Serum Lipase Activity Is Increased in Disease States Other than Acute Pancreatitis: Amylase Revisited

For more than 50 years, total serum amylase activity has been the biochemical test most commonly used to confirm the clinical diagnosis of acute pancreatitis. Serum amylase activity has been hoisted onto this pedestal by default, because until recently it has been the only reproducible and rapid diagnostic assay available in clinically emergent settings. As a result of our longstanding dependence and need for accurate interpretation of serum amylase values, considerable knowledge has accumulated during the past two decades about pancreatic and nonpancreatic human isomylases. Their organs of origin, substrate specificity (1), electrophoretic properties (2), and their circulatory clearance and organ metabolism (3, 4) have all been extensively investigated. Moreover, we now know that hyperamylasemia is associated with a wide variety of clinical conditions other than acute pancreatitis (5).

Despite its limitations, however, hyperamylasemia has become the biochemical yardstick for confirming the clinical diagnosis of acute pancreatitis against which newer, unproven assays are measured.

In this issue of Clinical Chemistry, two articles examine the use of serum lipase activity assayed with Kodak Ektachem technology in diagnosing acute pancreatitis. Tetrault reviewed the medical records of >100 patients who had both lipase and amylase assays performed and in whom either lipase or amylase (or both) was increased above the upper reference limit (6). Interestingly, he found that 84% of patients categorized as having abdominal disorders apparently unrelated to the pancreas had hyperlipasemia without an increase in serum amylase activity. Lott and Lu (7) reviewed the charts of their 81 patients and report that lipase has a higher diagnostic efficiency than amylase in acute pancreatitis. They also found, however, that many patients with multisystem disease or acute abdominal processes different from acute pancreatitis have either an abnormal serum lipase activity or an electrophoretic form of lipase, L2, that apparently is not normally found in serum but can be detected in human pancreatic juice by electrophoresis. Thus, patients without apparent pancreatitis, but with complex processes or other abdominal pathology, often had hyperlipasemia. This group of patients is most challenging for clinicians, because appropriate therapy in such patients often depends on an accurate diagnosis. To the extent (and only to the extent) that the categorization of these patients was correct, the reported observations raise the possibility that, despite its touted specificity, serum lipase activity may not be more specific for pancreatic inflammation than is total serum amylase activity.

The diagnosis of acute pancreatitis is always made with some degree of uncertainty in the absence of direct macro- and microscopic inspection of the gland. Most patients with alterations in circulating amylase or lipase homeostasis, however, do not require laparotomy or percutaneous pancreatic biopsy, which is associated with significant morbidity. Often, chart review is the most practical way of categorizing patients, but this relies on indirect, imprecise assessments of pancreatic inflammation such as historical data, physical signs, and imaging studies, which may not be systematically recorded or performed in all patients. Such variation is difficult to control for in retrospective analyses, but bias can be minimized by blinding the reviewer to the laboratory studies under investigation. Although it presents a particular challenge when the test(s) under scrutiny are an integral part of the medical record (e.g., serum amylase and lipase activity), this detail of study design is nonetheless important. In neither of the two articles was it explicitly stated that care was taken to blind the reviewer to serum amylase and lipase values—knowledge of which may have influenced the classification of individual patients. Analysis of performance data for lipase and amylase (and therefore conclusions about the clinical usefulness of these tests) may be critically affected by observer bias, because calculations of sensitivity and specificity of these tests depend on accurate assignment of diagnosis.

Pancreatic triacylglyceride lipase in humans is a glycosylated protein with a molecular mass of ~48 000 Da (8) that appears to be expressed only in pancreatic tissue (9). Like amylase, pancreatic lipase is synthesized and secreted into the intestinal lumen and is released into the circulation in catalytically active form; this enzyme is thus a candidate diagnostic enzyme for acute pancreatitis because its lipolytic activity potentially can be assayed rapidly. Intraluminal activity is inhibited by physiological concentrations of bile salts, but this inhibition is reversed by a polypeptide cofactor, colipase, that is expressed only in the pancreas (10) and is released in a less active proform (11) that apparently is activated intraluminally via a poorly understood mechanism. In the presence of bile salts and colipase, lipase hydrolyzes dietary long-chain triglycerides to produce more-polar fatty acids and 2-monoglycerides.

With the emerging methodological metamorphosis designed to assay pancreatic lipase rapidly with automated equipment, the specificity of unconventional substrates and the effect of untested bile salt analogs such as those used in the Ektachem assay will require careful scrutiny. As we have learned from studies of circulating isoamylases, the presence of circulating nonpancreatic

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1Ed. note: A third article (Kazmierczak et al., pp 356-60) assesses the diagnostic utility of not only lipase and amylase but also phospholipase A.
isolipases—e.g., hepatic, intestinal, lingual, gastric, and lipoprotein lipases—may contribute to serum lipolytic activity. Only after the circulating forms of lipases and their substrate specificities are characterized, therefore, can the value and limitations of new serum lipase assays be clearly defined. From this standpoint, we appear to be in a much better position to evaluate the clinical usefulness of recently described rapid pancreatic isoamylase immunoassays (12–15).

Newer substrates for lipase may also undergo hydrolysis by esterases, which are expressed in a variety of pancreatic and nonpancreatic tissues. In fact, Lott and Lu hypothesize that pancreatic cholesterol esterase is responsible for the L3 portion of the Ektachem-generated activity. Virtually nothing is known, however, about circulating activities or forms of cholesterol esterase in health or disease. Alternatively, the L3 form of lipase may represent an isof orm of pancreatic lipase that does not possess the epitope recognized by the anti-pancreatic lipase monoclonal antibody used in this study. Characterization of the L3 form will be important because it is likely to contribute to serum “lipolytic” activity in acute pancreatitis as assayed by the Ektachem method, owing to its accelerated rate of circulatory release by the inflamed organ.

Our lack of knowledge about the underlying pathogenesis of acute pancreatitis in humans presents the greatest obstacle to the development of a specific and sensitive diagnostic test. Indeed, different causes of acute pancreatitis (e.g., inflammation caused by toxins such as valproic acid or ethanol vs injury from blunt trauma) may very likely have different underlying pathogenetic mechanisms. To gain insights into the pathogenesis of acute pancreatitis, recent collaborative efforts involving the Washington University School of Medicine are investigating the cell biology of the human exocrine pancreas with use of freshly dispersed, viable human pancreatic acini from cadaver donors.

As long as above-normal values of pancreatic enzymes that are normally released into serum are used for diagnosis, negating uncertainties of interpretation will persist. Is the increase attributable to an accelerated rate of release from an injured pancreas or to a delayed rate of clearance caused by hypovolemia or diseased organs that are responsible for catabolism? Investigators will continue to determine the best cutoff value for optimal diagnostic performance. Identification of circulatory markers induced by pancreatic inflammation but not normally released into serum perhaps offers the best promise for a diagnostic test. It is intriguing to speculate that the L2 form of lipase reported by Lott and Lu represents a circulating lipase–(pro)colipase complex released by the injured pancreas. Such complexes have been observed during purification of lipase from delipidated human pancreas. In affinity chromatography with anti-human pancreatic lipase monoclonal antibodies coupled to agarose, lipase–colipase complexes bind to the column and can be removed by sequential passage of the eluted material over an affinity column involving anti-human colipase monoclonal antibodies (unpublished data). Ordinarily, colipase is undetectable in serum (16), presumably because it is cleared rapidly. Thus, detection of serum lipase–(pro)colipase complexes in acute pancreatitis may prove diagnostically useful. Furthermore, detection of an activated form of colipase within the complex may be useful in predicting the presence of peripancreatic fat necrosis, or the development of more distant complications that may be related to lipolysis, e.g., extramedullary fat necrosis (17) or encephalopathy (18). In comparison with isoamylases, our understanding of circulating isolipases and their role in the diagnosis of acute pancreatitis is in its infancy.

References

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