

Pancreatic Hyperenzymemia: Clinical Significance and Diagnostic Approach

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Introduction

An increase in the serum concentration of pancreatic enzymes (amylase and lipase) is commonly an expression of inflammatory or neoplastic pancreatic disease. However, an elevation of pancreatic enzymes, generally mild, may be a non-specific phenomenon without any clinical implication.

The large spreading of the serum pancreatic enzymes dosage in clinical practice, particularly in emergency rooms, results in a large number of patients with elevated amylase and/or lipase serum levels without clinical evidence of pancreatic disease [1, 2].

This generally involves a ever-increasing number of instrumental and biochemical investigations to exclude pancreatic disorders, with a waste of resources from a cost-effective point of view.

This review emphasizes the biological mechanisms behind these serological alterations, the possible causes, the clinical implications and the diagnostic approach.

The Mechanism Underlying Pancreatic Hyperenzymemia

The causes of increased levels of serum pancreatic enzymes may be related to pancreatic disease. In the absence of pathologies of the pancreas, the mechanism for this biochemical alteration is still unclear, even if some hypotheses have been postulated.

Pancreatic enzymes (more than 20) are synthesized in the endoplasmic reticulum of pancreatic acinar cells and sorted in the trans-Golgi network [3]. In acinar cells, digestive enzymes are transported by zymogen granuli as inactive pro-enzymes [3]. Under cholinergic or hormonal stimulation, zymogens release their contents into the acinar lumen by fusing their membranes with the cellular membrane (*exocytosis*) and, then, the enzymes are transported into the duodenum via the ductal system and activated after contact with the brush-border enzyme enterokinase (enteropeptidase) in the lumen of the small intestine [3, 4, 5]. Intracellular Ca^{2+} concentration is important for these processes and, under physiological resting conditions, pancreatic acinar cells maintain a Ca^{2+} gradient across the plasma membrane, with low intracellular Ca^{2+} facing high extracellular Ca^{2+} concentrations [6]. A rapid Ca^{2+} release from the intracellular stores in response to hormonal stimuli is a signaling mechanism which regulates exocrine pancreatic secretion [6].

Other tissues may synthesize the amylases, but the pancreas and the salivary glands have amylase concentrations which are several orders of magnitude higher than those in other tissues [1, 7]. Similarly, serum lipases appear to be mainly of pancreatic origin, but other organs, including the stomach, duodenum, small bowel, colon, heart, liver and tongue, may produce lipase [7, 8, 9, 10, 11, 12, 13]. Lipase concentration in the pancreas is 5,000-

↑ Release of Pancreatic Enzymes into the Blood		↓ Renal Clearance	
<i>Mild duct obstruction</i>		<i>Acinar cells damage</i>	
		<i>Renal diseases</i>	<i>Macroamylasemia</i>
Biliary causes	Biliary lithiasis Sphincter of Oddi dysfunction (SOD) Periampullar tumours Anatomic anomalies Choledochocoele	Inflammatory Neoplastic Impaired renal function	Celiac disease Crohn's disease Ulcerative colitis Autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus) Liver diseases HIV Lymphoma Thyroid cancer Renal cells carcinoma
Pancreatic causes	Autoimmunity Pancreatic Tumours Anatomic Anomalies Gene mutations (?) Santorinicele		
Duodenal causes	Paravaterian diverticulum Periampullar tumours		

Figure 1. Pathogenetic mechanisms and possible causes for increased serum levels of pancreatic enzymes.

fold greater than in other tissues [13, 14]. More than 99% of pancreatic lipase is excreted from the apical poles of the acinar cells into the ductal system of the gland, whereas less than 1% diffuses from the basilar pole of the acinar cells into the lymphatics and capillaries (the exogenous-endogenous partition) and subsequently reaches the general circulation [12].

Independent of their origins, about 25% of serum amylase and lipase are excreted by the kidney [12, 15], but amylase is partially reabsorbed by the renal tubular system [12, 16], whereas the reabsorption of lipase is almost complete [17]. It is thought that circulating pancreatic enzymes are removed by the reticulo-endothelial system in the body, and the liver is suspected to be a major organ for amylase removal [18, 19].

Increased levels of pancreatic enzymes may be secondary to an imbalance between pancreatic release and renal clearance [20], but liver damage is also suspected to play a role in inducing pancreatic hyperenzymemia [21].

The elevation of serum pancreatic enzymes may be secondary to an increased release of

pancreatic enzymes from the pancreas in inflammatory or neoplastic disease of the pancreas [22]. The pathological mechanism is probably related to a disruption of pancreatic acini or to an alteration of the normal exocytosis process, with the secretion of the zymogen contents at the basolateral side of the acinar cells [23]. The pancreatic enzymes are therefore released into the interstitial space and later reabsorbed directly or via the lymphatics into the bloodstream.

In the absence of pancreatic disease, the possible causes of an increased enzyme release from the pancreas are an obstruction of the pancreatic duct system, generally mild, or direct acinar cell damage, both of which alter the normal exocytosis process in the acinar cells (Figure 1). There is evidence that an obstructive mechanism in the pancreatic ductal system may determine a disturbance of the normal exocytosis process in pancreatic acinar cells [6] which leads to a basolateral migration of the zymogens and a subsequent discharge of the pancreatic pro-enzymes into the interstitial space (leakage phenomenon) [24]. This mechanism has been demonstrated experimentally, and postulated for the

hyperenzymemia following endoscopic maneuvers on the papilla of Vater [25]. Experimentally, pancreatic duct obstruction determines rapid changes in the response of the acinar cells to secretory stimuli (acetylcholine and cholecystokinin) and leads to complex pathological alterations in the intracellular Ca^{2+} -signaling pattern inducing premature digestive enzyme activation [6].

Anatomic alterations of the pancreaticobiliary junction are rare anomalies which cause various pathological conditions in the biliary tract and the pancreas, and may be associated with serum pancreatic hyperenzymemia [26]. Pancreaticobiliary maljunction might induce pancreatitis or an increase in serum pancreatic enzymes by inducing an obstruction in Wirsung's duct or by determining bile reflux into the pancreatic duct via the anomalous connection [26].

The pathogenesis of serum pancreatic enzyme elevations in metabolic disorders (diabetic ketoacidosis, acidemia) remains unclear. It has been postulated that it results from direct injury to the pancreas with enzyme leakage from the acini and decreased renal clearance [27, 28], but other Authors have suggested a possible role of acidosis in the pancreatic and extrapancreatic secretion of amylase and lipase [29].

Hyperamylasemia may be associated with lung and ovarian cancer [30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40]. It has been suggested that the cause may be an ectopic production of pancreatic enzymes by the tumors, but some Authors have also postulated that the tumor cells may cause an inflammatory response resulting in marked release of the pancreatic enzymes normally produced in these tissues into the blood stream. This hypothesis seems to be confirmed by some studies which have documented hyperamylasemia in nonmalignant pulmonary disorders including pulmonary infarction, "heroin lung" and pneumonia [38, 41, 42] as well as non-malignant ovarian disease [43].

Some Authors have postulated that, in patients with dyslipidemia, particularly hypertriglyceridemia but also hypercholesterolemia or both conditions, there may be an

accumulation of fat inside the pancreatic acinar cell, disturbing exocytosis [44].

In liver diseases, hyperenzymemia may be secondary to pancreatic acinar cell damage [21, 45, 46, 47, 48, 49, 50, 51] since hepatitis B [52, 53] or C [54, 55] viruses may be detected in the pancreas, to impaired clearance of the pancreatic enzymes by the liver reticulo-endothelial system in advanced chronic liver diseases or cirrhosis or to drugs used to clear the virus [56].

Serum pancreatic hyperenzymemia may be secondary to impaired renal clearance related to renal diseases, inflammatory [57, 58, 59, 60] or neoplastic [61, 62, 63, 64, 65, 66, 67, 68] (Figure 1). In postoperative patients, the reason for increased serum levels of pancreatic enzymes may be due to a decreased rate of excretion into the urine, rather than direct pancreatic cellular damage, at least in cardiovascular surgery [69, 70].

In patients who have undergone hepatic resection, hyperamylasemia is probably caused by portal congestion [71] or by a Pringle maneuver used during hepatectomy [72]. However, we cannot exclude the fact that the increase in serum pancreatic enzymes may also be directly associated with hepatic resection and a reduced clearance of pancreatic enzymes by the liver reticulo-endothelial system, as postulated for advanced liver diseases.

However, an increase in the serum levels of pancreatic enzymes may be due to the presence of macroenzymes, macroamylase or macrolipase. Macroenzymes [73, 74] are enzymes of high molecular mass which are formed in serum by self-polymerization or by association with other proteins. Because of their high molecular mass, they escape normal glomerular filtration and accumulate in plasma, with a longer serum half-life. In the majority of cases, the nature of these macroenzymes is an association with an immunoglobulin (IgG or IgA). Most of the serum enzymes routinely measured in the clinical laboratory have been described in lipid aggregates or as exhibiting immunoglobulin macroforms [75, 76, 77, 78]. Macroamylase is an enzymatically active

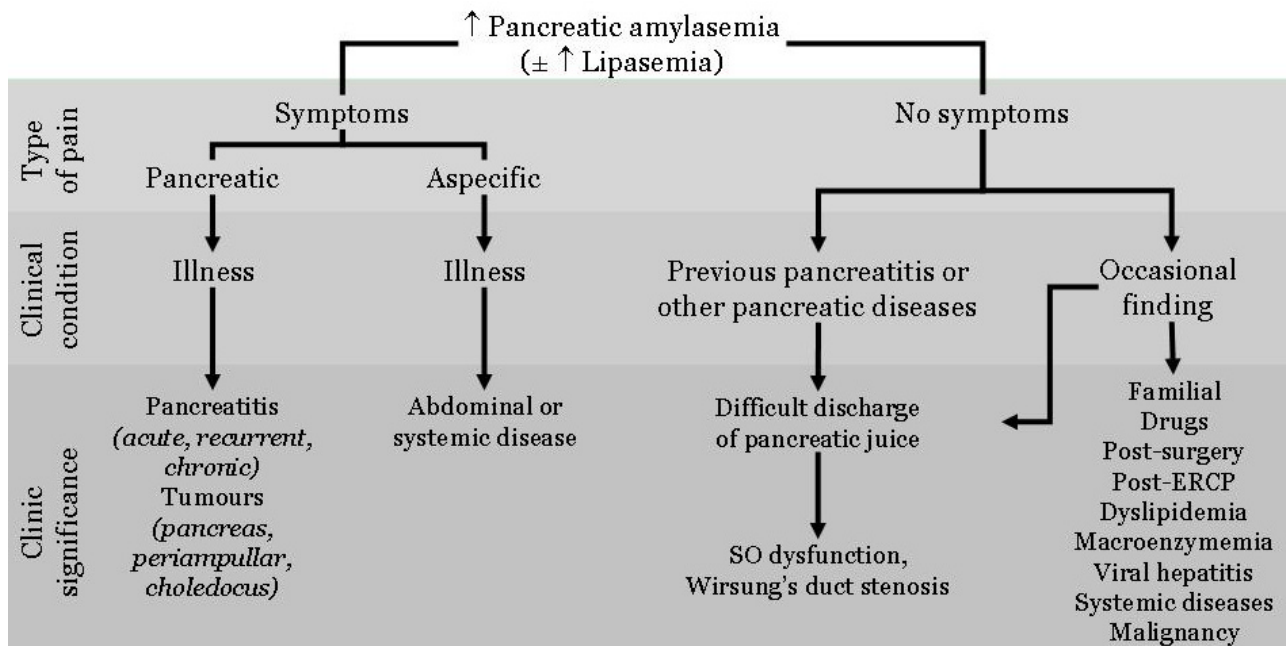


Figure 2. Clinical significance of pancreatic hyperenzymemia.

complex, formed by both salivary and pancreatic amylases bound to immunoglobulin type A (IgA) [79, 80, 81]. The complex can be formed with either kappa or lambda type IgA and is usually filtered very slowly from the blood by the kidney [80, 81]. Macrolipase is a macromolecular form of immunoglobulin-associated lipase (IgG and IgA) [82, 83], but other reports demonstrate an association with alpha₂-macroglobulin [84].

Familial asymptomatic hyperamylasemia is a condition described in family members spanning more than one generation with a pattern of inheritance consistent with an autosomal dominant condition [85]. The causes of this rare condition are still obscure, through a genetic defect is obviously postulated.

Possible Causes of Pancreatic Hyperenzymemia

In the presence of pancreatic hyperenzymemia, we should consider the symptoms reported by the patients (Figure 2). In the presence of pancreatic-type pain or other less frequent symptoms specific for pancreatic diseases (i.e. maldigestion or recent onset of diabetes), we should consider

the diagnosis of pancreatitis (acute, chronic) or pancreatic cancer (intraductal mucin-producing, adenocarcinoma, others), but other possible abdominal diseases (gastro-intestinal, biliary, ovarian or vascular) cannot be excluded (Table 1).

In the presence of aspecific symptoms, we should investigate the clinical history of patients in order to evaluate a possible association between the increase of serum pancreatic enzymes and a systemic disease (Table 2).

In asymptomatic patients, a familial history of pancreatic diseases and hyperamylasemia is necessary in order to decide upon the diagnostic work up. In the presence of familial inflammatory or neoplastic pancreatic diseases - particularly if they are present in first degree relatives and there are additional risk factors - an in-depth investigation is suggested. On the contrary, the presence of high levels of serum pancreatic enzymes in asymptomatic relatives presupposes a probable diagnosis of familial hyperenzymemia.

A previous diagnosis of inflammatory pancreatic disease involves careful research of the cause of the pancreatitis, particularly a dysfunction of the sphincter of Oddi or a possible recurrence of biliary microlithiasis. It

Table 1. Possible abdominal pathology associated with abdominal pain and pancreatic hyperenzymemia.

	References
Gut	
Biliary lithiasis	[13, 89]
Peptic ulcer	[90, 91, 92, 93, 94, 95]
Acute cholecystitis	[96, 97, 98]
Acute abdomen	[99, 100, 101]
Intestinal obstruction	[13, 102, 103]
Obstruction of the afferent intestinal loop after gastrectomy	[104]
Periampullar diverticulum	[88, 105, 106]
Intestinal infarction	[107]
Inflammatory bowel diseases	[67, 108, 109, 110, 111, 112, 113]
Gastroenteritis	[114, 115]
Genital tract	
Ovarian tumours	[31, 33, 36, 37, 116, 117, 118, 119, 120]
Acute salpingitis	[43, 121]
Endometriosis	[122, 123, 124]
Ectopic pregnancy	[125, 126, 127, 128]
Vascular	
Thrombosis	[129, 130]
Dissecting aortic aneurysm	[131]
Ruptured abdominal aortic aneurysm	[132, 133, 134]
Abdominal trauma	[97, 136, 137, 138]

is possible that pancreatic hyperenzymemia is a result of difficulty in discharging pancreatic juice throughout the sphincter of Oddi secondary to sphincter of Oddi dysfunction, biliary lithiasis or microlithiasis, not enough to trigger a new episode of pancreatitis but sufficient to determine a “leakage”

phenomenon, with increased release of pancreatic enzymes into the blood. In patients with a previous diagnosis of pancreatic tumor, we should investigate the possible involvement of the pancreatic duct by the tumor, instrumentally re-evaluate the pancreas after surgery to exclude the

Table 2. Possible systemic diseases associated with pancreatic hyperenzymemia.

	References
AIDS	[139, 140, 141, 142]
Trauma	[135, 143, 144, 145, 146, 147, 148]
Acidemia	[149]
Shock	[143, 150]
Diabetic chetoacidosis	[27, 29, 151, 152, 153, 154, 155]
Critically ill patients	[156, 1157]
Intracranial bleeding	[158]
Eating disorders	[159, 160, 161, 162, 163, 164, 165, 166, 167]
Acute porphyria	[168, 169]
LES	[170, 171]
Rheumatic diseases	[172]
Chronic liver diseases (virus C and B)	[21, 45, 173, 174, 175, 176]
Hepatocellular carcinoma	[177]
Toxic epidermal necrolysis	[178]
Leptospirosis	[179, 180, 181]
Renal diseases	[57, 58, 59, 182, 183, 184]
Sarcoidosis	[185]
Pheochromocytoma	[186, 187]
Multiple myeloma	[64, 188, 189, 190]
Retroperitoneal plasmacytoma	[191]
Hematologic malignancies	[66, 192]
Colon cancer	[39]
Renal cell carcinoma	[63]
Breast carcinoma	[193]
Lung tumours	[30, 32, 34, 35, 38, 39, 40, 194, 195]

Table 3. Drugs associated with pancreatic hyperenzymemia.

	References
Paracetamol	[196]
Steroids	[197]
Azathioprine	[108, 198]
Ephedrine	[199]
Ritodrine	[199]
Chemotherapy	[200]
Roxithromycin	[201]
Cyclosporine	[202]
Clozapine	[203]
Pentamidine	[204]
Didanosine	[205]

possibility of a relapse of the neoplasia (particularly intraductal mucin-producing tumors) or difficulty in discharging pancreatic juice through the anastomosis.

In patients with asymptomatic hyperenzymemia without previous episodes of pancreatitis or a diagnosis of pancreatic cancer, we should carefully investigate possible associated diseases, particularly celiac disease but also B or C virus hepatitis.

Pancreatic hyperenzymemia may also be observed in patients with dyslipidemia, and similarly to what has been observed in hepatic steatosis, those with pluri-metabolic syndrome are probably the high risk patients.

Elevated serum pancreatic enzymes have been reported in patients treated with drugs (Table 3) and an accurate drug history should be taken.

Hyperenzymemia may be also detected in patients who underwent surgery, obviously pancreatic, but also abdominal or cardiac (Table 4).

Diagnostic Approach to Pancreatic Hyperenzymemia

The detection of symptomatic or asymptomatic pancreatic hyperenzymemia

presupposes researching the possible cause, pancreatic or extra-pancreatic (Figure 3). From this point of view, it is important to evaluate the symptoms associated with biochemical alterations.

Clinically, in patients with pancreatic-type symptoms, an inflammatory or neoplastic disease of the pancreas should be suspected. Therefore, the patients should undergo abdominal ultrasonography (US) and/or computed tomography (CT), and biochemical tests to diagnose pancreatitis or pancreatic cancer. Magnetic resonance (MR) may be postponed mainly because the stimulation of the pancreatic fluid secretion by secretin in an altered pancreas may aggravate pancreatic damage in the presence of inflammation. Furthermore, since in the acute phase of pancreatitis, exocrine secretion is impaired in animals [86] and in humans [87], magnetic resonance cholangiopancreatography (MRCP) with secretin stimulation may give incorrect information about pancreatic duct morphology and sphincter of Oddi function.

In asymptomatic patients, those with a documented familial history of pancreatic hyperenzymemia or with a recognized cause of serum alterations (Figure 1, Tables 1, 2, 3) should be evaluated with a first level instrumental examination, i.e. abdominal US. In the absence of these findings or in the presence of pancreatic US abnormalities, a second level instrumental evaluation of the pancreas is suggested.

Despite the high cost, MRCP with secretin stimulation is probably the best approach, because it gives morphologic and functional information. The probability of finding a pancreatic cause for the biochemical alteration at MR is high since, in a previous study, pancreatic ductal morphology was

Table 4. Type of surgery associated with pancreatic hyperenzymemia.

	References
Pancreatic	
Abdominal	[13, 206, 207]
Hepatic	[71, 72, 208, 209, 210, 211]
Biliary	[212]
Cardiovascular	[70, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225]
Liver transplantation	[226]
Post-ERCP	[69, 227, 228]

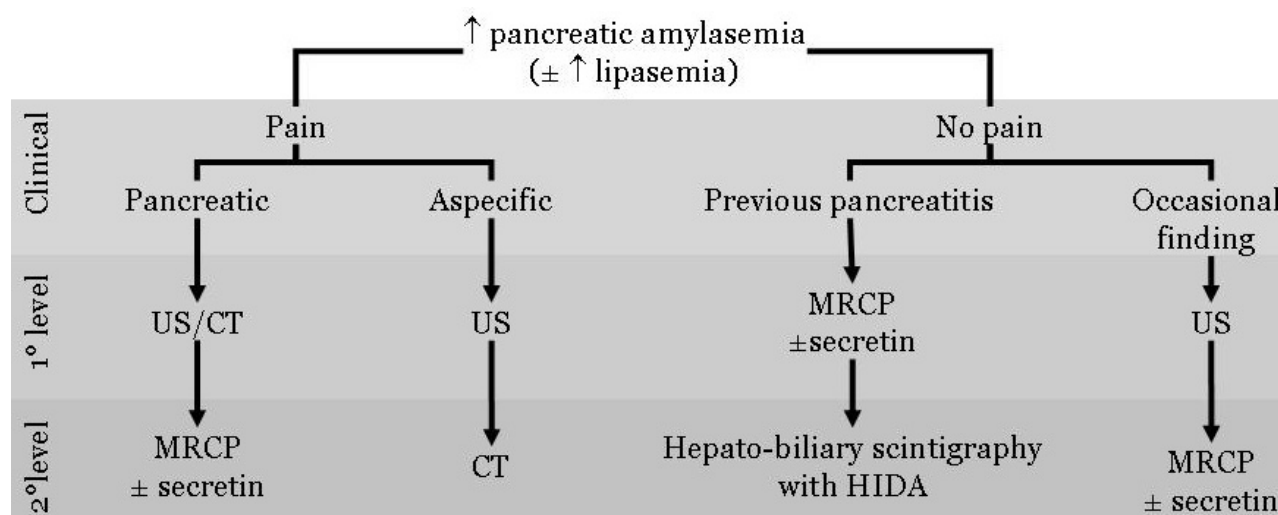


Figure 3. Possible diagnostic algorithm in patients with pancreatic hyperenzymemia.

abnormal in more than 50% of patients with asymptomatic hyperamylasemia and hyperlipasemia [88].

In conclusion, several conditions other than pancreatitis can be the cause for elevated serum amylase and/or lipase levels in patients both with and without abdominal pain, such as altered secretion and clearance of pancreatic enzymes, detection of pancreatic enzymes of non-pancreatic origin or painless pancreatic diseases. In the presence of pancreatic hyperenzymemia, a careful evaluation of the clinical history, drug use and symptoms are important in deciding the diagnostic work-up. In patients without evident reasons for biochemical alteration, the possible causes should be carefully investigated. The first step is certainly to eliminate the possibility of the existence of pancreatic disease and MRCP with secretin stimulation probably represents the best approach to the problem, since it gives morphological and functional information about the pancreatic gland which has been found to be abnormal in a high percentage of patients having elevated serum pancreatic enzymes. The next diagnostic step includes all the examinations required to identify the possible causes of pancreatic hyperenzymemia. A definitive diagnosis of the cause of hyperenzymemia is strongly suggested in order to avoid unnecessary biochemical and instrumental investigations over time and to set the patient's mind at ease.

Keywords Amylases /metabolism; Cholangiopancreatography, Endoscopic Retrograde; Diagnosis; Hyperamylasemia /etiology; Lipase /metabolism; Magnetic Resonance Imaging

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