow healthy lifestyle habits—that is no smoking, less alcohol and sugary drinks, frequent exercise, weight loss, and healthy diet choices. Secondary causes of hypertriglyceridemia should be sought and treated and high LDL cholesterol lowered with statins. Triglycerides should be medically lowered with (*a*) statins, (*b*) fibrates, and (*c*) omega-3 fatty acids, in addition to healthy lifestyle changes in high-risk individuals, when triglycerides are >1.5 mmol/L (100 mg/dL) in Canada (60); >1.7 mmol/L (150 mg/dL) in Japan (62), India (64), and Brazil (65); ≥2.3 mmol/L (200 mg/dL) in Europe (58) and China (63); >4.5 mmol/L (400 mg/dL) in the UK (61); and >5.6 mmol/L (500 mg/dL) in the United States (57).

For prevention of acute pancreatitis, treatment with fibrates and/or omega-3 fatty acids in addition to lifestyle interventions is recommended for individuals with plasma triglycerides persistently >10 mmol/L (880 mg/dL) in guidelines from Europe (58), the UK (61), and China (63). American Endocrine Society guidelines recommend that plasma triglycerides should be lowered when >5.6 mmol/L (500 mg/dL) (59). Cardiology societies suggest that lowering of triglyceride concentrations >5.6 mmol/L (500 mg/dL) is reasonable and definitely indicated at concentrations >11.3 mmol/L (1000 mg/dL) (57). Guidelines from Japan (62), India (64), and Brazil (65) recommend intervention at triglyceride concentrations >5.6 mmol/L (500 mg/dL).

Current guidelines for acute pancreatitis prevention do not recommend treating individuals with mild to moderate hypertriglyceridemia, though individuals with mild to moderate hypertriglyceridemia probably would benefit from a similar treatment strategy as in ASCVD prevention, with statins as a first choice.

Preiss et al. (66) in a meta-analysis examined the association between use of statin or fibrate therapy and the incidence of acute pancreatitis by including both published and unpublished data from 28 large randomized controlled cardiovascular outcome trials in participants with normal to mildly elevated plasma triglycerides. Based on 16 placebo-controlled statin trials including a

Table 2. Global guideline recommendations for ASCVD and pancreatitis prevention.

		Recommended intervention	
Guideline	Hypertriglyceridemia definition	ASCVD risk[a]	Pancreatitis risk
USA, AHA/ACC (57)	>1.7 (150) F	>5.6 (500)	>5.6 (500)>11.3 (1000)
Europe, EAS/ESC (58)	> 1.7 (150) F	≥2.3 (200)	>10 (880)
USA/Europe,[b] Endocrinology (59)	>1.7 (150) F	>1.7 (150)	>5.6 (500)
Canada (60)	Not defined	>1.5 (100)	NA
UK (61)	Not defined	>4.5 (400)	>10 (880)
Japan (62)	>1.7 (150) F	>1.7 (150)	>5.6 (500)
China (63)	>1.7 (150) F	≥2.3 (200)	>10 (880)
India (64)	>1.7 (150) F	>1.7 (150)	>5.6 (500)
Brazil (65)	>1.7 (150) F	>1.7 (150)	>5.6 (500)

Numbers are mmol/L (mg/dL).
Abbreviations: AHA, American Heart Association; ACC, American College of Cardiology; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; F, fasting sample; NA, not available.
[a]In high-risk individuals.
[b]Collaboration with the American Association of Clinical Endocrinologists and the European Society of Endocrinology.

total of 113 800 individuals with a mean follow-up of 4.1 (SD 1.5) years, it was shown that statin treatment was associated with reduced risk of acute pancreatitis [risk ratio 0.8 (95% CI, 0.6–1.0; $P = 0.03$)]. In 5 trials including a total of 39 614 individuals during a mean follow-up of 4.8 (SD 1.7) years, individuals on high-intensity vs low-intensity statin treatment had a risk ratio of 0.8 (0.6–1.1; $P = 0.21$) for acute pancreatitis. The combined risk ratio for acute pancreatitis in favor of statins was 0.8 (0.7–1.0; $P = 0.01$). Based on information from 7 fibrate trials including 40 162 participants during a mean follow-up of 5.3 (SD 0.5) years, the authors found a risk ratio of 1.4 (1.0–2.0; $P = 0.05$) for acute pancreatitis for individuals on fibrate treatment compared to placebo (66). The fact that statin in contrast to fibrate treatment was associated with lower risk of acute pancreatitis could be because statins, in addition to lowering triglycerides, also have documented anti-inflammatory effects (67) and/or because fibrates and not statins increase the risk of gallstones (68, 69). Importantly, almost all the landmark statin trials that Preiss et al. analyzed excluded patients with moderate hypertriglyceridemia and in some cases even very mild hypertriglyceridemia; however, the fibrate trials included some individuals with mild to moderate hypertriglyceridemia. Not surprisingly, the absolute rate of acute pancreatitis in these studies was very low, and it could be argued that such episodes were not related to hypertriglyceridemia, since these studies excluded hypertriglyceridemia patients. Unfortunately, the question of what lipid-lowering medication patients with mild to moderate hypertriglyceridemia or severe hypertriglyceridemia should take in order to reduce future risk of pancreatitis has not been investigated in an appropriately powered double-blind randomized controlled trial (RCT).

The PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes) trial, which recruited specifically individuals with mild to moderate hypertriglyceridemia and ASCVD, also examined risk of acute pancreatitis; however, that study did not find any convincing reduction of acute pancreatitis events in the pemafibrate group compared to placebo (HR: 0.94, 95% CI, 0.53–1.65, $P = 0.91$). The study included individuals with diabetes and mild to moderate hypertriglyceridemia (2.3–5.6 mmol/L/200–499 mg/dL) followed for a median of 3.4 years. Only 26 patients in the pemafibrate group and 28 in the placebo group developed an episode of acute pancreatitis, and the pemafibrate group had an approximately 0.8 mmol/L (70 mg/dL) reduction in plasma triglycerides at month 4 (70).

Omega-3 fatty acids can decrease triglyceride concentrations at high administered doses, and RCTs have evaluated the effect of omega-3 fatty acids on cardiovascular disease outcomes with conflicting results. The role of omega-3 fatty acids in the prevention of pancreatitis is unclear.

Based on the existing evidence, the first choice in triglyceride-lowering treatment for the prevention of acute pancreatitis in individuals with mild to moderate hypertriglyceridemia should be high-intensity statins—which would also be beneficial for ASCVD prevention in these individuals.

Future Management of Hypertriglyceridemia

Recently, new and more efficient plasma triglyceride-lowering treatments have been developed. These new drugs enhance the activity of LPL via different mediators and thereby facilitate removal of triglycerides from plasma. Evinacumab, an ANGPTL3 antibody, has been shown to lower plasma triglycerides up to 50% when administered subcutaneously and up to 90% when administered intravenously (71). Currently, evinacumab is being tested in a phase II RCT for the prevention of recurrent acute pancreatitis in individuals with severe hypertriglyceridemia. Subcutaneously administrated APOC3 antisense oligonucleotides reduce circulating concentrations of apoC-III and have been shown to reduce plasma triglycerides by up to 60% (72). Various apoC-III inhibitors developed by different pharmaceutical companies are currently being tested in phase 2 and phase 3 RCTs in individuals with severe hypertriglyceridemia and in individuals with familial chylomicronemia syndrome. A study testing the safety and efficacy of volanesorsen shows lowering of triglycerides and potential reducing acute pancreatitis events (73). New data indicates that interfering with ANGPTL3 is less effective for triglyceride reduction compared to anti-APOC3 therapies. ANGPTL3 inhibition does not appear to work in lipoprotein lipase deficiency and its efficacy in mixed hyperlipidemia phenotypes is inconsistent (74). Importantly, the absolute risk of pancreatitis is very small in patients with mild to moderate hypertriglyceridemia and the cost, risk, and inconvenience of these medications is so great that their use for reducing risk of acute pancreatitis in these patients is not realistic—anti-APOC3 therapies should be reserved for those with severe hypertriglyceridemia. However, use of these new therapies will contribute important knowledge in relation to whether or not the relationship between elevated plasma triglycerides and acute pancreatitis is causal and perhaps also define a desirable concentration for plasma triglyceride-lowering to reduce risk of (recurrent) acute pancreatitis.

Conclusion and Perspective

Evidence from observational and genetic studies suggests elevated plasma triglycerides are causally associated with increased risk of acute pancreatitis. Not only severe but also mild to moderate hypertriglyceridemia is associated with acute pancreatitis. The disease mechanism for the latter

could simply be that mild to moderate hypertriglyceridemia is a marker of future risk of severe hypertriglyceridemia. Other possible mechanisms could implicate the pivotal role of inflammatory processes; as FFAs are potent enhancers of inflammation, they might be an important mediator in the association between elevated plasma triglycerides and increased risk of acute pancreatitis. Primary or secondary hypertriglyceridemia as a potential cause of acute pancreatitis should be identified in everyone with a first episode of acute pancreatitis, and triglyceride-lowering interventions should be considered to prevent recurrent episodes of acute pancreatitis. Results from ongoing RCTs with efficient plasma triglyceride-lowering agents and acute pancreatitis as an outcome are awaited.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: apo, apolipoprotein; FFA, free fatty acids; LDL, low-density lipoprotein; LPL, lipoprotein lipase; ANGPTL3, angiopoietin-like 3; ASCVD, atherosclerotic cardiovascular disease; CRP, C-reactive protein; HR, hazards ratio; RCT, randomized controlled trial.

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References

1. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet 2014;384:626–35.
2. Borena W, Stocks T, Jonsson H, Strohmaier S, Nagel G, Bjørge T, et al. Serum triglycerides and cancer risk in the metabolic syndrome and cancer (Me-Can) collaborative study. Cancer Causes Control 2011;22:291–9.
3. Christian JB, Bourgeois N, Snipes R, Lowe KA. Prevalence of severe (500 to 2,000 mg/dl) hypertriglyceridemia in United States adults. Am J Cardiol 2011;107:891–7.
4. Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BG. Body mass index, triglycerides, and risk of acute pancreatitis: a population-based study of 118 000 individuals. J Clin Endocrinol Metab 2020;105:dgz059.
5. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. Gastroenterology 2019;156:254–72.e11.
6. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, Petrov MS. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 2016;1:45–55.
7. Björnson E, Packard CJ, Adiels M, Andersson L, Matikainen N, Söderlund S, et al. Investigation of human apoB48 metabolism using a new, integrated non-steady-state model of apoB48 and apoB100 kinetics. J Intern Med 2019;285:562–77.
8. Stryer L. Biochemistry. New York (NY): W.H. Freeman and Company; 1995.
9. Ginsberg HN, Packard CJ, Chapman MJ, Boren J, Aguilar-Salinas CA, Averna M, et al. Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies-a consensus statement from the European Atherosclerosis Society. Eur Heart J 2021;42:4791–806.
10. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2014;2:655–66.
11. Rifai N, Rita Horvath A, Wittwer CT. Tietz textbook of clinical chemistry and molecular diagnostics. Amsterdam (the Netherlands): Elsevier; 2018.
12. Aarsand AK, Díaz-Garzón J, Fernandez-Calle P, Guerra E, Locatelli M, Bartlett WA, et al. The eubivas: within- and between-subject biological variation data for electrolytes, lipids, urea, uric acid, total protein, total bilirubin, direct bilirubin, and glucose. Clin Chem 2018;64:1380–93.
13. Nordestgaard BG. A test in context: lipid profile, fasting versus nonfasting. J Am Coll Cardiol 2017;70:1637–46.
14. Klotzsch SG, McNamara JR. Triglyceride measurements: a review of methods and interferences. Clin Chem 1990;36:1605–13.
15. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, et al. Acute pancreatitis. Lancet 2020;396:726–34.
16. Forsmark CE, Swaroop Vege S, Wilcox CM. Acute pancreatitis. N Engl J Med 2016;375:1972–81.
17. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN. American Gastroenterological Association institute guideline on initial management of acute pancreatitis. Gastroenterology 2018;154:1096–101.
18. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11.
19. Huang W, de la Iglesia-García D, Baston-Rey I, Calviño-Suarez C, Lariño-Noia J, Iglesias-Garcia J, et al. Exocrine pancreatic insufficiency following acute pancreatitis: systematic review and meta-analysis. Dig Dis Sci 2019;64:1985–2005.
20. Das SL, Singh PP, Phillips AR, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis:

a systematic review and meta-analysis. Gut 2014;63:818–31.
21. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:738–46.
22. Gorelick FS, Lerch MM. Do animal models of acute pancreatitis reproduce human disease? Cell Mol Gastroenterol Hepatol 2017;4:251–62.
23. Barreto SG, Habtezion A, Gukovskaya A, Lugea A, Jeon C, Yadav D, et al. Critical thresholds: key to unlocking the door to the prevention and specific treatments for acute pancreatitis. Gut 2021;70:194–203.
24. Jin M, Bai X, Chen X, Zhang H, Lu B, Li Y, et al. A 16-year trend of etiology in acute pancreatitis: the increasing proportion of hypertriglyceridemia-associated acute pancreatitis and its adverse effect on prognosis. J Clin Lipidol 2019;13:947–53.e1.
25. Adiamah A, Psaltis E, Crook M, Lobo DN. A systematic review of the epidemiology, pathophysiology and current management of hyperlipidaemic pancreatitis. Clin Nutr 2018;37:1810–22.
26. Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BRG. Low-grade inflammation in the association between mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis: a study of more than 115,000 individuals from the general population. Clin Chem 2019;65:321–32.
27. Pascual I, Sanahuja A, Garcia N, Vazquez P, Moreno O, Tosca J, et al. Association of elevated serum triglyceride levels with a more severe course of acute pancreatitis: cohort analysis of 1457 patients. Pancreatology 2019;19:623–9.
28. Joury A, Alshehri M, Mahendra A, Anteet M, Yousef MA, Khan AM. Therapeutic approaches in hypertriglyceridemia-induced acute pancreatitis: a literature review of available therapies and case series. J Clin Apher 2020;35:131–7.
29. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. JAMA Intern Med 2016;176:1834–42.
30. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. JAMA Intern Med 2013;173:162–4.
31. Sherling DH, Perumareddi P, Hennekens CH. Metabolic syndrome. J Cardiovasc Pharmacol Ther 2017;22:365–7.
32. Prizment AE, Jensen EH, Hopper AM, Virnig BA, Anderson KE. Risk factors for pancreatitis in older women: the Iowa Women's Health Study. Ann Epidemiol 2015;25:544–8.
33. Krishna SG, Behzadi J, Hinton A, El-Dika S, Groce JR, Hussan H, et al. Effects of bariatric surgery on outcomes of patients with acute pancreatitis. Clin Gastroenterol Hepatol 2016;14:1001–10.e5.
34. Garbarino J, Sturley SL. Saturated with fat: new perspectives on lipotoxicity. Curr Opin Clin Nutr Metab Care 2009;12:110–6.
35. Logsdon CD, Ji B. The role of protein synthesis and digestive enzymes in acinar cell injury. Nat Rev Gastroenterol Hepatol 2013;10:362–70.
36. Hansen SEJ, Madsen CM, Varbo A, Tybjærg-Hansen A, Nordestgaard BG. Genetic variants associated with increased plasma levels of triglycerides, via effects on the lipoprotein lipase pathway, increase risk of acute pancreatitis. Clin Gastroenterol Hepatol 2021;19:1652–60.e6.
37. Yuan S, Giovannucci EL, Larsson SC. Gallstone disease, diabetes, calcium, triglycerides, smoking and alcohol consumption and pancreatitis risk: Mendelian randomization study. NPJ Genom Med 2021;6:27.
38. Jin J-L, Sun D, Cao Y-X, Zhang H-W, Guo Y-L, Wu N-Q, et al. Intensive genetic analysis for Chinese patients with very high triglyceride levels: relations of mutations to triglyceride levels and acute pancreatitis. EBioMedicine 2018;38:171–7.
39. Smelt AHM. Triglycerides and gallstone formation. Clin Chim Acta 2010;411:1625–31.
40. Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Elevated body mass index as a causal risk factor for symptomatic gallstone disease: a Mendelian randomization study. Hepatology 2013;58:2133–41.
41. Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. Structure 1999;7:169–77.
42. Jarc E, Petan T. Lipid droplets and the management of cellular stress. Yale J Biol Med 2019;92:435–52.
43. Rocha DM, Caldas AP, Oliveira LL, Bressan J, Hermsdorff HH. Saturated fatty acids trigger tlr4-mediated inflammatory response. Atherosclerosis 2016;244:211–5.
44. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.
45. Habtezion A. Inflammation in acute and chronic pancreatitis. Curr Opin Gastroenterol 2015;31:395–9.
46. Chang CC, Chiou CS, Lin HL, Wang LH, Chang YS, Lin HC. Increased risk of acute pancreatitis in patients with rheumatoid arthritis: a population-based cohort study. PLoS One 2015;10:e0135187.
47. Alkhayyat M, Abou Saleh M, Grewal MK, Abureesh M, Mansoor E, Simons-Linares CR, et al. Pancreatic manifestations in rheumatoid arthritis: a national population-based study. Rheumatology (Oxford) 2021;60:2366–74.
48. Chang C-C, Chang Y-S, Wang S-H, Lin S-Y, Chen Y-H, Chen JH. Primary Sjogren's syndrome and the risk of acute pancreatitis: a nationwide cohort study. BMJ Open 2017;7:e014807.
49. Lai S-W, Lai H-C, Lin C-L, Liao K-F, Tseng C-H. Chronic osteomyelitis correlates with increased risk of acute pancreatitis in a case-control study in Taiwan. Eur J Intern Med 2015;26:429–32.
50. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. Circ Res 2016;118:547–63.
51. Balling M, Nordestgaard BG, Langsted A, Varbo A, Kamstrup PR, Afzal S. Small dense low-density lipoprotein cholesterol predicts atherosclerotic cardiovascular disease in the Copenhagen General Population Study. J Am Coll Cardiol 2020;75:2873–5.
52. Balling M, Afzal S, Davey Smith G, Varbo A, Langsted A, Kamstrup PR, Nordestgaard BG. Elevated LDL triglycerides and atherosclerotic risk. J Am Coll Cardiol 2023;81:136–52.
53. The Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499–506.
54. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA 2016;316:1289–97.
55. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. JAMA 2019;321:364–73.
56. Nordestgaard BG, Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. J Lipid Res 1988;29:1491–500.
57. Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, et al. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;78:960–93.
58. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227–337.
59. Newman CB, Blaha MJ, Boord JB, Cariou B, Chait A, Fein HG, et al. Lipid management in patients with endocrine disorders: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2020;105:dgaa674.
60. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. Can J Cardiol 2021;37:1129–50.

61. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. London (UK): National Institute for Health and Care Excellence; 2016.
62. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb 2018;25:846–984.
63. Joint Committee for Guideline Revision. 2016 Chinese guidelines for the management of dyslipidemia in adults. J Geriatr Cardiol 2018;15:1–29.
64. Puri R, Mehta V, Iyengar SS, Narasingan SN, Duell PB, Sattur GB, et al. Lipid association of India expert consensus statement on management of dyslipidemia in Indians 2020: part III. J Assoc Physicians India 2020;68:8–9.
65. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated cardiovascular prevention guideline of the Brazilian Society of Cardiology–2019. Arq Bras Cardiol 2019; 113:787–891.
66. Preiss D, Tikkanen MJ, Welsh P, Ford I, Lovato LC, Elam MB, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA 2012;308:804–11.
67. Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniades C, Stefanadis C. Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. J Am Coll Cardiol 2014;63: 2491–502.
68. Palmer RH. Effects of fenofibrate on bile lipid composition. Arteriosclerosis 1985;5:631–8.
69. von Bergmann K, Leiss O. Effect of short-term treatment with bezafibrate and fenofibrate on biliary lipid metabolism in patients with hyperlipoproteinaemia. Eur J Clin Invest 1984;14:150–4.
70. Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, et al. Triglyceride lowering with pemafibrate to reduce cardiovascular risk. N Engl J Med 2022;387:1923–34.
71. Ahmad Z, Banerjee P, Hamon S, Chan K-C, Bouzelmat A, Sasiela WJ, et al. Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. Circulation 2019;140:470–86.
72. Tardif JC, Karwatowska-Prokopczuk E, Amour ES, Ballantyne CM, Shapiro MD, Moriarty PM, et al. Apolipoprotein C-III reduction in subjects with moderate hypertriglyceridaemia and at high cardiovascular risk. Eur Heart J 2022;43:1401–12.
73. Gouni-Berthold I, Alexander VJ, Yang Q, Hurh E, Steinhagen-Thiessen E, Moriarty PM, et al. Efficacy and safety of volanesorsen in patients with multifactorial chylomicronaemia (compass): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2021;9:264–75.
74. Rosenson RS, Gaudet D, Ballantyne CM, Baum SJ, Bergeron J, Kershaw EE, et al. Evinacumab in severe hypertriglyceridemia with or without lipoprotein lipase pathway mutations: a phase 2 randomized trial. Nat Med 2023;29:729–37.