



## CLINICAL USEFULNESS OF LIPASE AND AMYLASE - AN UPDATE

Natarajan K.<sup>1</sup>, Selvam V.<sup>2</sup> Dr. Anbazhagan M.<sup>3</sup> and Dr. Swaminathan S.\*<sup>4</sup>

<sup>1</sup>Deputy Quality Manager, Techmed Health Centre & Diagnostic Pvt Ltd. Siva Building, No.1, Krishna Street, North Usman Road T.Nagar, Chennai - 600 017.

<sup>2</sup>Quality Manager, Techmed Health Centre & Diagnostic Pvt Ltd Siva Building, No.1, Krishna Street, North Usman Road T.Nagar, Chennai - 600 017.

<sup>3</sup>Consultant Biochemist, Techmed Health Centre & Diagnostic Pvt Ltd Siva Building, No.1, Krishna Street, North Usman Road T.Nagar, Chennai - 600 017.

<sup>4</sup>Director of Laboratory Services & Consultant Biochemist, Techmed Health Centre & Diagnostic Pvt Ltd Siva Building, No.1, Krishna Street, North Usman Road T.Nagar, Chennai - 600 017.

\*Corresponding Author: Dr. Swaminathan S.

Director of Laboratory Services & Consultant Biochemist, Techmed Health Centre & Diagnostic Pvt Ltd Siva Building, No.1, Krishna Street, North Usman Road T.Nagar, Chennai - 600 017.

Article Received on 19/06/2017

Article Revised on 09/07/2017

Article Accepted on 30/07/2017

### ABSTRACT

Both serum Amylase and Lipase are very useful in the diagnosis of Acute Pancreatitis. Its clinical usefulness in Diabetic Mellitus as well as liver and kidney diseases are being explored and many experimental studies have been done in this direction. This review article highlights the research findings done during the last two decades on the role of Amylase and Lipase in the laboratory diagnosis of digestive, gastro duodenal, Diabetes Mellitus, liver and kidney diseases. More studies are required in this area for the diagnosis and treatment modalities for the above organs and to recommend the routine use of these two enzymes when other laboratory findings are inconclusive.

**KEYWORDS:** Amylase, Lipase, Nafld, Ckd, Esrd, Ap, Cp.

### INTRODUCTION

The starch splitting enzyme amylase is secreted in two organs, mouth called ptyalin and pancreas (pancreatic  $\alpha$ -amylase). Lipase is produced by pancreas. Both together complete the process of carbohydrate and lipid digestions. Their role is to digest fats and globules substances. For a total diagnosis involving digestion and organ functions such as pancreas, liver and kidney, measurement of both these enzymes will be diagnostically useful. This review article highlights their role in the above organs functions.

#### Lipase and Amylase in Acute Pancreatitis

Receiver operator characteristic (ROC) analysis of the initial sample received from patients in the emergency department showed improved diagnostic accuracy for serum pancreatic lipase. A clinically useful cut-off point would be at the diagnostic threshold; 208 U/L (normal <190 U/L) for serum pancreatic lipase and 114 U/L (normal 27–100 U/L) for serum amylase where the sensitivity was 90.3 and 76.8% and the specificity was 93 and 92.6%. 18.8% of the acute pancreatitis patients did not have elevated serum amylase while only 2.9% did not have elevated serum pancreatic lipase on the first emergency department measurement, suggesting that

serum pancreatic lipase is a more accurate biomarker of acute pancreatitis than serum amylase.<sup>[1]</sup>

Compared with the placebo group, liraglutide-treated patients had increased serum lipase and amylase of 28.0% and 7.0%, respectively. Levels were increased at 6 months and then remained stable<sup>[2]</sup>. In a population with Type 2 diabetes (T2DM) at high cardiovascular risk, there were numerically fewer events of acute pancreatitis among liraglutide-treated patients (regardless of previous history of pancreatitis) compared with the placebo group. Liraglutide was associated with increases in serum lipase and amylase, which were not predictive of an event of subsequent acute pancreatitis<sup>[2]</sup>. Pancreatitis is one of the commonest diseases of the gastrointestinal tract, characterized by epigastric pain of moderate to severe intensity, which radiates to the back, elevation of pancreatic lipase and amylase enzymes, and changes in pancreatic parenchyma in imaging methods. The most common etiologies vary, generally the most frequent being biliary lithiasis and alcohol, followed by hypertriglyceridemia and among the less frequent causes is drug-induced pancreatitis.<sup>[3]</sup>

Significant risk factors for developing more severe acute pancreatitis (MSAP) or severe acute pancreatitis (SAP)

in patients admitted with mild acute pancreatitis (MAP) included BMI ( $\geq 25$  kg/m<sup>2</sup>), APACHE-II ( $\geq 5$ ) a scoring system used to measure the severity of diseases in patients admitted to Intensive care units, and plasma glucose level on admission ( $>200$  mg/L). These factors should be used in the prediction of more severe pancreatitis in patients admitted with MAP.<sup>[4]</sup> Pancreatic enzymes were significantly elevated in all the patients with a mean serum lipase level of 1795 U/L (normal value:  $<190$  U/L) and a mean serum amylase level of 584 U/L (normal value:  $<100$  U/L). Ultrasonography evidence of Acute pancreatitis (AP) (bulky pancreas) was seen in some patients, and few patients had minimal left-sided pleural effusion. Thrombocytopenia (platelet count  $<100,000$ /cumm), renal dysfunction (serum creatinine  $>1.4$  mg/dl), and hyperbilirubinemia were seen in all the patients. AP is a very rare complication of malaria, and a high index of suspicion is required in patients presenting with severe malaria and abdominal pain.<sup>[5]</sup>

### Lipase and Amylase in Liver Diseases

Twenty four months of follow-up showed asymptomatic patients on a free diet, with a mild deranged Liver Functional Tests (LFT) and a normal Amylase and Lipase. The recurrence of AP has not been observed until the present day. Recurrent episodes of AP in young adults, without a history of alcohol abuse or evidence of gallstones, might be an atypical presentation of midgut malrotation and it should be in the differential diagnosis, and in such cases, a Ladd's operation is beneficial and an endoscopic procedure does not obtain advantages.<sup>[6]</sup>

Abnormally high serum pancreatic isoamylase activity was present in 34.4% of patients with mucinous cystic lesions, in 40% of patients with chronic pancreatitis (CP), and none in patients with pancreatic ductal adenocarcinoma (PDAC); whereas serum lipase activity was abnormally high in 25% of patients with mucinous cystic lesion, in 48.6% of patients with CP, and in 12.5% of patients with PDAC. In some patients with mucinous cystic lesions and histologically confirmed severe dysplasia, abnormally high levels of both serum pancreatic amylase and lipase were present in patients. High serum concentrations of pancreatic amylase and lipase were found in no more than half of the patients with mucinous cystic lesions. High levels of pancreatic enzymes were not associated with a greater risk of malignancy.<sup>[7]</sup>

The mean values  $\pm$  SD of the control group were compared with those of the patient group for serum amylase level and serum lipase level. On the ROC analysis for amylase level, AUC was 0.740, and sensitivity and specificity were 38.7% and 94.1%, respectively, with a cutoff value of 27.5 U/L. On the ROC analysis for lipase level, AUC was 0.748, and sensitivity and specificity were 33.3% and 95.9%, respectively, with a cutoff value of 10.5 U/L, suggesting

that low serum pancreatic enzyme levels can be used to aid in detection of CP.<sup>[8]</sup>

Pancreaticopericardial fistula (PPF) is an extremely rare clinical problem encountered in patients with CP. The diagnosis should be suspected if a patient presents with pericardial effusion on a background of CP. Significantly raised amylase in the pericardial fluid offers an important clue for the diagnosis. Computerised Tomography (CT) is the initial imaging modality to look for pancreatic and pericardial changes. The therapeutic options include medical, endoscopic or surgical interventions. Medical and endoscopic therapies are the preferred modes of treatment while surgery is reserved for those who fail these measures.<sup>[9]</sup>

After adjusting for all the metabolic risk factors in the multivariate regression analysis (MVRA) with the amylase levels as the dependent variable, Insulin secretion sensitivity index (ISSI-2) was the major independent contributor to the serum amylase levels. Meanwhile, in a comparison of the groups with the highest and lowest quartiles of serum amylase levels, the mean difference in logISSI-2 was 0.902 (95% CI 0.823 to 0.982), and after adjusting for metabolic risk factors, the mean difference in logISSI-2 was 0.610 (0.537 to 0.683). Serum amylase levels in the normal range are positively associated with integrated islet  $\beta$  cell function in patients with early T2DM, as assessed by ISSI-2.<sup>[10]</sup>

In a study involving the diagnostic criteria of gestational diabetes mellitus (GDM), they had significantly lower levels of serum amylase than those without GDM. The prevalence rate of GDM decreased across serum amylase increasing tertiles. Correlation analysis showed that serum amylase level was negatively correlated with fasting plasma glucose (FPG), 1hPG, 2hPG, HOMA-IR, triglyceride, free fatty acid, and thyroid stimulating hormone. Multiple logistic regression analysis (MLRA) showed that low serum amylase level predicted increased risk of GDM. These findings suggest that low serum amylase level is significantly associated with increased risk of GDM.<sup>[11]</sup>

Serum amylase levels were significantly lower in non-alcoholic fatty liver disease (NAFLD) patients with metabolic syndrome (MetS) compared with NAFLD patients without MetS and healthy controls (42, 45, and 53 IU/L, respectively). The serum amylase levels of patients with elevated glucose, elevated triglycerides, and low high density lipoprotein cholesterol (HDL-c) patients were significantly lower than in case of normal parameters. MLRA showed that a relative serum amylase level increase was an independent factor predicting advanced fibrosis (FIB-4  $\geq 1.3$ ) in NAFLD participants compared with NAFLD patients without MetS and healthy controls, serum amylase levels were significantly lower in NAFLD patients with MetS. Moreover, a relative serum amylase increase may be an independent factor of more advanced hepatic fibrosis.<sup>[12]</sup>

The prevalence of NAFLD increased significantly from 22.5% to 42.4% (all grades) and from 9.2% to 24.0% (moderate or severe grade) from the highest to the lowest quartile of serum amylase. MLRA showed that, compared with the highest quartile of serum amylase, the lowest quartile of serum amylase was significantly associated with any-grade NAFLD and with moderate-to-severe NAFLD, even after adjusting for MetS or diabetes. The association between low serum amylase (LSA) and any-grade NAFLD disappeared after further adjustment for body mass index or waist circumference, whereas the association between LSA and moderate or severe NAFLD remained statistically significant respectively. The results suggest that LSA may be associated with moderate or severe NAFLD in asymptomatic adults independent of MetS, diabetes and obesity. These results warrant confirmation in further studies.<sup>[13]</sup>

Serum amylase levels were abnormally elevated in 35% liver cirrhosis and chronic active hepatitis (CAH), whereas serum lipase levels were elevated in 21% liver cirrhosis and CAH. In 33% hyperamylasemic patients, the hyperamylasemia was of pancreatic type. Macroamylasemic complexes were not detected in hyperamylasemic sera. Patients with liver cirrhosis had serum levels of amylase and lipase significantly higher than both the healthy subjects and the patients with CAH, while no significant differences were found in serum levels of these enzymes in patients with CAH as compared to the healthy subjects. A decreased liver metabolism of serum amylase and lipase in patients with chronic infective liver disease, especially in those having liver cirrhosis, may lead to an accumulation of these enzymes in the blood.<sup>[14]</sup>

#### Lipase and Amylase in Diabetes Mellitus

Plasma adipose triglyceride lipase (ATGL) levels significantly increased in patients with T2DM and hypertension compared with normal group. No gender differences were found among plasma ATGL levels. Furthermore, plasma ATGL level was positively correlated with total cholesterol and HDL-c in simple regression analysis of pooled data, whereas, in multiple stepwise regression analysis, diastolic blood pressure, total cholesterol and HOMA-IR were independently related factors with plasma ATGL levels. Which indicates the potential link of ATGL with the pathogenesis of insulin resistance and T2DM.<sup>[15]</sup>

FPG and HbA1c estimates were consistently higher in T1 and T2 DM patients, while no significant changes were observed in the estimates of serum insulin between the normal and diabetic patients. The reduction in serum pancreatic amylase was recorded in both types of diabetes, which amounted to 71% for T1DM and 49% for T2DM. On the other hand, reduction in serum lipase was only detected in T1DM amounting to 31%. Correlation of the reduction in serum amylase and lipase levels with the duration of disease revealed a remarkable

decrease in both enzymes in patients with long-standing disease (76% and 39%) in T1DM patients. Whereas, patients with very low serum insulin estimates, the reduction in serum amylase was 77% while serum lipase level was reduced by 42%. Similarly, the reduction in serum amylase in T2DM was higher in patients with longer duration of illness (59%) and in patients with low serum insulin value (79%), while reduction in serum lipase was only detected in patients with very low serum insulin (34%). No differences in all measured parameters between males and females were recorded in T1 and T2 DM patients. Although most of diabetic research has been focused on dyslipidemia as a major risk factor for cardiac, cerebral and renal complications, the studies clearly illustrates an impairment of pancreatic exocrine function in T1 and T2DM and hence the analysis of serum pancreatic enzymes could be an additional informative parameter for the assessment of chronicity and progress of the illness as well as the response to therapy.<sup>[16]</sup>

Elevation of pancreatic enzymes is common in children with diabetic ketoacidosis (DKA), but clinical pancreatitis is rare. Pancreatic enzyme levels reach a peak 12–24 hrs after initiation of treatment for DKA. Pancreatic enzyme elevation is associated with increased blood urea nitrogen (BUN) concentrations at presentation but is not associated with abdominal pain<sup>[17]</sup>. Either or both enzymes were above the upper limit of normal in 22.7% of subjects; 16.6% had an elevated lipase level (including 1.2% >3-fold elevated), and 11.8% (n = 1094) had an elevated amylase level (including 0.2% >3-fold elevated). In MLRA, severely reduced kidney function was associated with the largest effect on increasing activity of both. However, even among subjects with normal kidney function, 12.2% and 7.7% had elevated lipase and amylase levels. In a study of T2DM patients, nearly 25% had elevated lipase or amylase levels without symptoms of AP. The clinician must take these data into account when evaluating abdominal symptoms in T2 DM patients.<sup>[18]</sup>

#### Lipase and Amylase in Renal Diseases

Serum levels of amylase and lipase are frequently increased in patients Chronic Kidney Disease (CKD). Relatively low serum pancreatic enzyme levels in CKD may represent a state of pancreatic insufficiency and may contribute to protein-energy wasting (PEW).<sup>[20]</sup> Serum amylase activity was found to be an independent predictor of mortality in End-Stage Renal Disease (ESRD) patients. Relatively low serum pancreatic enzyme levels in CKD may be regarded as a novel component of the malnutrition-inflammation-atherosclerosis syndrome.<sup>[19]</sup>

In a majority of CKD patients presented to emergency room with symptoms suggestive of AP, only 17.4% had more than a threefold increase in serum amylase and/or lipase levels fulfilling the diagnostic criteria of AP. They included pre-dialysis in 58.13% CKD patients and in

41.86% ESRD patients on regular hemodialysis (HD). Among the pre-dialysis CKD patients, 68% patients developed acute kidney injury (AKI), 70% of those patients returned back to their baseline renal functions after 3-4 weeks. Gallstones were the cause of pancreatitis in 16.3% patients while no cause was identified in 67.4%. 20.9% of patient developed admission to the intensive care unit (ICU). Patients with less than threefold increase in serum amylase and lipase levels responded well to conservative management and had a favorable clinical course. In severe AP the mortality rate can be as high as 40-58% especially in association with comorbid conditions. In some CKD patients however, the overall mortality rate was 2.3%, probably due to the predominance of milder forms of pancreatitis.<sup>[20]</sup>

Mean values of both amylase and lipase levels in the patient group was higher than healthy controls. There was no significant difference in amylase and lipase levels according to the treatment modality in the patient group. The correlations between creatinine clearance (CrCl) and amylase or lipase were found to be inverse only when the CrCl falls below 50 mL/min. Serum amylase and lipase levels are about 1.5 times and 2.2 times higher in chronic renal failure patients than healthy controls regardless of treatment modality. The elevations of amylase and lipase levels are inversely correlated with CrCl when it falls below 50 mL/min.<sup>[21]</sup>

The mean activity of serum pancreatic enzymes was significantly higher in patients with ESRD compared to that in the healthy controls. 68.7% of ESRD patients had serum amylase and lipase levels higher than normal in. In continuous ambulatory peritoneal dialysis (CAPD) cases, 66.7% had higher levels of both enzymes. However, 83.7% and 86.5% HD patients had elevated levels of serum amylase and lipase, respectively. Only 1.3% and 5.2% out of 77 ESRD cases had threefold elevated levels of amylase and lipase, respectively. Serum pancreatic enzymes are often elevated within threefold normal in ESRD patients. Thus, AP must be considered if enzyme levels are more than threefold normal in association with clinical manifestations.<sup>[22]</sup>

Currently, serum total amylase, pancreatic isoamylase (P-amylase), lipase, trypsin (ogen), phospholipase A2 (PLA2), and elastase I are advocated to be useful in diagnosing pancreatic diseases. However, the most useful among the above six enzymes in patients with impaired renal function has not been fully clarified. Elastase I was significantly elevated only in patients with a CrCl of 10 mL/min or less, whereas others were elevated already in patients with a CrCl below 40 mL/min; in patients with a CrCl between 13 and 39 mL/min, lipase tended to be less frequently raised than others, except elastase I, although the difference was statistically insignificant; in patients with a CrCl between 40 and 74 mL/min, lipase was less frequently elevated than others, except elastase I and phospholipase A2 (PLA2); in patients with a CrCl of 10 mL/min or below,

elastase I tended to be less frequently elevated than others, although the difference was statistically insignificant; and the degree of elevation was within 2.5 times the upper limits of reference values in all enzymes, except trypsin(ogen). Elastase I was least vulnerable to impaired renal function followed by lipase. Hence combined assays of elastase I and lipase for detecting pancreatic diseases in patients with renal insufficiency is recommended. When cut-off levels are set at 2.5 times the upper limit of reference values, P-amylase or PLA2 can replace lipase.<sup>[23]</sup>

## CONCLUSIONS

This review articles has highlighted many research findings during the last two decades on the clinical and diagnostic usefulness of measuring both Amylase and lipase. Measurements of these two digestive enzymes must be done together to gather clinical informations for the diagnosis of a variety of disorders/diseases associated with gastroduodenal, pancreas, liver, cardiac, Kidney, and DM. According to research findings both the enzymes were found to be useful to evaluate and correlate diseases involving liver, kidney, pancreas and altered carbohydrates & fats metabolism. The contents of this review article has also highlighted the two enzymes as additional tests to evaluate & correlate other tests for diagnosis of the above organs mentioned and such findings will be very useful to decide at the treatment modalities. The contents found in the review articles will be useful for future researchers in this field to do more work on the clinical usefulness of both Amylase & Lipase and to set guidelines to recommend its routine use in certain types of organ malfunctions.

**Conflict of Interest:** None

## REFERENCE

1. Ross C. Smith, James Southwell-Keely, Douglas Chesher, Should Serum Pancreatic Lipase Replace Serum Amylase As A Biomarker of Acute Pancreatitis?: ANZ Journal of Surgery, June 2005; 75(6): 399-404.
2. Steinberg WM<sup>1</sup>, Buse JB<sup>2</sup>, Ghorbani MLM<sup>3</sup>, Ørsted DD<sup>3</sup>, Nauck MA<sup>4</sup>; LEADER Steering Committee; LEADER Trial Investigators. Amylase, Lipase, and Acute Pancreatitis in People With Type 2 Diabetes Treated With Liraglutide: Results From the LEADER Randomized Trial. *Diabetes Care*. 2017; 40(7): 966-972. doi: 10.2337/dc16-2747. Epub, 5 May 2017.
3. Chapela SP<sup>1,2</sup>, Paz SLA<sup>1</sup>, Ballesterio FM<sup>1</sup>. Pancreatitis Induced by Cocaine. *Case Rep Gastroenterol*. 2017 Apr 19; 11(1): 212-218. doi: 10.1159/000468511. eCollection 2017 Jan-Apr.
4. Jin Z<sup>1,2</sup>, Xu L<sup>2</sup>, Wang X<sup>2</sup>, Yang D<sup>1</sup>. Risk Factors for Worsening of Acute Pancreatitis in Patients Admitted with Mild Acute Pancreatitis. *Medical Science Monitor*, 2017 Feb 26; 23: 1026-1032.



5. Abhilash KP<sup>1</sup>, Ahmed AS<sup>1</sup>, Sathyendra S<sup>1</sup>, Abraham OC<sup>1</sup>. Acute Pancreatitis due to Malaria: A case report of five patients and review of literature. *Journal of Family Medicine and Primary Care*, 2016 Jul-Sep; 5(3): 691-694. doi: 10.4103/2249-4863.197302.
6. Alessandri G<sup>1</sup>, Amodio A, Landoni L, De' Liguori Carino N, Bassi C. Recurrent acute pancreatitis in bowel malrotation. *European Review for Medical and Pharmacological Sciences*, 2016 Nov; 20(22): 4719-4724.
7. Pezzilli R<sup>1</sup>, Melzi d'Eril G, Barassi A. Pancreas. Can Serum Pancreatic Amylase and Lipase Levels Be Used as Diagnostic Markers to Distinguish Between Patients With Mucinous Cystic Lesions of the Pancreas, Chronic Pancreatitis, and Pancreatic Ductal Adenocarcinoma, 2016 Oct; 45(9): 1272-1275. doi: 10.1097/MPA.0000000000000638.
8. Kwon CI<sup>1</sup>, Kim HJ, Korc P, Choi EK, McNulty GM, Easler JJ, El Hajj II, Watkins J, Fogel EL, McHenry L, Zimmerman MK, Sherman S, Lehman GA. Pancreas. Can We Detect Chronic Pancreatitis With Low Serum Pancreatic Enzyme Levels?, 2016 Sep; 45(8): 1184-8. doi: 10.1097/MPA.0000000000000612.
9. Nasa M<sup>1</sup>, Patil G<sup>1</sup>, Choudhary NS<sup>1</sup>, Puri R<sup>1</sup>. Pancreaticopericardial fistula: a rare complication of chronic pancreatitis. *BMJ Case Rep*, 2016 May 17; 2016. pii: bcr2016215163. doi: 10.1136/bcr-2016-215163.
10. Zhuang L<sup>1</sup>, Su JB<sup>2</sup>, Zhang XL<sup>3</sup>, Huang HY<sup>2</sup>, Zhao LH<sup>2</sup>, Xu F<sup>2</sup>, Chen T<sup>3</sup>, Wang XQ<sup>2</sup>, Wu G<sup>2</sup>, Wang XH<sup>2</sup>. Serum Amylase Levels in Relation to Islet  $\beta$  Cell Function in Patients with Early Type 2 Diabetes. *PLoS One*, 2016 Sep 8; 11(9): e0162204. doi: 10.1371/journal.pone.0162204. eCollection 2016.
11. Zheng R, Zhang J, Ying Z, Zheng N. Low Serum Amylase is Associated with Gestational Diabetes Mellitus in Chinese Pregnant Women. *Clinical Laboratory*, 2015; 61(10): 1423-8.
12. Yao J, Zhao Y, Zhang J<sup>1</sup>, Hong Y, Lu H, Wu J. Serum amylase levels are decreased in Chinese non-alcoholic fatty liver disease patients. *Lipids in health and disease*, 2014 Dec 7; 13: 185. doi: 10.1186/1476-511X-13-185.
13. Nakajima K<sup>1</sup>, Oshida H, Muneyuki T, Saito M, Hori Y, Fuchigami H, Kakei M, Munakata H. Independent association between low serum amylase and non-alcoholic fatty liver disease in asymptomatic adults: a cross-sectional observational study. *BMJ Open*. 2013 Jan 3; 3(1). pii: e002235. doi: 10.1136/bmjopen-2012-002235.
14. Pezzilli R<sup>1</sup>, Andreone P, Morselli-Labate AM, Sama C, Billi P, Cursaro C, Barakat B, Gramenzi A, Fiocchi M, Miglio F, Bernardi M. Serum pancreatic enzyme concentrations in chronic viral liver diseases. *Digestive Diseases and Sciences*, 1999 Feb; 44(2): 350-5.
15. Xu S<sup>1</sup>, Yang G, Yang M, Li S, Liu H, Li L. Elevated adipose triglyceride lipase in newly diagnosed type 2 diabetes mellitus with hypertension. *The American Journal of the medical science*, 2011 Dec; 342(6): 452-5. doi: 10.1097/MAJ.0b013e318218482f.
16. Aughsteen AA, Abu-Umar MS, Mahmoud SA. Biochemical analysis of serum pancreatic amylase and lipase enzymes in patients with type 1 and type 2 diabetes mellitus. *Saudi Medical Journal*, 01 Jan 2005; 26(1): 73-77.
17. Quiros, J Antonio MD; Marcin, James P. MD, MPH; Kuppermann, Nathan MD, MPH; Nasrollahzadeh, Farid MD; Rewers, Arleta MD, PhD; DiCarlo, Joseph MD; Neely, E Kirk MD; Glaser, Nicole MD. Elevated serum amylase and lipase in pediatric diabetic ketoacidosis, July 2008; 9(4): 418-422.
18. William M. Steinberg, MD,\* Michael A. Nauck, MD,<sup>†</sup> Bernard Zinman, MD,<sup>‡</sup> Gilbert H. Daniels, MD,<sup>§</sup> Richard M. Bergenstal, MD,<sup>||</sup> Johannes F.E. Mann, MD,<sup>¶</sup> Lasse Steen Ravn, MD, PhD,<sup>#</sup> Alan C. Moses, MD,<sup>#</sup> Mette Stockner, MD,<sup>#</sup> Florian M.M. Baeres, MD,<sup>#</sup> Steven P. Marso, MD,<sup>\*\*</sup> and John B. Buse, MD, PhD<sup>††</sup>, on behalf of the LEADER Trial investigators. LEADER 3—Lipase and Amylase Activity in Subjects With Type 2 Diabetes. *Pancreas*, 2014 Nov; 43(8): 1223–1231.
19. Ozkok A<sup>1</sup>, Elcioglu OC, Cukadar T, Bakan A, Sasak G, Atilgan KG, Alisir S, Kanbay M, Covic A, Odabas AR. Low serum pancreatic enzyme levels predict mortality and are associated with malnutrition-inflammation-atherosclerosis syndrome in patients with chronic kidney disease. *International Urology and Nephrology*, 2013 Apr; 45(2): 477-84. doi: 10.1007/s11255-012-0237-6. Epub 2012 Aug 2.
20. Nasir K<sup>1</sup>, Ahamd A. Clinical course of acute pancreatitis in chronic kidney disease patients in a single kidney center (PGTi) in Karachi. *Arab Journal of Nephrology and Transplant*, 2012 May; 5(2): 87-90.
21. Lee SY<sup>1</sup>, Lee KT, Kang TW, Moon W, Lee SS, Hwang JY, Lee JK, Paik SW, Rhee JC. Pancreatic enzyme elevations in Korean chronic renal failure patients. *The Korean Journal of Gastroenterology*. 2005 Feb; 45(2): 125-9.
22. Jiang CF<sup>1</sup>, Ng KW, Tan SW, Wu CS, Chen HC, Liang CT, Chen YH. Serum level of amylase and lipase in various stages of chronic renal insufficiency. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2002 Feb; 65(2): 49-54.
23. Seno T<sup>1</sup>, Harada H, Ochi K, Tanaka J, Matsumoto S, Choudhury R, Mizushima T, Tsuboi K, Ishida M. Serum levels of six pancreatic enzymes as related to the degree of renal dysfunction. *The American Journal of Gastroenterology*, 1995 Nov; 90(11): 2002-5.