

The Elevation of Pancreatic Enzymes in Serum and Their Distribution at Different Stages of Renal Insufficiency Among Diabetic Patients Attending Goba Referral Hospital

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Introduction: Acute pancreatitis is auto-cell destruction that is manifested by increased leakage of amylase and lipase into circulation. During pancreatitis, the activity of serum amylase and lipase is elevated three times above the upper limit of the normal range. This elevation was observed in both prediabetic and diabetic patients. Severe acute pancreatitis can result in acute kidney injury and other multi-organ dysfunction, which is one of the reasons for death.

Objective: This study aimed to evaluate the elevation of serum amylase and lipase and their distribution at different stages of renal insufficiency among diabetic patients.

Methods: This study included 286 diabetic patients (36 type 1 and 250 type 2), and data were collected from May 1 to June 30, 2019. The study design used was an institution-based cross-sectional study. A face-to-face interview was used to collect data, and serum creatinine, amylase, and lipase levels were measured using a chemistry analyzer. For data entry and statistical analysis, respectively, Epidata software version 3.02 and SPSS version 21 were used.

Results: The mean serum amylase among diabetic patients suffering from G3b and G4 was 106.79 IU/L \pm 118.18 IU/L and 104.85 \pm 90.42 IU/L, respectively. Their mean serum lipase activity was 105.07 IU/L \pm 127.54 IU/L and 106.98 IU/L \pm 88.35 IU/L, respectively. Serum lipase activity was elevated above the normal range and three times above the upper limit of the normal range with a magnitude of 11.2% and 4.2%, respectively. Similarly, 9.1% and 0.7% of diabetic patients had increased serum amylase above the normal range and three-fold above the normal range, respectively.

Conclusion: As glomerular filtration decreases, particularly in moderate-to-severe chronic kidney disease, serum amylase and lipase activity rise above the upper limit.

Keywords: acute pancreatitis, chronic kidney disease, diabetes mellitus, serum amylase, serum lipase

Introduction

Acute pancreatitis (AP), is self-tissue digestion by activated pancreatic enzymes that results in inflammation, edema, necrosis, hemorrhage, and liquefaction. During the occurrence of AP serum activity of amylase and lipase increases threefold above the upper limit of the normal range (ULN).¹ Diabetic patients experienced two to three times the severity of acute pancreatitis as non-diabetic individuals.^{2,3} The activity of serum lipase was also elevated between prediabetes and Type 2 diabetes mellitus (T2DM). The existence of pancreatitis was positively correlated with duration of DM, level of fasting blood sugar (FBS), HbA1C, and creatinine level.⁴

The combination of acute pancreatitis and chronic kidney disease is common, and most of the time, their combination is misunderstood.⁵ Glomerular filtration rate (GFR) is one of the best indicators of renal function.⁶ It measures renal

clearance of endogenous filtration markers from blood circulation.⁷ Therefore, GFR is used to diagnose and stage the degree of kidney disease and its prognosis.⁸ Acute kidney disease and chronic kidney disease are interrelated, and both of them can result in reduction of GFR.⁹

Recurrent episodes of acute pancreatitis lead to chronic pancreatitis. Serum pancreatic enzymes elevated three times above ULN during the occurrence of acute pancreatitis and later on reduced to normal range or very low (insufficient) level in chronic pancreatitis.¹⁰ About 27.1% of patients suffering from acute pancreatitis lead to chronic pancreatitis that is manifested by Pancreatic exocrine insufficiency (PEI).¹¹ PEI among diabetic patients was one of the secondary complications of diabetic neuropathy.¹² They had reduced autonomic function than their matched normal individuals.¹³

More than 40% of diabetic patients may suffer from chronic pancreatitis.¹⁰ Due to a decrease in pancreatic enzymes as in the case of chronic pancreatitis, it leads to mal-digestion in the intestine. The prevalence of PEI among Type 1 diabetes mellitus (T1DM) and T2DM was 26–44% and 12–20%, respectively.¹⁴ The magnitude of PEI was higher among T1DM than T2DM (44.44% vs 18.0%).¹⁵ Pancreatic exocrine dysfunction is one of the causes that results in under-nutrition in kidney disease due to decreased digestion enzyme activity and their insufficiency.¹⁶

Moreover, severe acute pancreatitis (SAP) can result in acute kidney injury (AKI) and further complications can lead to multiple organ dysfunctions.¹⁷ About 8.4% and 11.1% of patients suffering from acute pancreatitis may have multiple organ failure including kidney and systemic inflammatory response syndrome, respectively.¹⁸ Among various causes of chronic kidney disease (CKD), T2DM and T1DM account for 30–50% and 3.9%, respectively.¹⁹ Globally, T2DM is the second leading cause of CKD and CKD-related death in 2019 and the incidence of DM-CKD comorbidity was 2.62 million worldwide.²⁰

Globally, 34 individuals suffered from acute pancreatitis per 100,000 general populations annually. It varies across the continents with most incidences in Northern and Eastern Europe. Acute pancreatitis kills 1.16 people per 100,000 in the general population each year. The risk of pancreatitis increased with the duration of disease and rate of pancreatic parenchyma cell destruction. The risk of post-pancreatitis DM is 2.54 times higher among those who have acute pancreatitis attacks than those who have not.²¹

Significantly, the high mortality causes of diabetic patients were due to multi-organ failure. Among those causes, patients with AP and suffering from acute kidney injury were demonstrated by a sudden rise in serum creatinine and reduced urine output. About half of them (54.16%) completely recovered from renal failure and their pancreatic function resolved. But, 37.5% passed away due to acute-phase health derangements.²² Even though antidiabetic drugs decrease the risk of pancreatitis, T2DM patients are at a high risk (1.5–3 times) than non-diabetic.²³

A clinical review conducted on pancreas and DM relation indicated that among patients who develop pancreatitis 31% of them suffered from severe pancreatitis and had elevated glycosylated hemoglobin levels, while 7% of them had mild pancreatitis. In addition to this, about 10% to 15% of the cases developed diabetic ketoacidosis (DKA) with AP.²⁴ According to a cohort study conducted in the UK out of 148, 903 T2DM 301 of them developed AP. T2DM Patients were 2.89 times at high risk for AP than non-diabetic.²⁵

Objective

This study aimed to evaluate serum amylase and lipase elevation among diabetic patients and their distribution at different stages of renal insufficiency.

Methods

The study was included 286 (250 T2DM and 36 T1DM) diabetic patients attending Goba referral hospital diabetic follow-up from May 1 to June 30, 2019. The institution-based cross-sectional study design was used, and all adult diabetic patients were included in the study. Primarily, the data were collected for the assessment of the magnitude and factors associated with pancreatic exocrine insufficiency among diabetic patients, and the current study was extracted from it which focuses on the pancreatic enzymes elevation rather than its deficiency. Therefore, it is a follow-up study to our previous study on

Magnitude of pancreatic exocrine insufficiency and associated factors among adult diabetic patients attending Madda Walabu University Goba referral hospital, South east Ethiopia, 2019.¹⁵

Ethical clearance written by a Ref No: IHRPGD/554/2019 was obtained from Jimma University institutional review board and written consent was obtained from each study participant. The participants were informed about the purpose of the study, and the study was done without violating Helsinki Declaration. The interview was conducted by trained nurses, and venous blood was collected from each study participant by laboratory personnel.

Serum creatinine, serum amylase, and serum lipase were analyzed by an automated clinical chemistry analyzer.

Principle for amylase measurement: amylase directly reacts with a specific substrate 2-chloro-4-nitrophenyl-maltotrioxide (CNPG3). The release of 2-chloro-4-nitrophenol (CNP) from the substrate results in an increase in absorbance. The absorbance read at 405 nm is directly proportional to the serum activity of amylase.

Principle for lipase measurement: The chromogen lipase substrate 1,2-0-dilauryl-rac-glycero-3-glutaric acid ester is cleaved by the catalytic action of alkaline lipase solution to form 1,2-0-dilauryl-rac-glycerol and an unstable intermediate, glutaric acid-ester. This decomposes spontaneously into alkaline solution to form glutaric acid and methylresorufin. The color intensity of the red dye formed is directly proportional to the lipase activity and can be determined photometrically.

Principle for creatinine measurement: Uses the Jaffe reaction method by which, in an alkaline medium, creatinine forms a yellow-orange-colored complex with picric acid. The rate of color formation is proportional to the concentration of creatinine present and may be measured photometrically. Creatinine in alkaline picrate solution forms a color solution. The rate of formation of complex is measured by using a kinetic procedure. The intensity of the color is proportional to the creatinine concentration at a wavelength of 500 nm.

The glomerular filtration rate was calculated by using the MDRD equation. Raw data were entered into Epidata software version 3.02 and checked and cleaned before its export to SPSS version 21 for statistical analysis. Descriptive statistics, cross-tabulation, and mean difference calculation were performed using SPSS statistical software. Staging of CKD was done based on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD by using GFR calculated by the MDRD equation (see Table 1).²⁶

The normal range for serum amylase and lipase was considered as follows:

Amylase: normal range (28 IU/L – 100 IU/L)^{27,28} Lipase: normal range (13–60 U/l).²⁹

Result

Almost half (48.8%) of the diabetic patients had mildly reduced GFR (60–89.99 mL/min/1.73 m²). Even though none of them had renal failure, severe, moderate to severe, and mild-to-moderate reduction accounts for 1.4%, 6.0%, and 9.5%, respectively (refer to Table 2). Diabetic patients suffering from G3b and G4 stages glomerular filtration impairment had also increased mean serum amylase and lipase activity. Accordingly, they had a mean serum amylase activity of 106.79 IU/L ± 118.18 IU/L and 104.85 ± 90.42 IU/L, respectively, with a higher variation that was also higher than those having normal glomerular filtration rate. Similarly, the mean of serum lipase activity was 105.07 IU/L ± 127.54 IU/L and 106.98 IU/L ± 88.35 IU/L among those with G3b and G4 stages, respectively (refer to Table 3).

Table 1 Stages of CKD by Using GFR

GFR Category	GFR (mL/min/1.73 m ²)	Description
G1	≥ 90	Normal or high
G2	60–89.99	Mildly decreased
G3a	45–59.99	Mildly to moderately decreased
G3b	30–44.99	Moderately to severely decreased
G4	15–29.99	Severely decreased
G5	< 15	Kidney failure

Abbreviations: CKD, Chronic Kidney Disease; GFR, Glomerular Filtration Rate.

Table 2 Frequency and Distribution of GFR Category Among Diabetic Patients Attending Goba Referral Hospital

GFR Category	Frequency Number (%)
G1 (Normal or high)	99 (34.6%)
G2 (Mildly decreased)	139 (48.6%)
G3a (Mildly to moderately decreased)	27 (9.4%)
G3b (Mildly to moderately decreased)	17 (5.9%)
G4 (Severely decreased)	4 (1.4%)
G5 (Kidney failure)	0

Table 3 Mean and SD of Serum Amylase and Lipase at Different Stages of CKD Among Diabetic Patients Attending Goba Referral Hospital

GFR Category	Serum Amylase (IU/L)		Serum Lipase (IU/L)	
	Mean \pm SD	95% CI	Mean \pm SD	95% CI
G1 (n = 99)	57.25 \pm 40.23	49.71–65.37	45.83 \pm 53.45	36.38–56.66
G2 (n = 139)	46.60 \pm 23.21	43.09–50.63	38.77 \pm 29.95	34.13–44.10
G3a (n = 27)	46.81 \pm 32.23	35.77–59.82	45.34–61.39	24.54–71.57
G3b (n = 17)	106.79 \pm 118.18	56.04–164.23	105.07 \pm 127.54	49.94–168.02
G4 (n = 4)	104.85 \pm 90.42	36.43–211.57	106.98 \pm 88.35	25.86–202.37

Abbreviations: CKD, Chronic Kidney Disease; GFR, Glomerular Filtration Rate; SD, Standard Deviation; IU/L, International Unit per Liter.

About 10% of diabetic patients had increased serum amylase activity beyond the normal range. Furthermore, two of them (0.7%) had serum amylase activity increment three-fold above ULN. Moreover, Diabetic patients' serum lipase activity was significantly elevated than their serum amylase activity. Thus, the increment of serum lipase activity above the normal range accounts for 11.2% without including those who had its increment three times above ULN, which was 4.2% (refer to Table 4).

Table 4 Descriptive Statistics of Pancreatic Enzyme Abnormalities at Different Stages of Renal Insufficiency Among Diabetic Patients Attending Goba Referral Hospital

Serum Enzyme Activity		GFR Category n (%)					
Category	Sub-Category	G1 n (%)	G2 n (%)	G3a n (%)	G3b n (%)	G4 n (%)	Total n (%)
Serum amylase	Decreased	14 (4.9)	30 (10.5)	7 (2.4)	5 (1.7)	0 (0)	56 (19.6%)
	Normal	73 (25.5)	104 (36.4)	17 (5.9)	6 (2.1)	2 (0.7)	202 (70.6%)
	Increased	12 (4.2)	5 (1.7)	3 (1.0)	4 (1.4)	2 (0.7)	26 (9.1%)
	Increased > 3X ULN	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	2 (0.7%)
Serum lipase	Decreased	15 (5.2)	27 (9.4)	8 (2.8)	5 (1.7)	0 (0)	55 (19.2%)
	Normal	73 (25.5)	94 (32.9)	14 (4.9)	4 (1.4)	2 (0.7)	187 (65.4%)
	Increased	7 (2.4)	17 (5.9)	3 (1.0)	4 (1.4)	1 (0.3)	32 (11.2%)
	Increased > 3X ULN	4 (1.4)	1 (0.3)	2 (0.7)	4 (1.4)	1 (0.3)	12 (4.2%)

Abbreviations: GFR, Glomerular Filtration Rate; ULN, Upper Limit of Normal range.

Discussion

The current study showed that serum amylase activity among diabetic patients increased above the normal range and more than three times beyond the ULN. However, Jiang et al, 2002 reported a higher proportion of serum amylase activity among patients suffering from end-stage renal disease (ESRD) which was 60.7%, and a similar magnitude of its elevation three-fold above ULN with the current study, which was 1.3%.³⁰ Albai et al, 2017 also reported 3.7% of diabetic patients had pancreatitis.³¹

About 32% of patients with pancreatitis suffered from renal injury. Accordingly, diabetic patients were at high risk of death in SAP with AKI by a factor of 1.62 times in comparison to non-diabetics. The risk of death significantly rises with alcohol abuse, serum amylase >200 IU/L, serum creatinine >2.4 mg/dl.³² As the severity of renal disease worsens, the serum amylase is also elevated. The mean serum amylase level in control, chronic kidney disease, and end-stage kidney disease patients was 67.12 ± 16.79 U/l, 91.83 ± 28.1 U/l and 100.7 ± 42.82 U/l, respectively.³³

In the current study, serum lipase was elevated above the normal range and three times above the ULN among diabetic patients. Similarly, Malloy et al, 2012 also reported 13% and 6% of T2DM had elevated serum lipase and amylase above ULN, respectively.³⁴ Among 224 patients with hypertriglyceridemia (HTG), the serum amylase level was three times higher than its normal was 21.43% among all study participants, 23.8%, and 18.6% among patients with TG levels above 1000 mg/dl and 500 mg/dl–1000 mg/dl, respectively.³⁵ Among 72 patients with AP, 34 (47.2%) of them had DM and their average serum amylase activity and lipase activity were 1290 ± 1930 U/L and 2781 ± 4322 U/L, respectively.³⁶ T2DM patients were at a high risk (crude HR: 2.89, 95% CI: 2.56–3.27) for AP than non-diabetics. The rate of AP increased with the habit of alcohol abuse, smoking, increased BMI, and co-morbid conditions.²⁵ The existence of end-stage kidney disease elevates serum lipase significantly. Accordingly patients having end-stage kidney disease had a serum lipase level of 64.08 ± 15.03 U/l; while those who had kidney disease without end-stage renal disease and the control group had a serum lipase level of 57.36 ± 20 U/l and 26.55 ± 6.38 U/l, respectively.³³

Furthermore, increased activity of serum amylase and lipase were significantly associated with severely reduced kidney function. However, 12.2% and 7.7% of T2DM with normal kidney function had also elevated activities of serum lipase and amylase, respectively. About 22.7% of T2DM with and without acute pancreatitis had elevated activities of either serum amylase or lipase or both. Their serum lipase and amylase activity were elevated above the normal range with a magnitude of 16.6% and 11.8%, respectively. Among them, 1.2% and 0.2% had elevated serum lipase and amylase activity three times above ULN, respectively.³⁷ The existence of acute pancreatitis can lead to multi-organ failure. Therefore, it can serve as an indicator for multiple organ insufficiency.¹⁸

Conclusion

As the glomerular filtration decreased from moderate to severe to severe, their serum amylase and lipase activity increased. The diabetic patients suffered from asymptomatic pancreatitis after the onset of the disease which was diagnosed with elevation of serum pancreatic enzymes. They had increased serum amylase and lipase by a magnitude of 9.1% and 11.2%, respectively. Moreover, 0.7% and 4.2% of diabetic patients had elevated serum amylase and lipase >3X ULN respectively. Therefore, it is better to consider pancreatic impairment as one of the diabetic complications.

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Disclosure

The authors declare that there are no financial and other conflicts of interest regarding this article.

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