Can we detect chronic pancreatitis with low serum pancreatic enzyme levels?

Running title: Pancreatic enzyme levels in chronic pancreatitis

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Disclosure statement

All authors state that there are no conflicts of interest in this study.
Abstract

Objectives:

The aims of this study are to evaluate whether serum pancreatic enzyme levels could be used to aid screening for chronic pancreatitis (CP).

Methods:

170 healthy volunteers were screened and prospectively enrolled in the control group. 150 patients who were diagnosed with calcific CP were enrolled in the patient group by retrospective review. Serum amylase and lipase levels were compared between the two groups.

Results:

The mean values ± S.D. of the control group were compared with those of the patient group for serum amylase level (48.1 ± 13.2 U/L vs. 34.8 ± 17.2 U/L, p<0.001), and serum lipase level (26.4 ± 11.3 U/L vs. 16.3 ± 11.2 U/L, p<0.001). On the receiver operation characteristic curve analysis for amylase level, area under the curve was 0.740 (95% confidence interval), and sensitivity and specificity were 38.7% and 94.1%, respectively, with a cut-off value of 27.5 U/L. On the receiver operation characteristic curve analysis for lipase level, area under the curve was 0.748 (95% confidence interval), and sensitivity and specificity were 33.3% and 95.9%, respectively, with a cut-
off value of 10.5 U/L.

Conclusions:

Our results suggest that low serum pancreatic enzyme levels can be used to aid in detection of CP.

Key Words: Amylase; Lipase; Pancreatitis, Chronic; Diagnosis

Abstract word count: 200
Introduction

Chronic pancreatitis (CP) is defined as progressive inflammatory destruction of pancreatic secretary parenchyma with replacement by fibrous tissue, resulting generally in irreversible dysfunction of both endocrine and exocrine pancreatic function (1-2). CP is usually diagnosed based on clinical-historical information, results of imaging findings, pancreatic functional tests and chronically or intermittently elevated pancreatic serum enzymes (3, 4). Serum amylase and lipase are obtained in nearly all suspected CP patients. When low serum values are obtained, does the clinician use this information to aid in CP diagnosis or is the value ignored (or perhaps considered laboratory error)?

The lipase expression can be detected to varying extent in the lingual salivary glands, gastric fundus, duodenum, liver, and the adipose tissue. But the main organ of lipase secretion is the pancreas. Total pancreatectomy patients commonly have low serum lipase levels (5, 6). In CP, damage may affect pancreatic enzyme synthesis and entry into and clearance from the circulation. This may result in low serum enzyme levels. In the pathologic tissue analysis, pancreatic tissue in CP demonstrates decrease of both amylase and lipase activity. Notably, amylase activity is more decreased than lipase activity (7).

The correlation between severe exocrine insufficiency and low pancreatic juice enzyme levels is well known. Older reports note low serum pancreatic enzymes, especially lipase, in up to 50% of
patients with CP (8-11). Although the role of elevated serum lipase levels as a valid tool for diagnosing acute pancreatitis and acute episodes of CP has been well established, the low serum lipase levels in CP have not yet attracted much recent attention. Low serum amylase and lipase levels in CP are not discussed in several recent publications (3, 12-19). Serum amylase and lipase remain as readily available and inexpensive tests. Methodologies for pancreatic enzymes measurement reports from older literature earlier than the year 2000 are different from that used in many modern laboratories.

The aims of this study are 1. To determine if amylase and lipase levels as assessed by modern day methods are low in a portion of CP patients, 2. To compare serum pancreatic enzyme levels between CP patients and healthy controls, and 3. To evaluate whether serum pancreatic enzyme levels could be used to aid screening for CP.

**Methods**

Healthy volunteers were screened and prospectively enrolled in the control group. Patients who were diagnosed with calcific CP and underwent ERCP were enrolled in the patient group. Serum amylase and lipase levels were compared between the two groups. This study was approved by Indiana University Institutional Review Board prior to the commencement of the study.
1) Control group

Healthy paid volunteers were screened and prospectively enrolled in the control group from April 1, 2014 to March 15, 2015. Informed consent was obtained from all such volunteers before enrollment. Inclusion criteria and exclusion criteria were represented in the Table 1. Aliquots blood samples from a single draw were analyzed for serum pancreatic enzyme levels.

2) Patient group

Patients who were diagnosed with calcific CP and underwent ERCP in Indiana University Health between January 1, 2012 and May 31, 2014 were enrolled in the patient group. All information was obtained by retrospective medical record review from patients identified through the IU ERCP procedure database. Calcific CP was diagnosed based on clinical symptoms and pancreatic calcifications detected by imaging studies (CT, MRI, or ERCP). Serum amylase and lipase were obtained and analyzed a few hours before the ERCP by the routine clinical laboratory of the Indiana University Health. Patients were excluded from the study if they were younger than 18 years or older than 79 years or pregnant or had a condition, such as chronic kidney disease, previous gastrointestinal or pancreatic surgery that may affect serum amylase and lipase levels.

3) Analysis of serum pancreatic enzymes
All serum amylase level and lipase level in the both groups were measured using same automated chemistry analyzer (AU 5822 analyzer; Beckman Coulter, Inc., Brea, CA). Our validated reference range for amylase and lipase are between 19 U/L and 86 U/L, and between 7 U/L and 59 U/L, respectively.

Serum amylase and lipase levels were compared between the two groups. If a patient had blood drawn several times during enrollment period, the lowest level among the results was used for analysis. Patients with an abnormal high serum pancreatic enzyme level before ERCP were enrolled in the study only when their levels returned to below the upper limit of normal and pain was resolved or improved after ERCP.

4) Statistical analysis

Pearson’s chi square test and student t-test were used to analyze the differences between two groups. Student t-test was used to analyze the variables among the subgroups in control group. Receiver operating characteristics (ROC) curve analysis was constructed and the area under the curve (AUC) was calculated to determine the diagnostic performance of serum pancreatic enzymes. The level of variables were described as mean ± standard deviation (S.D.). P<0.05 was considered significant. Statistical analysis was performed with IBM® SPSS® Statistics (Version 22.0.0; SPSS Inc., Chicago, IL, USA).
Results

A total of 180 healthy volunteers were screened and enrolled in the control group. Ten healthy volunteers were excluded due to abnormal high levels of pancreatic enzymes (5.6%), resulting in a total of 170 healthy volunteers finally enrolled in the control group (44 men, 126 women with a mean age of 48.1 years; range, 20-78 years). A total of 220 patients were identified with calcific CP and underwent 370 ERCP procedures, of which 70 patients were excluded: 33 patients with persistent elevations of pancreatic serum enzyme levels; 11 patients with history of other gastrointestinal disease or previous gastrointestinal operation; 9 patients with age <18 or >79; 9 patients with inadequate information; 5 patients with chronic kidney disease; 3 patients with neoplastic disease. A total of 150 patients (76 men, 74 women with a mean age of 54.0 years; range, 23-78 years) were enrolled in the patient group (Fig. 1).

The characteristics of the study participants are presented in Table 2. There were significant differences in mean age (mean values ± S.D.; 48.1 ± 15.9 vs. 54.0 ± 12.2, respectively, p<0.001) and sex ratio (male : female; 44 : 126 vs. 76 : 74, respectively, p<0.001) between control group and patient group due to differences of frequency of volunteer subgroups. The mean serum amylase level was significantly higher in the control group compared with that of the patient
group (normal range, 19-86 U/L: 48.1 ± 13.2 U/L vs. 34.8 ± 17.2 U/L, respectively, $p<0.001$). The mean lipase level was also significantly higher in the control group compared with that of the patient group (normal range, 7–59 U/L: 26.4 ± 11.3 U/L vs. 16.3 ± 11.2 U/L, respectively, $p<0.001$) (Fig. 2).

Because of non-equal distribution of sex and age in the volunteer group, subgroup analyses were done in the control for the evaluation of age-related and sex-related differences. Between younger-age (age 18-49) and older-age (age 50-79) subgroups, there was no significant difference of serum amylase and lipase levels (amylase: 46.9 ± 11.6 U/L vs. 45.0 ± 11.4 U/L, respectively, $p=0.326$; lipase: 24.1 ± 10.1 U/L vs. 25.9 ± 10.7, respectively, $p=0.303$). Between male and female subgroups, there was no significant difference of serum amylase and lipase levels (amylase: 46.5 ± 14.2 U/L vs. 48.7 ± 12.8 U/L, respectively, $p=0.362$; lipase: 29.6 ± 13.5 U/L vs. 25.3 ± 10.2 U/L, respectively, $p=0.058$) (Table 3).

Interestingly, no one in the healthy volunteer group had values of serum amylase and lipase levels below the reference range (normal range). Using mean value minus 2 S.D. of control group, 45 patients (30%) had low amylase level (mean level, 16.5 ± 4.7 U/L), 28 patients (18.7%) had low lipase level (mean level, 3.1 ± 0.4 U/L), 16 patients (10.7%) had both levels low and 57 patients (38.0%) had either of both levels low.

We next generated the receiver operation characteristic (ROC) curves to assess the potential
usefulness of low serum pancreatic enzyme levels as diagnostic modalities for CP (Fig. 3 and Table 4). On the ROC curve analysis for amylase level, AUC was 0.740 (95% confidence interval), and sensitivity and specificity were 70.0% and 70.6%, respectively, with an optimum diagnostic cut-off value of 41.5 U/L. Specificity of serum amylase level for diagnosis of CP was 94.1% with a cut-off value of 27.5 U/L. On the ROC curve analysis for lipase level, AUC was 0.748 (95% confidence interval), and sensitivity and specificity were 69.3% and 68.8%, respectively, with an optimum diagnostic cut-off value of 19.5 U/L (Fig. 3 and Table 3). Specificity of serum lipase level for diagnosis of CP was 95.9% with a cut-off value of 10.5 U/L. If both serum amylase and lipase levels are lower than normal range, sensitivity and specificity are 10.7% (16/150) and 100% (170/170), respectively. If either serum amylase or lipase level is lower than normal range, sensitivity and specificity are 30.0% (45/150) and 100% (170/170), respectively.

Discussion

Nearly every patient with clinically suspected CP has a serum amylase and lipase drawn. If values are elevated, suspicions for pancreatic diseases are increased and further studies are often done. If values are normal, no specific next step is suggested. If values are low, many clinicians (personal observation) have no increased suspicion of CP. Our study was done to re-evaluate the utility of
low serum pancreatic enzyme levels for diagnosing chronic pancreatitis.

Our results show that patients with established calcific CP (with obviously advanced disease) had significantly lower levels of serum pancreatic enzymes than healthy control group. Furthermore, when compared to healthy control group, 57 patients (38%) out of 150 patients had at least 1 enzyme level more than 2 S.D. below the levels of control group. These results suggest that low levels in routine pancreatic serum enzyme tests should not be deemed “normal” nor dismissed clinically unimportant.

Low serum lipase and amylase levels in CP were observed long ago (8-11). Could this observation apply to currently used laboratory methodology? This study confirms prior studies and emphasizes the diagnostic values of low serum pancreatic enzymes. We conducted an ROC curve analysis to determine the diagnostic possibility of detecting patients with a CP. As can be seen in Fig. 3 and Table 4, the AUC for serum amylase level and serum lipase level were both greater than 0.7, with sensitivity and specificity ranging between 65% and 70% depending on the optimal cut-off value. These values were somewhat different from the values presented by the diagnostic modalities of CP, but the specificity increased rapidly to beyond 90% with lower cut-off values. Specificity of serum amylase was 94.1% with cut-off level of 27.5 U/L and 100% when the level was lower than 18.5 U/L. Specificity of serum lipase was 95.9% when the cut-off level was 10.5 U/L and 100% when the cut-off level was lower than 7.5 U/L. These results suggest that normal
subjects do not show values below a certain level and that this cut-off may be useful for the
diagnosis of CP. The clinician should not ignore low serum amylase and lipase levels as they
suggest chronic pancreatitis in absence of pancreas resection surgery.

Previously reported noninvasive or indirect laboratory tests have highly variable accuracy in
suggesting a diagnosis of CP depending on the severity of the disease (18, 19). Serum trypsin
level has similarly been found to be low in up to 50% of calcific CP patients and moderate
sensitivity in late disease state with steatorrhea. Some reports mentioned this in discussion of
chronic pancreatitis, while the sensitivity is at least intermediate, the specificity is near 100% (10,
18, 19). This would appear to have equal diagnostic values for amylase and lipase low values. The
serum trypsin assay has not replaced amylase and lipase in clinical practice due to requiring
several days to obtain a result, and two-fourfold more expensive than serum amylase and lipase
levels in our hospital.

Our contention is clinically to take further advantage of serum amylase and lipase values which
are already drawn on virtually all suspected pancreatic disease patients. Low analysis cost of
serum amylase and lipase levels are especially valuable in 3rd world countries. Clinicians should
not overlook low pancreatic enzyme values but should suspect chronic pancreatitis and
recommend further detailed examinations.

A large-scale, prospective, follow-up study based on our results would be able to establish critical
diagnostic basis, such as using serum pancreatic enzyme level as an economic, long-term follow-up in patients with symptoms of CP but unremarkable findings from routine tests. If a patient’s levels are below certain levels or continuously decreasing, more accurate diagnostic tests can be recommended more confidently for confirmation of CP. Our study was not designed to detect the difference in pancreatic enzyme levels depending on the severity of CP or in the course of disease progression from recurrent pancreatitis to chronic calcific pancreatitis in a long-term follow-up. These could be addressed in future studies.

Limitations of our study are as follows. Healthy volunteers were enrolled prospectively but the subjects in the patient group were enrolled retrospectively. Although there is no statistical difference of serum amylase and lipase level between male and female subgroup, men and women were not evenly distributed across the healthy group due to low rate of volunteering in males, especially younger males. Patients with early-stage CP were not involved in this comparative study, and those differences in terms of the severity or cause of CP could not be investigated. We are not aware of other clinical conditions with low serum amylase and lipase level (except for resection surgery of pancreas or salivary glands, chronic salivary gland disease, or pancreatitis with extensive necrosis, etc.).

In conclusion, our results suggest that low serum amylase and lipase levels should not be discarded for patients, and that further testing may be warranted if there is the possibility of
underlying pancreatic disease. Also, low serum amylase and lipase levels as detected by modern methodology laboratory can be used to aid in the screening of CP. These results confirm previous studies stating up to 50% sensitivity for CP diagnosis. Further studies in non-calcific chronic pancreatitis are needed to clarify the pancreatic enzyme levels in regards to the demographic factors and severity status of chronic pancreatitis.

Acknowledgement

This work was partially funded by a gift from Maryam Al-Rashed and family of Riyadh, Saudi Arabia who had no involvement in the conduct of this study. We would like to thank Gwangil Kim, M.D. for his devoted cooperation during study.

References


### Table 1. Inclusion and exclusion criteria for control group

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 18 - 79.</td>
<td>• History of gastrointestinal disorders: any pancreatic disorder, bowel obstruction or inflammatory bowel disease (Crohn's disease or ulcerative colitis), peptic ulcer disease, gallstones or gastrointestinal tumors (any type).</td>
</tr>
<tr>
<td>• General good health.</td>
<td>• History of ovarian tumors (any type).</td>
</tr>
<tr>
<td>• Body weight 110 pounds (50 kg) or greater.</td>
<td>• History of lung tumors (any type).</td>
</tr>
<tr>
<td>• Agrees to participate and signs consent form.</td>
<td>• Major health disorders: diabetes, liver disorders, arthritis (osteoarthritis acceptable), myocardial infarction, or chronic obstructive pulmonary disease (chronic bronchitis or emphysema).</td>
</tr>
<tr>
<td>• Be able to complete General Health/Gastrointestinal Health History Survey.</td>
<td>• Family history of chronic pancreatitis or cystic fibrosis.</td>
</tr>
<tr>
<td>• Be willing to have bloodwork drawn.</td>
<td>• Pain in the upper abdomen greater than 5 days per year.</td>
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<td></td>
<td>• Alcohol intake greater than 2 drinks per day.</td>
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<td></td>
<td>• History of alcohol use of 10 drinks per day for greater than 2 years.</td>
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<td></td>
<td>• Does not wish to participate or to consent to have their laboratory results utilized in future studies.</td>
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<tr>
<td></td>
<td>• Pregnant.</td>
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<td></td>
<td>• Cigarette smoking history of more than 1 pack per day for 5 years or more.</td>
</tr>
</tbody>
</table>
Table 2. Baseline characteristics of control group and patient group

<table>
<thead>
<tr>
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<th>Control Group (n=170)</th>
<th>Patient Group (n=150)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.1 ± 15.9</td>
<td>54.0 ± 12.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>44 (25.9)</td>
<td>76 (50.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum amylase (U/L)*</td>
<td>48.1 ± 13.2</td>
<td>34.8 ± 17.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum lipase (U/L)**</td>
<td>26.4 ± 11.3</td>
<td>16.3 ± 11.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean values ± S.D. or n (%).

* Normal value: 19-86 U/L

** Normal value: 7-59 U/L
Table 3. Age related and sex related subgroup analysis in control group

<table>
<thead>
<tr>
<th>Age related subgroup</th>
<th>Serum amylase (U/L)*</th>
<th>Serum lipase (U/L)**</th>
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<tbody>
<tr>
<td>Age 18-49 (n=78)</td>
<td>46.9 ± 11.6</td>
<td>24.1 ± 10.1</td>
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<tr>
<td>Age 50-79 (n=73)</td>
<td>45.0 ± 11.4</td>
<td>25.9 ± 10.7</td>
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<table>
<thead>
<tr>
<th>P value</th>
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<tbody>
<tr>
<td>0.326</td>
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<td>0.303</td>
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</table>

Sex related subgroup

<table>
<thead>
<tr>
<th>Sex related subgroup</th>
<th>Serum amylase (U/L)*</th>
<th>Serum lipase (U/L)**</th>
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</thead>
<tbody>
<tr>
<td>Male (n=44)</td>
<td>46.5 ± 14.2</td>
<td>29.6 ± 13.5</td>
</tr>
<tr>
<td>Female (n=126)</td>
<td>48.7 ± 12.8</td>
<td>25.3 ± 10.2</td>
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<table>
<thead>
<tr>
<th>P value</th>
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<tbody>
<tr>
<td>0.362</td>
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<tr>
<td>0.058</td>
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</table>

Values are presented as mean values ± S.D.

* Normal value: 19-86 U/L

** Normal value: 7-59 U/L
Table 4. Sensitivity and specificity of serum pancreatic enzyme levels for chronic pancreatitis using variable cut-off values

<table>
<thead>
<tr>
<th>Level (U/L)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum amylase (Normal: 19-86 U/L)</td>
<td>18.5</td>
<td>16.0</td>
<td>100</td>
<td>100</td>
</tr>
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<td></td>
<td>27.5</td>
<td>38.7</td>
<td>94.1</td>
<td>85.3</td>
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<td></td>
<td>32.5</td>
<td>49.3</td>
<td>90.6</td>
<td>82.2</td>
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<td>38.5</td>
<td>64.0</td>
<td>80.0</td>
<td>73.8</td>
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<td></td>
<td>41.5</td>
<td>70.0</td>
<td>70.6</td>
<td>67.8</td>
</tr>
<tr>
<td>Serum lipase (Normal: 7-59 U/L)</td>
<td>7.5</td>
<td>27.3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>33.3</td>
<td>95.9</td>
<td>87.7</td>
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<td>19.5</td>
<td>69.3</td>
<td>68.8</td>
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Figure legends

Figure 1. Study enrollment flowchart. A total of 180 healthy volunteers were screened and 170 volunteers were enrolled in the control group. A total of 220 patients were diagnosed with chronic calcific pancreatitis and 150 patients were enrolled in the patient group.
Figure 2. Results of serum pancreatic enzyme level analysis between control group and patient group. Scatter dot graphs show significantly higher levels of serum pancreatic enzymes in the control group compared with those of the patient group (Student t-test).
Figure 3. Receiver operation characteristic (ROC) curve analysis for the diagnostic performance of serum amylase and lipase level for detection of chronic calcific pancreatitis. Area under the curves (AUCs) are 0.740 (95% confidence interval) for serum amylase level, and 0.748 (95% confidence interval) for serum lipase level.
180 healthy volunteers were screened and included.

170 healthy volunteers were finally included in control group.

10 healthy volunteers were excluded due to high level of pancreatic enzyme.

170 healthy volunteers were finally included in control group.

220 patients were diagnosed with chronic calcific pancreatitis.

150 patients were included in patient group.

70 patients were excluded:
- 33 patients with persistent abnormalities of pancreatic enzyme level;
- 11 patients with history of other gastrointestinal disease or previous gastrointestinal operation;
- 9 patients with age <18 or >79;
- 9 patients with inadequate information;
- 5 patients with chronic kidney disease;
- 3 patients with neoplastic disease.
Amylase (U/L) and Lipase (U/L) levels in control and patient groups. The graphs show the distribution of values with control and patient groups separated. The upper normal range is indicated by a horizontal dotted line. The p-values for both comparisons are < 0.001, highlighting significant differences.
ROC Curve

Area Under the Curve

Amylase  0.740
Lipase    0.748