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Low lipase levels as an independent marker of pancreatic cancer: a frequently neglected condition in clinical setting

PANCREAS

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Original Article

ABSTRACT

Background/Aims: Low lipase levels, which may be an indication of low production due to organ failure, are frequently encountered in a clinical setting, but are usually overlooked. This study examined the values of low serum lipase levels and other clinical parameters in the diagnosis of several clinical conditions, such as in pancreatic cancer.

Materials and Methods: Patients with low lipase levels (≤8 U/L) were included in this retrospective study. Clinical data, including diagnostic category, demographic properties, and biochemical and hematological measurements, including serum lipase levels, were extracted. A multivariate analysis was used to identify the independent predictors of certain diagnostic categories.

Results: A total of 198 patients with low lipase levels were included. Among these patients with low lipase levels, 45 (22.7%) were diagnosed with pancreas cancer. Multivariate analysis identified low lipase level as a significant predictor of pancreas cancer (OR 0.70 [%95 CI, 0.52–0.93], p=0.02). For predicting pancreatic cancer, an optimal cut-off value of ≤5.5 U/L for lipase was utilized, which had a sensitivity and specificity of 76% and 37%, respectively.

Conclusion: Low lipase levels close to zero may be an indication of pancreatic cancer and should not be underestimated in the clinical setting. However, large studies are warranted to delineate the exact diagnostic significance of such low lipase levels.

Keywords: Lipase, gastrointestinal malignancies, pancreatic cancer

INTRODUCTION

Pancreatic cancer is a deadly disease with an overall 5-year survival of 5% (1,2). This unfavorable prognosis of pancreatic cancer is due to delays in diagnosis, early metastasis, and its resistance to chemotherapeutic agents (3), highlighting the need for markers that can aid in early diagnosis and follow-up.

Elevated serum levels of pancreatic enzymes are frequently used for the diagnosis of pancreatic diseases. They are mainly increased in acute pancreatitis but alterations are also possible with other pancreatic conditions. Pancreatic enzyme levels may increase, decrease, or remain unchanged in pancreatic cancer (4). At some point during the course of the disease, levels may decrease, probably due to organ insufficiency.

Increased serum levels of amylase and lipase are good indicators for acute and recurrent pancreatitis (5). However, normal amylase levels can be observed in a substantial proportion of patients with pancreatitis (6); thus, lipase remains a more valuable tool. These pancreatic enzymes may also increase in a number of conditions, including in non-malignant hepatobiliary and gastrointestinal diseases, pulmonary failure, sepsis, subdural bleeding, renal failure, and pancreatic cancer (4,6-10). Low levels of pancreatic enzymes, on the other hand, particularly serum lipase, have rarely been addressed or associated with clinical conditions (4,11). In fact, mostly a lower limit is not usually defined for lipase levels, where a value close to zero is considered normal. Such extremely low lipase levels are frequently encountered in a clinical setting and are usually overlooked,

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although they may indicate low production due to excretory insufficiency.

This study examined the value of low serum lipase levels along with other parameters for predicting several clinical conditions, particularly to aid in the differential diagnosis of pancreatic cancer.

MATERIALS AND METHODS

Patients

Among all the patients that had serum lipase level assessments at the Biochemistry Department of Bezmialem Vakıf University, İstanbul, between May 2014 and May 2015, 198 adult patients with low lipase levels were included in this study. The department's database was screened retrospectively and medical records of the eligible patients were examined retrospectively to extract their demographical and clinical data. Inclusion criteria were as follows: patients ≥18 years with serum lipase levels equal to or smaller than 8 units per liter.

Data retrieval

Clinical diagnoses of the patients were recorded. For the purpose of analysis, two main diagnostic categories were used: malignant conditions and non-malignant conditions. Malignant conditions were further categorized and sub-categorized as follows: (1) gastrointestinal malignancies, including gastric ca, pancreas ca, colon/rectum ca, hepatobiliary malignancies, and esophageal cancer; (2) non-gastrointestinal malignancies, including hematological malignancies, lung and respiratory system cancers, and other non-gastrointestinal malignant conditions. The diagnoses of malignant conditions were based on pathological examination of either biopsy or surgical resection specimens.

In addition, demographical, biochemical, and hematological data were also extracted. In case a subject had more than one biochemical or hematological measurement, the value obtained closest to the time of definite diagnosis was used.

Biochemical and hematological assessments

Hemoglobin, white blood cell count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), fasting blood glucose, blood urinary nitrogen (BUN), creatinine. and lipase measurements were extracted from the medical records. All biochemical assessments except CRP levels were made using a photometric method with an Architect C 16000 device (Abbott, Japan), and the hematological assessments were made by Cell Dyne 3700 blood counter (Abbott, US) using a laser/impedance method. For CRP measurements, an Architect C 4000 device was used (Abbott, US).

Statistical analysis

SPSS version 21 was used for the analysis of data. Data are presented in number (percentage) or mean±SD, where appropriate. The Kolmogorov–Smirnov test and graphical methods were used to test the normality of data. The Mann–Whitney U test was used for the comparison of continuous variables. Logistic regression analysis was used for the multivariate analysis to identify the independent predictor(s) of malignancy types. A receiver operator characteristic curve (ROC) was generated to examine the accuracy of estimations and potential cut-off values. A p value smaller than 0.05 was considered an indication for statistical significance.

RESULTS

A total of 198 patients with low lipase levels were included. The mean age was 60.2±16.1 years. The number of male and female patients were 98 (49.5%) and 100 (50.5%), respectively. Table 1 shows the clinical/pathological features of all the patients. Among those patients with low lipase levels, more than half were diagnosed with malignancy (n=113, 57.1%), pancreas cancer being the most frequent type (n=45, 22.7%), followed by gastric cancer (n=19, 9.6%) and hematological malignancies (n=13, 6.6%). Table 2 shows the tested parameters and summarizes the results of the patients.

Multivariate analysis identified creatinine and lipase levels as significant predictors of GIS malignancies, with low levels indicating higher risk: creatinine, OR 0.32 (95% CI, 0.13–0.80), p=0.014; lipase, OR 0.76 (95% CI, 0.58–0.99), p=0.40. For non-GIS malignancies, on the other hand, low platelet counts, low AST levels, and high CRP emerged as significant predictors: platelet count, OR 0.995 (95% CI, 0.99–0.99), p=0.02; AST, 0.98 (95% CI, 0.96–0.99), p=0.031; and CRP, 1.06 (95% CI, 1.01–1.11). Odds ratios and confidence intervals were for per unit rise in the relevant parameters.

Table 3 shows the median lipase levels according to the diagnostic features. Significantly lower levels were found among pancreatic cancer and colon/rectum cancer cases (p<0.05 for both). Multivariate analysis identified only low lipase levels as a significant predictor of pancreas cancer (OR 0.70 [95% CI, 0.52–0.93], p=0.02); however, when creatinine levels were added to the model as a dichotomous variable, a low creatinine level (<0.57 mg/dL) emerged as a significant predictor

Table 1. Clinical/pathological features of all patients (n=198)

Final diagnosis	n (%)
No malignancy	85 (42.9%)
All malignancies	113 (57.1%)
GIS malignancies	81 (41.0%)
Gastric cancer	19 (9.6%)
Pancreas cancer‡	45 (22.7%)
Colon/rectum cancer	12 (6.1%)
Other GIS cancers*	5 (2.5%)
Non-GIS malignancies	32 (16.2%)
Hematological malignancies	13 (6.6%)
Lung and respiratory system Ca	8 (4.0%)
Other non-GIS cancers†	11 (5.6%)

*3 hepatobiliary cancers, 2 esophageal cancers; †3 breast cancers, 3 sarcomas, 2 gynecological malignancies and single cases of prostate cancer, testis cancer, and carcinoma of head and neck
‡38 (85%) of these cases were stage IV pancreatic cancer

Table 2. Biochemical and hematological findings of all patients (n=198)

Laboratory parameter	Mean±SD	Median (range)
Hb, g/dL	10.4±2.1	10.4 (5.2-15.8)
WBC, x10^3 cells/µL	9.7±7.2	7.3 (0.06-47.1)
Platelets, x10^3 cells/µL	214.9±126.7	200.5 (3.0-733.0)
MCV, fL	87.3±8.4	88.3 (28.1-107.7)
MCHC, g/dL	32.9±1.7	32.9 (24.2-39.4)
CRP, mg/dL	9.9±10.9	5.7 (0.03-48.2)
ALT, U/L	36.5±51.0	19.0 (3.0-329.0)
AST, U/L	51.6±80.0	28.5 (6.0-675.0)
FBG, mg/dL	128.7±75.7	112.0 (24.0-699.0)
BUN, mg/dL	20.3±16.2	15.0 (1.9-84.6)
Creatinine, mg/dL	1.0±1.1	0.7 (0.1-9.7)
Lipase, U/L	5.75±1.2	6.0 (2.0-8.0)

Hb: hemoglobin; WBC: white blood cell count; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration, ALT: alanine transaminase; AST: aspartate transaminase; FBG: fasting blood glucose; BUN: blood urinary nitrogen

Table 3. Comparison of median lipase levels according to the presence of malignant conditions

Total n=198	Present	Absent	P
Any malignancy (n=113, 57.1%)	6 (2-7)	6 (2-8)	0.144
GIS malignancy (n=81, 41.0%)	6 (3-7)	6 (2-8)	0.048
Gastric Ca (n=19, 9.6%)	5 (4-7)	6 (2-8)	0.081
Pancreas Ca (n=45, 22.7%)	5 (3-7)	6 (2-8)	0.005
Colon/rectum Ca (n=12, 6.1%)	7 (4-7)	6 (2-8)	0.013
Other GIS Ca (n=5, 2.5%)	6 (5-7)	6 (2-8)	0.441
Non-GIS malignancy (n=32, 16.2%)	6 (2-7)	6 (2-8)	0.500

GIS: gastrointestinal system
Data presented as frequency, percent and median (range)

of pancreas cancer (OR 2.42 [95% CI, 1.09–5.37], p=0.03). On the other hand, high CRP and low MCHC levels (CRP, OR 1.11 [95% CI, 1.02–1.20], p=0.01; MCHC, OR 0.58 [95% CI, 0.38-0.89], p=0.01) but not lipase levels emerged as significant predictors of colon/rectum cancer.

The area under the receiver operator characteristics (ROC) curve (Figure 1) of lipase levels for predicting pancreatic cancer was 0.632 (95% CI, 0.536–0.727, p<0.007). An optimal cut-off value of ≤5.5 U/L for lipase resulted in sensitivity and specificity levels of 76% and 37%, respectively, for predicting pancreatic cancer.

DISCUSSION

This study examined the clinical profile of patients with abnormally low serum lipase levels and identified it as a significant and independent predictor for pancreatic cancer. To the best of our knowledge, this is the first study focusing mainly on exceptionally low lipase levels and their relevance in a clinical setting.

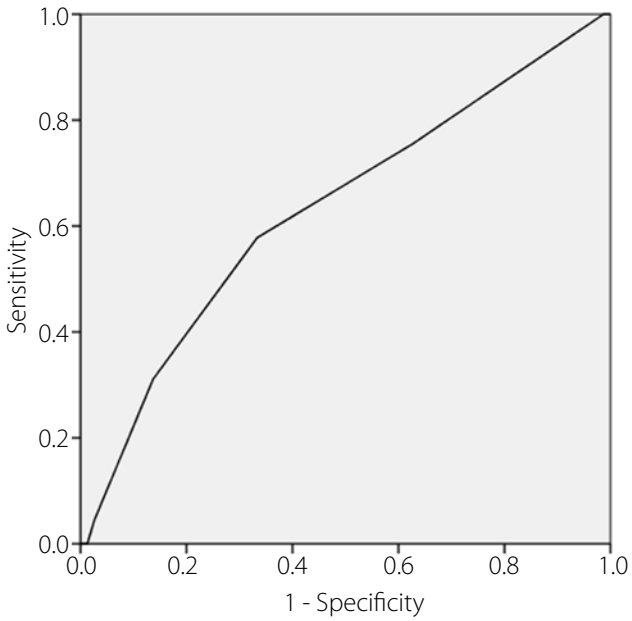

Figure 1. Receiver operator characteristics (ROC) curve of lipase levels for predicting pancreatic cancer

Serum lipase levels are valuable tools for the diagnosis of pancreatic diseases (12). However, low lipase levels have been rarely studied. Ventrucci et al. examined the levels of several pancreatic enzymes in patients with acute pancreatitis, chronic pancreatitis, pancreatic cancer, and non-pancreatic disease; and a remarkable proportion of patients with chronic pancreatitis presented with low serum lipase levels (4). The lower limit of the reference range was 8 U/L, similar to this study. In addition, exocrine pancreas function was evaluated using the secretin-cerulein test in some of the patients with chronic pancreatitis (13). Abnormally low levels of lipase were found among 21% of patients with chronic pancreatitis in clinical remission (4). In addition, abnormally low enzyme levels were associated with less than 20% of exocrine function as evaluated by the secretin-cerulein test. This is line with the findings of Osipenko and Venzhina (14), who found normal or low serum lipase levels in patients with excretory pancreatic insufficiency. Similarly, Hayakawa et al. (15) found an association with low lipase levels and advanced exocrine pancreatic insufficiency among patients with chronic pancreatitis. In that study, low lipase levels were present in 20% of the cases.

In pancreatic cancer patients, on the other hand, high and low serum lipase levels were found in 25% and 10% of cases, respectively (4). Similarly, Pezzilli et al. (16) found abnormally low lipase levels in 11% of pancreatic cancer patients. Nevertheless, the authors of the study by Ventrucci et al. (17), concluded that serum pancreatic enzymes neither have much diagnostic value for chronic pancreatitis in remission or pancreatic cancer, nor were they good markers of exocrine pancreas insufficiency, most probably due to the large variation (4). In an earlier study by Ventrucci et al. (17), a variable pattern of serum pancreatic enzymes was found with low, normal, or high levels among patients with pancreatic cancer.

Roch et al. (18) examined the association of abnormal (either low or high) serum pancreatic enzyme levels (lipase or amylase) with the risk of intraductal papillary neoplasms. Among patients without pancreatitis, both low and high pancreatic enzyme levels were associated with higher risk of malignancy when compared to the patients with normal pancreatic enzyme levels. In that study, the reference range for lipase levels was 22-51 U/L (18).

Low creatinine levels associated with pancreatic cancer in this study seem to be due to the decreased muscle mass in malignancy patients and it may also be considered a supplementary sign when interpreted together with low lipase levels.

Pancreatic lipase is a glycoprotein mainly found in pancreas and it mediates fat digestion (19). The tissue concentration of lipase is high in pancreas tissue, therefore pancreatic injury results in increased serum activity due to leakage. Thus, a rapid rise, for example, in acute pancreatitis can be explained by the release of enzymes to the circulation. The same mechanism may explain the increases in other conditions associated with pancreatic tissue destruction, such as pancreatic cancer. However, at the advanced stage of this malignant condition, similar to the case of chronic pancreatitis, an organ insufficiency may predominate, resulting in a low production of pancreatic enzymes and low serum enzyme activities. Such a relation has been partly demonstrated using the secretin-cerulein test for chronic pancreatitis and for other conditions associated with excretory pancreatic insufficiency (4, 14).

The main limitation of this study is its retrospective nature. Second, most pancreatic cancer cases were at their advanced stage, which explains the low creatinine levels in these patients, probably due to muscle wasting. Therefore, low lipase levels may not be valuable for the diagnosis of early stage pancreatic cancer. However, it is of note that most of these patients presented at an advanced stage. Third, the inclusion of only patients with low lipase levels is another potential limitation; therefore, the findings may not be generalized to the general population but rather they are limited to the clinical profile of the patients with exceptionally low lipase levels. Nevertheless, the findings provide preliminary information on how to interpret low lipase levels, and further large-scale clinical studies with low, high, and normal lipase levels would clarify such clinical associations.

In conclusion, not only high serum lipase levels, but also low levels close to zero should not be overlooked and may necessitate further investigation, since a substantial proportion of these patients have pancreatic cancer. In addition, for the subgroup of patients with low levels, the lipase level has a predictive value for pancreatic cancer. However, these findings need to be tested in larger patient populations with a wide spectrum of serum lipase levels.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bezmialem Vakıf University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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