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Hyperlipidemia and Pancreatitis

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A total of 117 patients with pancreatitis were studied during the acute attack and after remission, and 32.5% were found to have hyperlipidemia, nearly all of type IV. There did not seem to be a relationship between hyperlipidemia and alcohol intake, although nearly 80% of the patients were alcoholics. No defect in triglyceride turnover could be demonstrated by intravenous fat tolerance tests or postheparin lipolytic activity measurements. No correlation was found between hyperlipidemia and steatosis of the liver or diabetes.

It is suggested that the increase in serum triglyceride levels might be due to an increased synthesis or mobilization. It is also suggested that the hypertriglyceridemia does not directly induce an attack of pancreatitis, but might predispose a patient to develop pancreatitis when other provoking factors are also present.

For more than 100 years, an association between hyperlipidemia and acute pancreatitis has been known [1]. Although case reports concerning this association have appeared from time to time [2–4], it is only during the last 15–20 years that systematic investigations have been performed to determine the underlying mechanism of the hyperlipidemia and its possible significance as an etiologic factor in the production of acute pancreatitis [5–8]. It appears that the hyperlipidemia may be of the familial type, of familial and exogenous types in combination, or purely of exogenous origin [6, 7]. Some investigators have suggested that it is secondary to steatosis of the liver [9] or damage of the pancreas with or without diabetes [5]. Because the role of hyperlipidemia in pancreatitis is still controversial, we undertook a prospective study in patients with acute pancreatitis and chronic relapsing pancreatitis.

Materials and Methods

We studied a total of 135 patients, 76 with acute pancreatitis and 59 with acute exacerbations of chronic relapsing pancreatitis. Of these, the 117 patients who had 3 or more lipid studies performed on different occasions will be considered in this analysis. The patients ranged in age from 21 to 81 years with a median age of 46.5 years for those with acute pancreatitis and 41 years for those with chronic pancreatitis. The diagnosis of pancreatitis was based on a typical clinical picture combined with an elevation of serum amylase level. In 68% of the cases, the diagnosis was confirmed by operation, endoscopic retrograde cholangiopancreaticography (ERCP), ultrasonography, or autopsy.

Total serum cholesterol concentration was measured according to the method of Watson [10], and a level of 300 mg/dl or higher was considered abnormal. Serum triglycerides were measured by an enzymatic method [11, 12], and levels of 2.4 mmol/l or higher were considered abnormal. The type of hyperlipidemia was determined by agar gel electrophoresis. Two or more abnormal examinations were considered diagnostic of hyperlipidemia. Four or more abnormal examinations, along with not more than 1 normal result, were considered diagnostic of constant hyperlipidemia. Needle liver biopsy by the Menghini technique was performed in 88 patients. An intravenous fat tolerance test

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Table 1. Overall results of blood lipid studies in 117 patients who had at least 3 such studies on different occasions.

	Number of patients	Percent of group	Lipid studies total number	Studies mean per patient
Pancreatitis with normal lipids	79	67.5	422	5.3
Pancreatitis with varying hyperlipidemia	29	24.8	204	7.0
Pancreatitis with constant hyperlipidemia	9	7.7	57	6.3
Total	117	100	683	5.8

(IVFTT) was performed in 25 patients and 11 controls. The test consists of intravenous infusion of 500 ml of 10% Intralipid® in 1 hour. Thereafter, serum triglyceride levels were determined every 1/2 hour for 5 hours. From this, the elimination coefficient K was calculated. A large dose of Intralipid® was chosen in order to avoid the influence of the patient's own serum triglyceride levels. Serum amylase concentration was determined by the Phadebas® tablet method using Versatol E as a standard. The upper limit of the normal range was 400 units (U) per liter (l).

Postheparin lipolytic activity (PHLA) was measured in plasma samples drawn exactly 10 minutes after intravenous injection of heparin in a dose of 60 I.U. per kg body weight, according to the method of Faergeman and Damgaard [13]. Total PHLA includes hepatic lipolytic activity, which is resistant to 1 M sodium chloride. Therefore, hepatic lipolytic activity was measured after addition of sodium chloride to the assay to give a concentration of 1 M in the incubation medium. Peripheral lipoprotein lipase activity was calculated as the difference between total PHLA and hepatic lipolytic activity.

Results

Of the 117 patients, 79 (68%) had normal lipids, 29 (25%) had varying amounts of hyperlipidemia, and 9 (8%) had constant hyperlipidemia (Table 1).

Table 2. Etiologic factors in 117 patients with pancreatitis.

	Normolipidemic		Hyperlipidemic	
	Number	%	Number	%
Biliary disease	16	20.2	3	7.8
Alcoholism	51	64.6	28	73.6
Biliary disease and alcoholism	9	11.4	5	13.2
Hyperparathyroidism	1	1.3	0	
Unknown	2	2.5	2	5.3

The known etiologic factors are shown in Table 2. Alcoholism played a role in more than 75% of the patients. There was no significant difference in the incidence of alcoholism between the normolipidemic and hyperlipidemic groups of patients.

Of the 38 patients with hyperlipidemia, 95% had the type IV disorder (Table 3). In 12 patients, type IV hyperlipidemia was combined with an increase in low density lipoprotein cholesterol, and in 4 patients chylomicrons were intermittently found. Only 1 patient had a solitary type II A hyperlipidemia.

Remarkably 38% of the 117 patients were found to have increased high density lipoprotein (HDL) levels (Table 4). No significant difference was found in HDL concentrations between the normolipidemic and hyperlipidemic patients, or between the alcoholic and nonalcoholic patients.

Of the 88 patients who underwent needle liver biopsy, steatosis of the liver was present in 47%. The steatosis was usually of a mild degree. The hyperlipidemic patients had a higher incidence of steatosis than the normolipidemic patients, but the difference was not statistically significant (Table 5).

The hyperlipidemic patients did not show an impaired turnover of triglycerides as measured by the intravenous fat tolerance test (IVFTT). The K values (elimination coefficient) were 3.5 in the 13 normolipidemic patients with pancreatitis, 4.4 in the 12 hyperlipidemic patients with pancreatitis, and 4.3 in the 11 control patients. These values were not significantly different from each other. Despite the high dosage of triglycerides used, no pancreatitis or other adverse reactions were provoked.

Table 3. Types of hyperlipidemia found in the 38 patients who had hyperlipidemia in association with pancreatitis.

	Patients	
Type of hyperlipidemia	No.	%
IIA	1	2.6
IIA and IV	8	21.1
IIA and IV and V	4	10.5
IV	24	63.2
unclassifiable	1	2.6

Table 4. High density lipoprotein (HDL) levels in 117 patients with pancreatitis.

	Normolipidemic patients			Hyperlipidemic patients		
	Total number	Percent of group	Number alcoholic	Total number	Percent of group	Number alcoholic
Increased HDL	26	33	17	18	47	16
Normal HDL	53	67	40	20	53	17

Total PHLA was similar in the normolipidemic and hyperlipidemic patients, but the hepatic fraction was significantly decreased in the hyperlipidemic patients (Table 6).

There was a tendency for the hyperlipidemic patients to have lower serum amylase levels that the normolipidemic patients with pancreatitis. Of the 268 serum amylase determinations in normolipidemic patients, 20% were above 1000 U/l, while of the 137 serum amylase determinations in hyperlipidemic patients only 10% were above 1000 U/l. This difference was statistically significantly different ($p < 0.05$).

During hospitalization there was a nonsignificant decrease in triglyceride levels in the hyperlipidemic patients. After discharge, the triglyceride levels increased again. Therefore, the hyperlipidemia did not appear to be a transient metabolic disorder found in connection with the acute attack of pancreatitis (Fig. 1).

Only 8 patients ultimately required treatment for diabetes, 5 of these only after a resection of the pancreas was performed.

Table 5. Finding of steatosis in 88 patients who underwent needle liver biopsy.

Biopsy finding	Normolipidemic patients	Hyperlipidemic patients
No steatosis	35	12
Mild steatosis	14	14
Moderate steatosis	8	3
Severe steatosis	1	1
Total with steatosis	23 (40%)	18 (60%)

Table 6. Postheparin lipose activity (PHLA) in 18 patients with pancreatitis.

	Normolipidemic patients Mean (n = 13)		Hyperlipidemic patients Mean (n = 5)	
	Activity	%	Activity	%
Total PHLA	229	—	212	—
Peripheral fraction	130	57	151	71
Hepatic fraction	99	43	61[1]	29

[1] $P<0.05$

Discussion

Since the publication of Specks in 1865 [1] an association between pancreatitis and hyperlipidemia has been known. The incidence of hyperlipidemia in patients with pancreatitis has been reported to range from 12% to 38% [5, 9, 14, 15]. The incidence of 32.5% in our study agrees well with the literature.

Patients with hyperlipidemia have been reported to be more prone to develop pancreatitis [7, 8, 16–19]. The forms of hyperlipidemia that have been encountered usually have been types I, IV, and V. The incidence of pancreatitis in patients with type I hyperlipidemia has been over 30%, in patients with type IV around 15%, and in patients with type V 27–41% [7, 8]. Since type IV is by far the most common of these types, it is understandable why 95% of our patients had type IV hyperlipidemia, either alone or in combination with some other type.

Few have claimed that the hyperlipidemia is only transient and disappears after the pancreatitis [15], although animal studies have shown that experimental pancreatitis can initiate hyperlipidemia [20–22]. Also in animal studies it has been observed that a high fat intake can provoke an attack of pancreatitis [23]. This phenomenon has been described

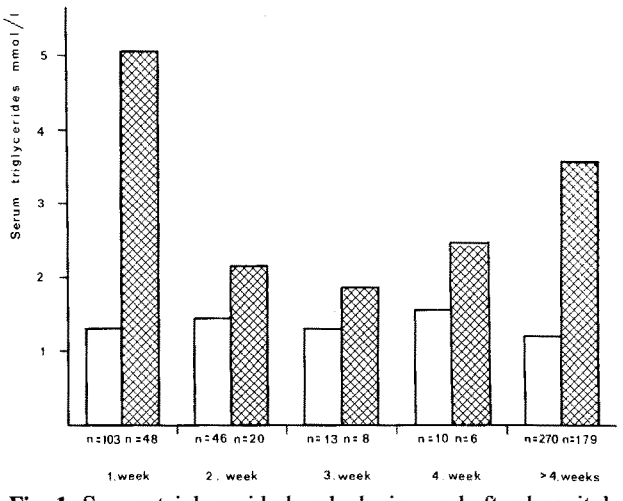

Fig. 1. Serum triglyceride levels during and after hospitalization for acute pancreatitis. Normolipidemic patients are shown in open columns and hyperlipidemic patients in cross-hatched columns.

in humans [24–26], but was not observed in our study, since no attacks were seen after IVFTT. The serum triglyceride levels are supposed to increase above 1000 mg/dl before an attack is provoked. In our IVFTT the serum triglyceride levels often increase to more than 30 mmol/l, which is much more than should be needed, but possibly this elevation is too transient. Most studies, including ours, have found that the abnormalities in lipid metabolism are constant [5, 8, 9, 14, 17]. It has been suggested that hypertriglyceridemia is usually seen in pancreatitis when steatosis of the liver or diabetes is present [5, 9, 27, 28]. We did not find that steatosis was significantly more common in these patients, and diabetes was remarkably uncommon. We observed a tendency, though not significant, for the triglycerides to decrease during the period of acute hospitalization, an observation also made by Gennes et al. [8]. Perhaps this tendency explains why some authors have considered the hyperlipidemia to be of a transient nature.

It has been claimed that a low lipid diet or pharmacological control of the hyperlipidemia can prevent recurrent attacks of pancreatitis [2, 8, 9, 17]. However, this should not be interpreted to mean that a sudden increase in serum triglycerides initiates the attack. Rather, increased serum triglycerides may predispose a patient to develop acute pancreatitis if exposed to other provoking factors such as alcohol or gallbladder disease.

Approximately 75% of the cases of pancreatitis are associated with alcoholism. Alcohol is known to cause an increase in serum triglycerides, although such an increase is often rather transient and especially occurs in patients who already have hyperlipidemia or steatosis [8, 27, 29–34]. The serum triglyceride concentration rarely increases to a level that might be expected, of itself, to precipitate pancreatitis. We did not find that hyperlipidemia was significantly more common in patients with alcoholism, which suggests that alcohol was not the main factor behind the hyperlipidemia in these patients. The hyperlipidemia in alcoholism could be due to an increased synthesis of triglycerides [30], or an increased mobilization from peripheral depots [35].

There is no agreement about the role of PHLA in the hyperlipidemia of pancreatitis. Some workers have found an acute decrease of PHLA and later normalization after the acute attack, while others have described the presence of PHLA inhibitors [15, 36, 37] and still others have found that PHLA was normal [6, 24, 38]. In our study involving mainly type IV patients, we found no changes in total PHLA, but a small decrease in the hepatic fraction. Our results confirm the observation that there is no good inverse correlation between PHLA and triglyceride concentrations [5, 6]. Alcohol should not influence PHLA concentration [34].

In general no decrease in the turnover of triglycerides has been found by us or others. However, a slower fat clearance rate has been reported in patients with elevated triglycerides, whether alcohol-induced or not [31]. Recent studies have shown that people with a moderate alcohol intake have a higher level of HDL than abstainers [39, 40]. We have often observed an elevation of HDL, but no significant difference between alcoholic and nonalcoholic patients. As other investigators have found, we observed lower serum amylase levels in patients with pancreatitis who had hyperlipidemia than in those without hyperlipidemia.

The induction of hyperlipidemia might not be the mechanism whereby alcohol predisposes to pancreatitis. Others have proposed that the mechanism involves stimulation of gastrin and secretin production [32], or formation of a plug in the pancreatic duct due to a relative increase in protein content in pancreatic juice [41].

In conclusion, our study confirms that hypertriglyceridemia is a common finding in patients with pancreatitis. It is a metabolic disorder also present after the remission of the acute attack. An increase in serum triglyceride levels did not seem to be involved directly in provoking pancreatitis. No certain relationship was found between hypertriglyceridemia and steatosis, diabetes, or alcohol intake in these patients. No defects in the turnover of triglycerides were found. The possibility of an increase in synthesis or mobilization was not investigated.

Acknowledgment

The PHLA measurements were performed by the laboratory of Dr. Finn Damgaard-Pedersen, Department of Clinical Chemistry A, Rigshospitalet, Copenhagen, Denmark.

Résumé

Cent dix-sept malades atteints de pancréatite aiguë ont été étudiés, soit pendant la crise, soit pendant les périodes de rémission. Une hyperlipidémie a été trouvée dans 32.5% des cas, presque toujours de type IV. Bien que 80% des malades soient des alcooliques, l'hyperlipidémie parait être sans relation avec l'alcoolisme. Le test de tolérance à l'administration i.v. de graisse et la mesure de l'activité lipolytique après administration d'héparine n'ont pas montré d'altération du turnover des triglycérides, mais uniquement une réduction modérée de la fraction hépatique de l'activité lipolytique. Nous n'avons observé aucune corrélation entre hyperlipidémie, stéatose hépatique et diabète.

L'élévation des triglycérides plasmatiques peut être due soit à une synthèse augmentée, soit à une libération accrue des dépôts périphériques. Nous avons l'impression que l'hypertriglycéridémie n'est pas directement responsable de la crise de pancréatite; elle peut être un élément prédisposant lorsqu'elle est associée à d'autres facteurs déclenchants.

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Invited Commentary

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We have been interested for many years [1] in the relationship between acute pancreatitis and hypertriglyceridemia and are pleased to see others becoming interested in this phenomenon. After a decade of clinical and laboratory investigation, convincing data have accumulated documenting hypertriglyceridemia as an important factor in the pathogenesis of acute pancreatitis. There are similarities between our work documenting that association and the study of Buch and colleagues. In 1973, in a consecutive series of patients presenting to The Johns Hopkins Hospital with acute pancreatitis, we noted a concomitant incidence of hypertriglyceridemia of 38% [2]. The authors in the present study documented a similarly high incidence of 33%. In addition, in a study published in 1974 [3], we found that the lipid abnormalities associated with acute pancreatitis were not transient and merely secondary to the pancreatitis, but persisted long after the attack had abated. This finding was also confirmed by the authors.

In other instances, however, our work is at variance with that reported in this study. In a series of 22 patients with acute pancreatitis and hypertriglyceridemia, lipoprotein typing performed during the acute attack revealed that 18 were type V, 2 were type I, and 2 were untyped [3]. When these patients were retyped later during their acute hospitalization, or during a subsequent elective admission, many had reverted to type IV. We concluded that types I and V were associated with the acute attack, and postulated that chylomicrons might be important in initiating the pancreatitis. Most of the patients undergoing lipoprotein typing in the present study were found to be type IV. The timing of the serum sample obtained for lipoprotein typing is not commented upon by the authors. We suspect that they were not obtained immediately upon admission, but a day or two later when the patients would have changed to type IV. The authors also reported a lipid tolerance or clearance test performed by infusing 500 ml of 10% Intralipid intravenously over a 1-hour period. They were unable to find a difference in clearance between the controls and the patients with pancreatitis and hypertriglyceridemia. The Intralipid load of triglycerides was only 50 gm, which may not provide a large enough load to differentiate between normals and those with a defect in clearance. From years of experience around the world with intravenous 10% Intralipid, it is well known that clearance is rapid and hypertriglyceridemia uncommon. In 1974, we reported our experience with an oral 250 gm lipid tolerance test performed on a control population and a group of patients who previously had had acute pancreatitis and hyperlipemia [3]. During the 24-hour period following the lipid load, only 2 of the 23 control patients elevated their serum triglycerides over 500 mg%. In contrast, 20 of the 22 patients who previously had a bout of pancreatitis and hypertriglyceridemia developed triglyceride levels over 500 mg%. We interpreted this as information supporting the concept of a defect in lipid clearance in these patients.

The authors suggest in their paper, without any supporting evidence, that increased triglycerides cannot initiate an attack of pancreatitis, but merely predispose a patient to an attack if exposed to other factors such as alcohol or gallbladder disease. This is contrary to our clinical and laboratory findings. We, and others, have followed many patients with familial type V hyperlipoproteinemia but no other known factors that predispose to acute pancreatitis. In these patients, attacks of pancreatitis occur when serum triglycerides reach extremely high levels, and these attacks can be prevented if triglyceride levels are controlled by dietary or drug management. In 1975, we published a study that involved admitting electively to a metabolic ward 12 patients who previously had had attacks of alcoholic pancreatitis with hypertriglyceridemia [4]. All were well at the time of admission and not drinking. All were placed on daily diets containing between 300 and 900 gm of triglyceride. Eleven of the 12 patients developed significant hypertriglyceridemia. Seven of the 11 patients with hypertriglyceridemia developed abdominal pain identical to the pain of prior attacks of pancreatitis, 4 developed serum amylase elevations, 1 a urinary amylase elevation, and 1 a serum lipase elevation. This study was interpreted as direct evidence supporting the concept that hypertriglyceridemia can initiate an attack of acute pancreatitis in the absence of other factors in a controlled hospital situation. Further investigative