Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.69980/p98yta98

DIAGNOSTIC CHALLENGES OF PANCREATITIS IN CKD: EFFECT OF RENAL DYSFUNCTION ON AMYLASE AND LIPASE LEVELS

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ABSTRACT

This study aims to investigate pancreatic enzyme levels in CKD patients with and without dialysis to determine an association between pancreatic enzymes and chronic renal failure. Also to quantify the percent increase in pancreatic enzyme in CKD since, there is a lack of concise data from Pakistan on the relationship between pancreatic enzymes and CKD or end-stage renal disease (ESRD) due to insufficient local studies. However, the diagnosis of pancreatitis in CKD patients is challenging due to elevated pancreatic enzyme levels with reduced estimated glomerular filtration rates (eGFR).

Method: This is a cross-sectional study conducted in the nephrology department of Liaquat National Hospital, Pakistan. Serum amylase, lipase, and creatinine levels were measured in all participants. Serum amylase and lipase above 140 U/L were considered elevated. The Cockcroft-Gault formula was used to calculate eGFR and a cut-off less than 60 mL/min/1.73 m² was labeled as CKD. Data were analyzed using SPSS version 25, with a p-value of < 0.01 considered statistically significant.

Results: The study included 196 CKD +/- dialysis patients. The mean serum creatinine level was 5.41 ± 3.30 mg/dl, and the mean eGFR was 13.5 mL/min/1.73 m². 174 (88.7%) of patients had elevated pancreatic enzymes. 174 CKD patients (88.7%)had raised amylase levels and 157 CKD patients (80.1%) had a raised lipase level.

Conclusion: Elevated amylase and lipase levels are frequently observed in CKD patients, which is not a novel finding. The study findings recommend considering alternative or adjunctive diagnostic modalities such as magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) for accurate diagnosis of acute pancreatitis in CKD patients.

Keywords: amylase, lipase, chronic kidney disease, pancreatitis, pancreatic enzymes

INTRODUCTION

Chronic kidney disease (CKD) was 27th on the list of causes of worldwide mortality in 1990[1] and is now expected to become the 5th highest cause of death globally[2]. It has a complex pathophysiology and is associated with other chronic diseases including cardiovascular diseases or can progress to end-stage renal disease (ESRD)[3]. The major risk factors for CKD include diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, urinary tract obstruction, recurrent infections, and nephrolithiasis. In the South Asian context, diabetes and nephrolithiasis have been reported as leading contributors to CKD[4,5].

The reported incidence of pancreatitis is 5.11 per 1000 person-years in hemodialysis patients while 5.86 per 1000 person-years in patients on peritoneal dialysis[6]. Pancreatitis is a potentially fatal disease associated with high mortality[7] The Unlucky fact regarding pancreatitis in patients with reduced GFR is the diagnosis of pancreatitis is not very straightforward because of raised pancreatic enzyme in CKD patients[8]. Serum amylase and lipase are the pancreatic enzymes used for the assessment[9] and monitoring of pathological states of the pancreas like alcohol-induced pancreatitis and stones in the gall bladder or common bile duct, whose frequency of occurrence is high in CKD[10]. Amylase is rapidly excreted by the kidney, thus patients with chronic kidney disease have elevated serum pancreatic enzymes. Few studies have revealed alterations in these enzyme levels like elevated amylase and decreased transaminases in CKD even in the absence of hepatic or pancreatic diseases leading to misdiagnosis[11,12].

Unfortunately, the data from Pakistan lacks concise information about pancreatic enzymes in the CKD or ESRD population. We in this study, aimed to survey pancreatic enzymes including amylase, and lipase levels in CKD patients with and without ESRD. The primary endpoint of this study was to evaluate the association between pancreatic enzyme levels and chronic renal failure. The secondary endpoints were to quantify the percent rise in pancreatic enzymes from baseline in CKD patients and to assess the effect of dialysis on pancreatic enzyme levels.

METHODS

This is a single-center descriptive observational study conducted in the nephrology department of Liaquat National Hospital, Pakistan. Ethical approval was obtained from the research board and the hospital's ethical committee. Patients with chronic kidney disease +/- required hemodialysis and aged 18 years and older who provided informed consent were included. Patients with overt causes of elevated pancreatic enzymes including gallstone pancreatitis, post Endoscopic retrograde cholangiopancreatography (ERCP), and intestinal obstructions were excluded from the study. The study was conducted over 6 months from 13th September 2020 to 12th March 2021. Data regarding Age, sex, nature of illness, and hemodialysis were obtained from the electronic medical record system (EMR) of the nephrology unit by a principal investigator.

Amylase and Lipase & Creatinine measurement: We measured serum amylase, lipase, and creatinine in all participants, and special care was made to check post-hemodialysis enzymes in patients undergoing hemodialysis. Trained nursing staff performed phlebotomies using a vacuum technique with a lithium heparin solution container to measure serum amylase, lipase, and creatinine. These samples were analyzed by a trained laboratory technician at the central biochemistry lab of the hospital using a colorimetric method after salivary amylase inhibition with monoclonal antibodies (Boeh-ringerMannheim, Germany)[12] for amylase, the colorimetric method (lipase monotest Boehringer-Mannheim, Germany)[10] for lipase and the Jaffe colorimetric method[11] for serum creatinine. Results were obtained through the electronic database system of the central laboratory. Values were enrolled on an Excel sheet by a principal investigator. Based on local laboratory, serum amylase above than 140 U/L (amylase: 28–140 U/L), and serum lipase greater than 140 U/L (13–140 U/L) were considered as raised. Though the CKD-EPI Pakistan (CKD-EPI PK) is validated for eGFR estimation in the Pakistani population, We used The Cockcroft-gault formula because of its implementation in the study institutional laboratory the study period. Chronic kidney disease was diagnosed according to The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for chronic kidney disease (CKD) that included patients who had an estimated glomerular filtration rate (eGFR) of less than 60

mL/min/1.73 m² for at least three months. Estimated glomerular filtration rate (eGFR) determined using following equation.

GFR = [(140 – age) × weight (kg) × (0.85 if female)] / (72 × serum creatinine [mg/dL])

Data was entered on SPSS version 25. Frequency and percentages were calculated for gender, and co-morbidities (identified from detailed history) including diabetes, hypertension, chronic kidney disease, and hemodialysis. The distribution of continuous variables (age, weight, serum amylase, serum lipase, and creatinine) was assessed for normality using the Shapiro–Wilk test. While, skewed variables (e.g., amylase, lipase) were reported as median with minimum and maximum values. Interquartile ranges (IQRs) could not be calculated due to dataset limitations. Group comparisons were performed using the Mann–Whitney U test for skewed continuous variables, and the Chi-square test for categorical variables. A p-value < 0.01 was considered statistically significant.

RESULTS

We included 196 patients, of whom 135 (68.9%) were on hemodialysis and 61 (31.1%) were managed conservatively without dialysis. There were 110 males (56.1%) and 86 females (43.9%). The average age was 56.0 ± 16.1 years, and mean weight was 62.9 ± 9.9 kg. Diabetes mellitus was present in 131 patients (66.8%), and hypertension in 184 patients (93.9%). All patients had chronic kidney disease, with mean serum creatinine of 5.41 ± 3.30 mg/dL and mean eGFR (Cockcroft–Gault) of 13.5 ± 3.36 mL/min/1.73 m² (Table 1).

Pancreatic enzyme abnormalities: Elevated pancreatic enzymes were found in 174 patients (88.7%). Raised amylase was present in 120/135 hemodialysis patients (88.9%) and 54/61 non-dialysis patients (88.5%). Raised lipase was observed in 110/135 hemodialysis patients (81.5%) and 47/61 non-dialysis patients (77.0%) (Table 2, Figure 1).

The median serum amylase was 110 U/L (range: 14–5608) in dialysis patients and 92 U/L (range: 3.3–1492) in non-dialysis patients. The median serum lipase was 82 U/L (range: 5–2476) in dialysis patients and 78 U/L (range: 5–4123) in non-dialysis patients. Differences between groups were not statistically significant (Mann–Whitney U test, p = 0.276 for amylase; p = 0.308 for lipase).

Importantly, 15.3% of CKD patients had normal pancreatic enzyme levels. None of the study participants had clinical features of pancreatitis; thus, the incidence of pancreatitis in our cohort was 0%.

Table:1 Descriptive Statics

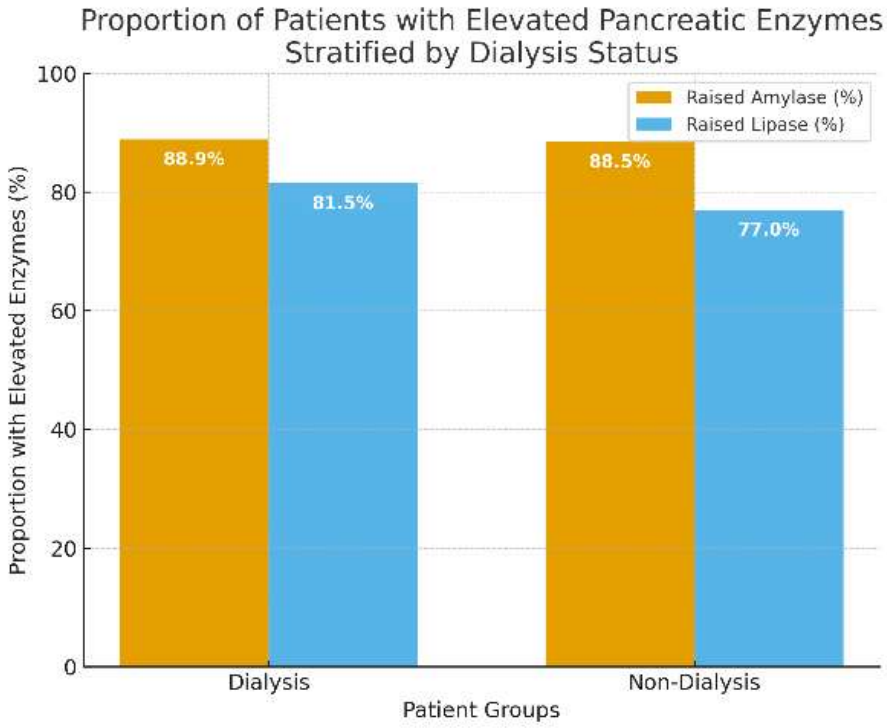
Variable	Overall (n=196)	Hemodialysis (n=135)	Non-Hemodialysis (n=61)
Age (years), Mean ± SD	56.0 ± 16.1	57.2 ± 15.8	53.8 ± 16.7
Weight (kg), Mean ± SD	62.9 ± 9.9	63.2 ± 10.1	62.4 ± 9.6
Male, n (%)	110 (56.1)	75 (55.6)	35 (57.4)
Female, n (%)	86 (43.9)	60 (44.4)	26 (42.6)
Diabetes mellitus, n (%)	131 (66.8)	92 (68.1)	39 (63.9)
Hypertension, n (%)	184 (93.9)	126 (93.3)	58 (95.1)
Serum creatinine (mg/dl), Mean ± SD	5.41 ± 3.30	5.62 ± 3.25	4.95 ± 3.38
eGFR (mL/min/1.73 m²), Mean ± SD	13.5 ± 3.36	13.2 ± 3.25	14.1 ± 3.52
Stage III (eGFR 30–59), n (%)	12 (6.1)	0 (0.0)	12 (19.7)
Stage IV (eGFR 15–29), n (%)	35 (17.9)	8 (5.9)	27 (44.3)
Stage V (eGFR <15, not on dialysis), n (%)	14 (7.1)	0 (0.0)	14 (23.0)
Stage V-D (on dialysis), n (%)	135 (68.9)	135 (100.0)	0 (0.0)

Table 2: Comparative Statistics of Pancreatic Enzymes in Dialysis vs Non-Dialysis CKD Patients

Enzyme	Dialysis group, n (%)	Non-dialysis group, n (%)	Difference	p-value
Raised Amylase	120 / 135 (88.9%)	54 / 61 (88.5%)	+0.4%	0.945
Serum Amylase, Median (Range) (U/L)	110 (14 – 5608)	92 (3.3 – 1492)	Higher in dialysis group	0.276
Raised Lipase	110 / 135 (81.5%)	47 / 61 (77.0%)	+4.5%	0.482
Serum Lipase, Median (Range) (U/L)	82 (5 – 2476)	78 (5 – 4123)	Slightly higher in dialysis group	0.308
eGFR (mL/min/1.73 m^2), Mean ± SD	13.2 ± 3.25	14.1 ± 3.52	Lower in dialysis group	0.167

Legend: eGFR was calculated using the Cockcroft–Gault formula (as per institutional laboratory protocol). p-values were calculated using the Chi-square test for categorical variables (raised enzyme frequencies) and the Independent t-test / Mann–Whitney U test for continuous variables (median enzyme levels, mean eGFR).

Fig.1: Statistics of Pancreatic Enzymes in CKD



DISCUSSION

In our study, we evaluated pancreatic enzyme levels in CKD with or without hemodialysis to assess whether the existing reference ranges for pancreatic enzymes will play a good role in determining the pancreatic abnormality in CKD and hemodialysis patients. Our study showed that the serum levels of amylase, and lipase were raised in CKD and dialysis patients. Just in line with the literature report that shows elevated pancreatic enzymes in dialysis patients[20] without any ongoing pancreatic pathology, we found that 174 patients (88.7%) patients had a raised pancreatic enzyme. 88.7% of CKD patients had elevated amylase and 80.1% had elevated lipase, irrespective of dialysis status. Similar to our study the literature review reveals elevation of both pancreatic enzyme including amylase and lipase in patients with low GFR[21]. Importantly, 15.3% of patients had normal enzyme

levels, and no participant developed clinical pancreatitis, making the incidence in our cohort 0%. So the pancreatic enzyme in the CKD population should always be analyzed in the light of clinical scenarios. The possible false positive results should be counter-confirmed by alternate diagnostic techniques for pancreatitis. Studies shows an association between raised pancreatic enzymes and the progression of CKD is reported[22]. Due to reduced eGFR, pancreatic enzymes are raised in CKD patients with no suspect of pancreatitis. These results highlight that enzyme elevation in CKD patients does not necessarily indicate pancreatitis. We found the single fold rise in pancreatic amylase in the study population. Previously different extents of rise in amylase in CKD population have been reported. In one study, Jiang C et al reported a threefold amylase level in the dialysis population[23]. In two more studies a two-fold increase in serum amylase in patients with CKD with or without hemodialysis has been reported[24,25]. Likewise in our study, we found a less than single fold rise in lipase level. No previous data regarding extent of rise in serum lipase in CKD/ hemodialysis papulation is available for comparison.

Pancreatitis is a severe, life-threatening condition with high mortality, necessitating specialized care from intensive care, gastroenterology, and surgical teams. Dialysis-dependent patients exhibit a higher incidence of acute pancreatitis[13]. Compared to hemodialysis, patients undergoing peritoneal dialysis have a greater incidence of acute pancreatitis[14,15]. Several risk factors for pancreatitis in peritoneal dialysis patients have been indentified including raised intra-abdominal pressure, fluid leaks, uremic toxins and local effect of peritoneal dialysate[6]. Additionally, morbidity associated with necrotizing pancreatitis is reported to be higher in peritoneal dialysis patients[9]. The incidence of acute pancreatitis among CKD patients remains unclear.

Hepatic and pancreatic diseases frequently co-exist with chronic kidney disease[16]. Estimating serum enzyme levels of ALP (alkaline phosphatase), ALT (alanine transaminase), AST (aspartate aminotransferase), GGT (gamma-glutamyl transferase), amylase, and lipase is crucial for diagnosing hepatic and pancreatic conditions such as nonalcoholic steatohepatitis (NASH), hepatitis, alcoholic liver disease, and pancreatitis[17]. These enzyme levels are used not only for diagnosis but also for assessing disease severity and treatment response[18]. While clinical symptomatology guides the suspicion of pancreatitis, pancreatic amylase testing in blood is essential for diagnostic confirmation. The presence of pancreatitis can delay important therapeutic procedures, including renal transplantation[19]. Therefore, it is imperative to accurately establish the diagnosis of the pancreatitis in CKD/ESRD patients and for that exact knowledge regarding the dynamics of pancreatic amylase and lipase in CKD milieu is worth important.

We checked pancreatic enzymes in CKD patients who underwent hemodialysis to study the effect of dialytic therapy on enzyme level. Median serum amylase was 110 (U/L) vs 92 (U/L) in dialysis vs non dialysis patients (p-value= 0.276). this shows no significant effect of dialysis on amylase level in CKD patients. The median serum lipase level in the patients who had undergone dialysis was 82 (U/L) vs 78 U/L in patients without dialysis (p value = 0.308). Therefore, we did not notice a difference in lipase in CKD with and without hemodialysis.

Limitations:

We suggest further larger studies to design new reference values for pancreatic enzymes in CKD and dialysis patients. furthermore, we suggest conducting studies on CKD patients with coexisting pancreatic disease to establish a reference range for pathological diagnosis of the pancreatic enzyme in renal failure.

One of the major limitations of our study is absence of an alternative test, including endoscopic ultrasound (EUS)+ to further confirm absence of pancreatitc disease in the presence of raised pancreatic enzymes. We would suggest such studies.

CONCLUSIONS

pancreatic enzymes including amylase and lipase are elevated in CKD patients and dialysis patients in the absence of pancreatitis. Although most CKD patients show elevated pancreatic enzymes, a subset maintain normal values. Pancreatic enzymes in CKD populations should be analyzed in

conjunction with suggestive clinical scenarios and alternative techniques should be used for the diagnosis of pancreatitis in CKD patients with or without dialysis.

Acknowledgement: No acknowledgement to be mentioned
Disclaimer: Ethical approval has been taken under [App#0617-2021-LNH-ERC]
Conflict of interest: The authors declared no conflict of interest**.**
Funding disclosure: there is no funding in this study.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-128
2. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011) 2022;12:7-11.
3. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. Renal fibrosis: mechanisms and therapies. 2019:3-15.
4. Rizvi SA, Manzoor K. Causes of chronic renal failure in Pakistan: a single large center experience. Saudi journal of kidney diseases and transplantation. 2002 Jul 1;13(3):376-9.
5. Salman B, Imtiaz S, Qureshi R, Dhrolia MF, Ahmad A. The causes of chronic kidney disease in adults in a developing country. J Nephrol Ren Dis. 2017;1(1):10-4172.
6. Lahoud C, Morcos Z, Njeim R, Tawfik M, Aslam T, El-Sayegh S. Understanding acute pancreatitis in end-stage renal disease: unraveling etiologies, clinical presentations, management strategies, and complications—a narrative review. Journal of Pancreatology. 2024 Dec 25;7(04):285-9.
7. Kroner PT, Mareth K, Raimondo M, Lee DD, Alsaad A, Aslam N, Abader P, Wadei HM. Acute pancreatitis in advanced chronic kidney disease and kidney transplant recipients: results of a US nationwide analysis. Mayo Clinic Proceedings: Innovations, Quality & Outcomes. 2019 Jun 1;3(2):160-8
8. Walkowska J, Zielinska N, Tubbs RS, Podgórski M, Dłubek-Ruxer J, Olewnik Ł. Diagnosis and treatment of acute pancreatitis. Diagnostics. 2022 Aug 15;12(8):1974.
9. Chen HJ, Wang JJ, Tsay WI, Her SH, Lin CH, Chien CC. Epidemiology and outcome of acute pancreatitis in end-stage renal disease dialysis patients: a 10-year national cohort study. Nephrology Dialysis Transplantation. 2017 Oct 1;32(10):1731-6..
10. Paul G. Lankisch, Bettina Weber-Dany, Patrick Maisonneuve and Albert B. Lowenfels. Frequency and severity of acute pancreatitis in chronic dialysis patient Nephrol Dial Transplant 2008;23: 1401-1405s.
11. Ray L, Nanda SK, Chatterjee A, et al. A comparative study of serum aminotransferases in chronic kidney disease with and without endstage renal disease: Need for new reference ranges. Int J Appl Basic Med Res 2015;5:31-35.
12. Bindu CM, Shankar V, Shetty PHV, et al. Serum amylase in patients with chronic kidney disease. IJCRR 2013; 5(17):10-15.
13. Costa-Moreira P, Vilas-Boas F, Teixeira Fraga A, Macedo G. Particular aspects of gastroenterological disorders in chronic kidney disease and end-stage renal disease patients: a clinically focused review. Scandinavian Journal of Gastroenterology. 2020 Feb 1;55(2):129-38.
14. Khan SI, Iqbal M, Chowdhury AA, Roy AS, Ahammed SU, Asadujjaman M, Rahman MA, Hossain MB, Rabbani MG, Islam MS, Salahuddin AZ. Comparison of Serum Amylase and Lipase Levels between Predialysis and Maintenance Haemodialysis CKD Patients. Mymensingh medical journal: MMJ. 2020 Jan 1;29(1):21-31.
15. Zhu Y, Dong J, Wang P, Huang H, Jin X, Zhou J, Shi J, Gu G, Chen J, Xu J, Song Y. Serum Lipase as Clinical Laboratory Index for Chronic Renal Failure Diagnosis. Clinical Laboratory. 2016 Jul 1;62(7):1265-70.

16. Regasa T, Dinku Y, Gezahegn B, Feleke Z, Regassa Z, Mamo A, Assefa T, Gezahegn H, Solomon D, Atlaw D, Dessie M. The elevation of pancreatic enzymes in serum and their distribution at different stages of renal insufficiency among diabetic patients attending Goba Referral Hospital. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022 Jan 1:2087-93.
17. Bindu CM, Shetty HV, Gupta D. Serum amylase in patients with chronic kidney disease. International Journal of Current Research and Review. 2013 Sep 1;5(17):10.
18. Vidal E, Alberici I, Verrina E, Italian Registry of Pediatric Chronic Dialysis. Acute pancreatitis in children on chronic maintenance dialysis. Pediatric Nephrology. 2019 Sep 1;34:1501-12.
19. Cheungpasitporn W, Thongprayoon C, Ungprasert P, Wijarnpreecha K, Raimondo M, Kroner PT. Acute pancreatitis in end-stage renal disease patients in the USA: a nationwide, propensity score-matched analysis. European Journal of Gastroenterology & Hepatology. 2019 Aug 1;31(8):968-72.
20. Lankisch PG, Weber-Dany B, Maisonneuve P, Lowenfels AB. Frequency and severity of acute pancreatitis in chronic dialysis patients. Nephrology Dialysis Transplantation. 2008 Apr 1;23(4):1401-5.
21. Golay V, Roychowdhary A. Acute pancreatitis in chronic kidney disease—a common but often misunderstood combination. Renal failure. 2012 Nov 1;34(10):1338-40.
22. Scurt FG, Ganz MJ, Herzog C, Bose K, Mertens PR, Chatzikyrkou C. Association of metabolic syndrome and chronic kidney disease. Obesity Reviews. 2024 Jan;25(1):e13649.
23. Singh PK, Tripathi M, Garg P, Singh RL, Pathak N, Shukla S, Singh P. Enzymes and Their Clinical Applications. InClinical Applications of Biomolecules in Disease Diagnosis: A Comprehensive Guide to Biochemistry and Metabolism 2024 Oct 16 (pp. 233-256). Singapore: Springer Nature Singapore
24. Sbeit W, Khoury T, Wengrower D, Livovsky DM, Fteiha B, Nubani A, Goldin E, Mahamid M. Nonalcoholic fatty liver disease and the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis: the hidden danger. Scandinavian Journal of Gastroenterology. 2021 Mar 4;56(3):369-73.
25. Tena B, Vendrell M. Perioperative considerations for kidney and pancreas-kidney transplantation. Best Practice & Research Clinical Anaesthesiology. 2020 Mar 1;34(1):3-14.