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NEPHROLOGY - ORIGINAL PAPER

Low serum pancreatic enzyme levels predict mortality and are associated with malnutrition–inflammation–atherosclerosis syndrome in patients with chronic kidney disease

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Abstract
Purpose Serum levels of amylase and lipase are frequently increased in patients with 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). We aimed to investigate the relationships of serum pancreatic enzyme levels with PEW, inflammation, and mortality in CKD patients.
Methods Two hundred and thirty CKD patients (male/female: 144/86; mean age, 59 $\pm$ 16 years) were enrolled. Serum total α-amylase and lipase activities were measured by enzymatic colorimetric assays. Mean follow-up time was 18 $\pm$ 10 months. Forty-seven patients (20 %) died during this period.
Results Serum amylase levels were increased in 95 patients (41 %) and serum lipase levels were increased in 71 patients (30 %) out of the 230 patients. Diabetic patients had significantly lower serum amylase levels than non-diabetic ones (86 $\pm$ 46 vs. 111 $\pm$ 60 IU/L, $p < 0.0001$). Patients with ischemic heart disease also had significantly lower serum amylase (82 $\pm$ 37 vs. 108 $\pm$ 60 IU/L, $p < 0.0001$) and lipase levels (39 $\pm$ 36 vs. 57 $\pm$ 57 IU/L, $p = 0.007$). Serum amylase and lipase levels were directly correlated with serum creatinine ($r = 0.173$, $p = 0.009$ and $r = 0.374$, $p < 0.0001$) and albumin ($r = 0.410$, $p < 0.0001$ and 0.287, $p < 0.0001$), and inversely correlated with CRP ($r = -0.223$, $p = 0.001$ and $r = -0.147$, $p = 0.027$). The Kaplan–Meier analysis revealed survival advantages for both high-amylase and high-lipase groups in end-stage renal disease (ESRD) (CKD stage 5) patients (log rank, $p < 0.001$ and $p = 0.02$, respectively). In the Cox regression analysis, serum amylase was found to be an independent predictor for mortality.
Conclusion Serum amylase activity was found to be an independent predictor of mortality in ESRD patients. Relatively low serum pancreatic enzyme levels in CKD may be regarded as a novel component of the malnutrition–inflammation–atherosclerosis syndrome.

Keywords Amylase · Atherosclerosis · Chronic kidney disease · End-stage renal disease · Inflammation · Malnutrition · Lipase · Protein-energy wasting · Survival

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Introduction

Chronic kidney disease (CKD) affects the physiological function of many organ systems, including the exocrine pancreas. Serum levels of pancreatic enzymes, especially amylase and lipase, are frequently increased in CKD patients, even in the absence of a clinically apparent pancreatic pathology [1]. However, a group of CKD patients have normal or low serum pancreatic enzyme levels, despite the decreased clearance due to the diminished residual renal function (RRF) [2]. Different serum pancreatic enzyme patterns in CKD patients may have different clinical implications.

In the model of acute pancreatitis, increased serum levels of pancreatic enzymes cause widespread cytokine release and systemic inflammatory response [3]. By extension, pancreatic enzymes may be regarded as uremic toxins and increased levels of these enzymes may contribute to increased inflammation, endothelial dysfunction, and mortality in CKD patients. At the opposite end of this spectrum, we hypothesize that relatively low serum amylase and lipase levels in CKD patients may represent a state of uremic pancreatic disease and insufficiency, which may contribute to protein-energy wasting (PEW) and increased mortality in CKD population. In a study investigating pancreatic exocrine insufficiency in HD patients, a significant decrease in the amylase and lipase from the duodenal aspirate was observed [4]. It was suggested that deficiencies in pancreatic enzyme secretion might have important roles in the etiology of the CKD-associated malnutrition syndrome.

With this background in mind, for the first time in the literature, we aimed to investigate the relationship between serum pancreatic enzyme levels and PEW together with possible effects on survival of CKD patients.

Subjects and methods

In this cross-sectional study, a total of 335 consecutive hospitalized CKD patients admitted to Istanbul Medeniyet University, Goztepe Training and Research Hospital, Nephrology Department, between the years 2007–2010 were evaluated. Patients with acute or chronic pancreatitis (3 patients), peritonitis (13 patients), malignancies (10 patients), severe infection and sepsis (33 patients), and suspected bile duct pathology (46 patients) were excluded. Finally, 230 CKD patients (males/females, 144/86; mean age, 59 ± 16 years) were enrolled to the study. Distribution of CKD stages were as follows: stage 2, 18 patients (8 %); stage 3, 47 patients (20 %); stage 4, 46 patients (20 %); stage 5, 119 patients (52 %). Etiologies of CKD were as follows: diabetes mellitus, 87 (37 %); hypertension, 62 (26 %); chronic glomerulonephritis, 29 (12 %); others, 22 (9 %); and unknown, 30 patients (13 %). Sixty-two patients (27 %) were on hemodialysis (HD) and 12 patients (5 %) were on peritoneal dialysis (PD). Comorbidities were as follows: 95 patients (41 %), diabetes mellitus; 175 patients (76 %), hypertension; 65 patients (28 %), ischemic heart disease; and 41 (17 %) patients had congestive heart failure.

Laboratory values including complete blood cell counts and serum levels of urea, creatinine, electrolytes, calcium, phosphorus, total protein, albumin, total cholesterol, triglycerides, parathyroid hormone, amylase, lipase, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) were measured. Serum total α-amylase and lipase activities were determined with enzymatic colorimetric assays (Olympus Life Science Research Europa GMBH).

Statistical analysis

Statistical package for social sciences for windows, version 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Between-group comparisons of continuous data for two groups were performed using the Student's *t* test or the Mann–Whitney U test when appropriate. Relationships were determined with Pearson's correlation coefficient. Correlations between numerical parameters with non-normal distribution were analyzed with Spearman's rho correlation test. Comparisons of more than two groups were made with one-way analysis of variance (ANOVA) using the Tukey's HSD test for post hoc analysis. Results are expressed as mean ± SD unless otherwise stated. For continuous variables that are not normally distributed, median (interquartile range) was used. Survival analysis of the groups was performed with Kaplan–Meier survival curves. Groups were compared with long rank test. The factors affecting mortality were analyzed with Cox regression test. All tests of significance were two sided, and differences were considered statistically significant when the p value was <0.05.

Results

Baseline demographic and laboratory values are presented in Table 1. Serum amylase levels were increased in 95 (41 %) and serum lipase levels in 71 patients (30 %) out of the 230 patients. Serum amylase levels according to CKD stages were as follows: stage 2, 80 ± 31 IU/L; stage 3, 94 ± 46 IU/L; stage 4, 101 ± 44 IU/L; and stage 5, 107 ± 65 IU/L. Serum lipase levels according to CKD stages were as follows: stage 2, 35 ± 33 IU/L; stage 3, 30 ± 16 IU/L; stage 4, 50 ± 53 IU/L; and stage 5, 64 ± 60 IU/L.

Serum amylase levels were increased in 35 (47 %) and serum lipase levels were increased in 31 (41 %) of the 74 dialysis patients. Patients under dialysis treatment had higher serum amylase levels compared to the non-dialysis group (107 ± 66 vs. 98 ± 50 IU/L, $p = 0.16$); however, it did not reach significance. Serum lipase values were significantly higher in the dialysis group (64 ± 58 vs. 46 ± 48 IU/L, $p = 0.018$). When the two dialysis modalities were compared, serum amylase (112 ± 65 vs. 84 ± 70 IU/L, $p = 0.18$) and lipase values (66 ± 62 vs. 54 ± 33 IU/L, $p = 0.53$) were similar between HD and PD patients.

Table 1 Baseline demographic and laboratory values of the study population

	Values ± SD/median (IQR) ($n = 230$)	Reference values
Age (years)	59 ± 16	
Sex (male/female)	144/86	
Body mass index (kg/m^2)	24 ± 6	
Glucose (mg/dL)	108 ± 39	70–106
Urea (mg/dL)	130 ± 70	17–43
Creatinine (mg/dL)	3.9 (2.4–6)	0.6–1.1
Uric acid (mg/dL)	7.1 ± 2.4	2.6–6
Total cholesterol (mg/dL)	185 ± 61	100–200
Triglyceride (mg/dL)	145 (104–207)	60–150
HDL (mg/dL)	40 ± 12	45–65
LDL (mg/dL)	120 ± 42	0–130
ALT (IU/L)	14 (10–21)	0–38
AST (IU/L)	18 (14–24)	0–31
ALP (IU/L)	84 (68–112)	30–120
GGT (IU/L)	25 (18–37)	0–38
LDH (IU/L)	243 ± 101	0–247
Total protein (g/dL)	6.3 ± 0.9	6.4–8.3
Albumin (g/dL)	3.2 ± 0.7	3.5–5.2
Sodium (mEq/L)	136 ± 4	134–146
Potassium (mEq/L)	4.5 ± 0.9	3.5–5.2
Calcium (mg/dL)	8.7 ± 4.2	8.8–10.6
Phosphorus (mg/dL)	4.6 ± 1.5	2.5–4.5
Fe (µg/dL)	47 (29–68)	70–180
Ferritin (ng/mL)	227 (104–390)	24–336
WBC (/mm^3)	7976 ± 2580	4000–10000
Hemoglobin (g/dL)	10.3 ± 2.1	11.5–16
Platelet (/mm^3)	240.000 ± 90.000	150000–500000
PTH (pg/mL)	146 (81–261)	12–88
CRP (mg/dL)	1.23 (0.52–4.70)	0–0.8
ESR (mm/h)	67 ± 34	0–20
Amylase (IU/L)	94 (61–130)	28–100
Lipase (IU/L)	37 (22–64)	0–57

SD standard deviation, *IQR* interquartile range, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Fe* iron, *HDL* high-density lipoprotein, *LDH* lactate dehydrogenase, *LDL* low-density lipoprotein, *GGT* gamma-glutamyl transferase, *PTH* parathyroid hormone, *WBC* white blood cells

The number of patients with increased amylase levels were not significantly different between dialysis and non-dialysis groups (60/156, 38 % vs. 35/74, 47 %; $p = 0.20$); in contrast, the number of patients with increased lipase levels was significantly higher in the dialysis group compared to the non-dialysis group (40/156, 25 % vs. 31/74, 41 %; $p = 0.013$).

The effects of residual renal functions (RRF) on pancreatic enzyme levels were also investigated. Serum amylase (101 ± 55 vs. 100 ± 61 IU/L, $p = 0.907$) and lipase levels (52 ± 54 vs. 52 ± 29 IU/L, $p = 0.996$) were similar between the groups with RRF and without RRF.

Diabetic patients had significantly lower serum amylase (86 ± 46 vs. 111 ± 60 IU/L, $p < 0.0001$) and creatinine (4.1 ± 2.4 vs. 4.9 ± 3.4 mg/dL, $p = 0.039$) levels compared to non-diabetic group. Patients with ischemic heart disease (IHD) were also older (65 ± 12 vs. 57 ± 47 years, $p < 0.0001$), and they had significantly lower serum amylase (82 ± 37 vs. 108 ± 60 IU/L, $p < 0.0001$) and lipase levels (39 ± 36 vs. 57 ± 57 IU/L, $p = 0.007$) despite similar serum creatinine levels (4.4 ± 3 vs 4.7 ± 3.1 mg/dL, $p = 0.58$).

Serum amylase levels were significantly correlated with serum urea ($r = 0.227$, $p = 0.001$), creatinine ($r = 0.173$, $p = 0.009$), lipase ($r = 0.566$, $p < 0.0001$), total protein ($r = 0.265$, < 0.0001), and albumin ($r = 0.410$, $p < 0.0001$) (Fig. 1) and inversely correlated with CRP ($r = -0.223$, $p = 0.001$) (Fig. 2) and ESR ($r = -0.156$, $p = 0.023$). Similarly, serum lipase levels were significantly associated with serum urea ($r = 0.435$, $p < 0.0001$), creatinine ($r = 0.374$, $p < 0.0001$), total protein ($r = 0.188$, $p = 0.005$), albumin (0.287, $p < 0.0001$), and negatively associated with CRP ($r = -0.147$, $p = 0.027$). Serum amylase and lipase levels were not associated with the body mass index values.

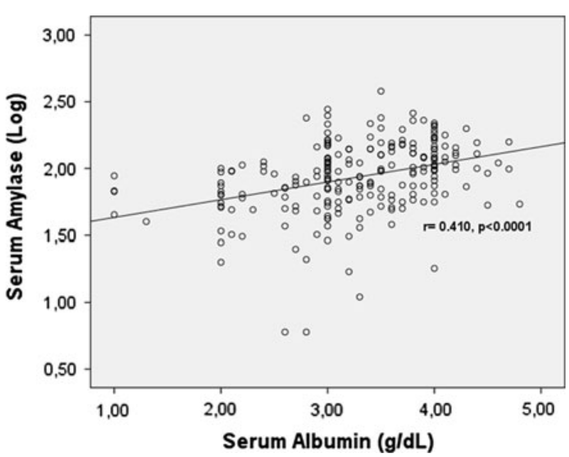

Fig. 1 Serum amylase levels were significantly positively correlated with serum albumin levels

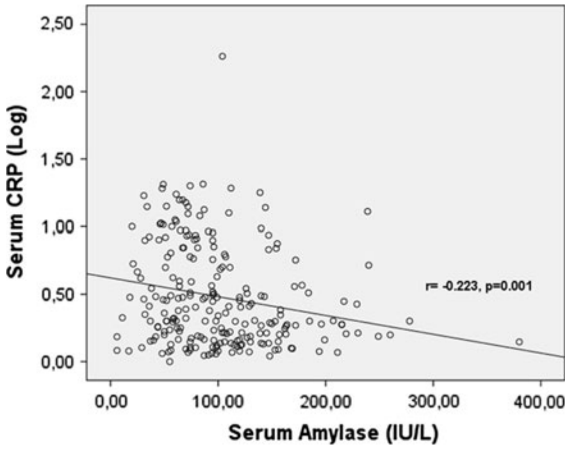

Fig. 2 Serum amylase levels were significantly negatively correlated with C-reactive protein

The mean follow-up time was 18 ± 10 months. Forty-seven patients (20 %) died during the follow-up period. Causes of death were as follows: 9 (19 %) died due to myocardial infarction, 3 (6 %) due to sepsis, 3 (6 %) due to chronic obstructive pulmonary disease, 3 (6 %) due to heart failure, 13 (29 %) due to other causes, and 16 (34 %) died due to an undetermined cause. Dead patients were significantly older, had higher serum CRP levels and lower serum amylase (Fig. 3), albumin, and hemoglobin levels compared to survivors (Table 2).

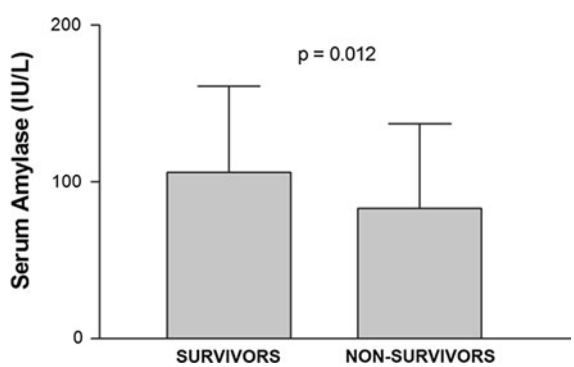

Fig. 3 Serum amylase levels were significantly higher in the survivors compared to non-survivors ($p = 0.012$)

Table 2 Comparison of the results of dead and alive patients

	Dead ($n = 47$)	Alive ($n = 183$)	p
Age (years)	66 ± 15	57 ± 16	<0.0001
Glucose (mg/dL)	108 ± 31	108 ± 41	0.909
Urea (mg/dL)	144 ± 69	126 ± 70	0.132
Creatinine (mg/dL)	5.2 ± 2.9	4.4 ± 3.1	0.117
Uric acid (mg/dL)	7.1 ± 3	7.1 ± 2.2	0.918
Total cholesterol (mg/dL)	176 ± 46	188 ± 64	0.263
Triglyceride (mg/dL)	155 ± 67	181 ± 127	0.057
HDL (mg/dL)	38 ± 11	41 ± 13	0.265
LDL (mg/dL)	116 ± 32	121 ± 44	0.467
ALP (IU/L)	88 (70–114)	83 (66–111)	0.235
GGT (IU/L)	31 ± 18	29 ± 18	0.517
LDH (IU/L)	269 ± 106	237 ± 99	0.066
Total protein (g/dL)	6 ± 1.2	6.4 ± 0.9	0.066
Albumin (g/dL)	2.8 ± 0.7	3.3 ± 0.6	<0.001
Calcium (mg/dL)	8.1 ± 1.2	8.8 ± 4.6	0.051
Phosphorus (mg/dL)	5.1 ± 2.1	4.5 ± 1.4	0.058
Ferritin (ng/mL)	309 (123–618)	200 (96–371)	0.030
WBC (/mm^3)	8209 ± 2411	7911 ± 2624	0.495
Hemoglobin (g/dL)	9.7 ± 2.2	10.4 ± 2	0.037
PTH (pg/mL)	152 (90–261)	145 (80–263)	0.271
CRP (mg/dL)	2.25 (1–9.90)	1 (0.42–3.11)	0.001
ESR (mm/h)	56 (33–110)	63 (42–90)	0.929
Amylase (IU/L)	68 (48–104)	98 (65–139)	0.012
Lipase (IU/L)	31 (21–57)	40 (22–60)	0.160

ALT alanine aminotransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Fe* iron, *HDL* high-density lipoprotein, *LDH* lactate dehydrogenase, *LDL* low-density lipoprotein, *GGT* gamma-glutamyl transferase, *PTH* parathyroid hormone, *WBC* white blood cells

Kaplan–Meier analysis revealed a survival advantage for the high amylase group compared to the low/normal amylase group in end-stage renal disease (ESRD) (CKD stage 5) patients (log rank (Mantel-Cox), $p < 0.001$) (Fig. 4). Similarly, survival advantage was observed in the high lipase group compared to low/normal lipase group in ESRD patients (log rank (Mantel-Cox), $p = 0.02$) (Fig. 5).

In the Cox regression analysis of ESRD patients, age, gender, serum creatinine, albumin, CRP, phosphorus, amylase, lipase, and presence of diabetes mellitus were included as independent variables (−2 log likelihood: 204.366, χ^2: 42.59, $p < 0.0001$). Serum amylase level was an independent predictor for mortality in the model together with serum albumin levels (Table 3). Every 10 IU/L decrease in serum amylase was associated with an 11 % increase in mortality (HR: 0.89, CI-95 %: 0.81–0.98). However, serum lipase levels were not found to be independently associated with mortality. In the Cox regression analysis of the non-ESRD CKD patients, neither serum amylase nor lipase levels were determined to be independent predictors of mortality.

Discussion

Protein-energy wasting and inflammation are commonly observed [5] and described as predictive factors for cardiovascular mortality in CKD patients [6–8]. "Malnutrition–inflammation–atherosclerosis (MIA) syndrome" disrupts the functions of many organ systems probably including the pancreas. However, the so-called "uremic pancreatic disease" and its

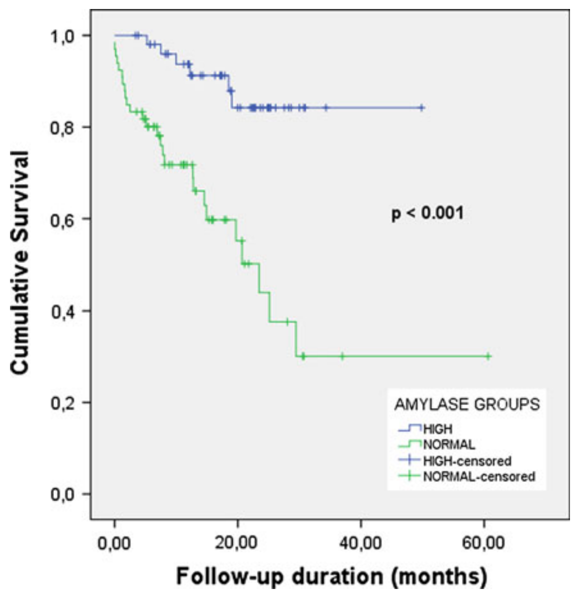

Fig. 4 Kaplan–Meier curve demonstrating the survival advantage of high amylase group compared to normal amylase group in ESRD patients

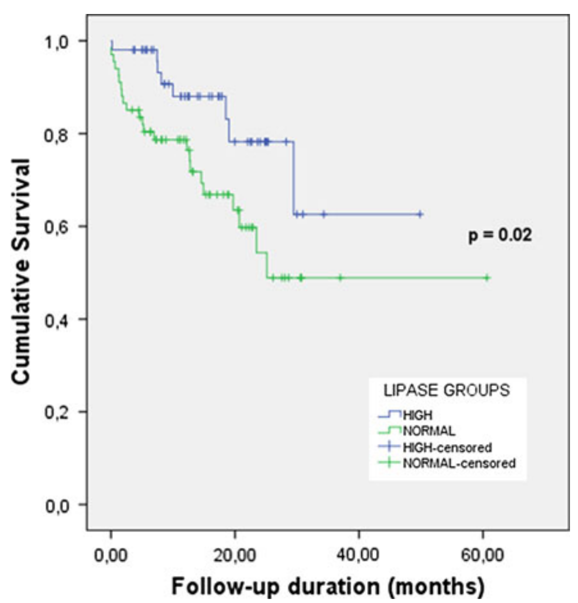

Fig. 5 Kaplan–Meier curve demonstrating the survival advantage of high lipase group compared to normal lipase group in ESRD patients

possible relationship with MIA syndrome have not been previously investigated in the literature.

Hyperamylasemia in clinical practice may result from pancreatitis, bile duct pathologies, loss of bowel integrity, chronic alcoholism, postoperative states, lactic acidosis, anorexia nervosa, amylase-secreting malignant neoplasms, diabetic ketoacidosis, and peritonitis [9]. Serum pancreatic enzyme levels, especially amylase and lipase, are known to be increased in patients with CKD although a group of patients have low/normal levels of these enzymes, even if they have ESRD.

Different patterns of pancreatic enzyme activities have been reported in previous studies performed in patients with CKD [2, 10–13]. Amylase was significantly increased in 73 (68 %) and lipase activity in 67 of 108 (62 %) patients in a study performed in CKD population [10]. Similar to aforementioned reports, we also found that serum amylase levels were increased in only 41 % and serum lipase levels increased in 30 % of all CKD patients. Patients under dialysis treatment had similar serum amylase compared to non-dialysis group; however, lipase values were significantly higher in the dialysis group. Serum lipase levels seem to be much more related to serum creatinine and urea levels compared to serum amylase levels.

The pathophysiology of increase in pancreatic enzyme levels, as well as why a group of patients had low/normal levels of these enzymes, is currently unknown. The serum pancreatic enzyme levels probably reflect the balance between the rate of enzyme secretion into and enzyme removal from the blood. Thus, increased enzyme levels may result either from an increased rate of enzyme entry into the circulation and/or a decreased metabolic clearance of these enzymes, due to CKD.

Serum amylase and lipase levels may be expected to be increased in CKD patients with unaffected, healthy pancreas. Failure of serum pancreatic enzymes to increase in CKD may be a reflection of uremic pancreatic disease and insufficiency. In a study performed on the pancreatic glands of 27 autopsied HD patients, histological evidence of pancreatitis was found in 51 % of the ESRD patients as compared to 14 % of the controls [14]. The pancreatitis was chronic in nature in 85 % of the affected ESRD patients. In another study performed in an experimental renal failure model [15], the secretory response was considerably changed by uremia and the pancreatic content of digestive enzymes progressively declined. Furthermore, the ultrastructural changes of uremic pancreatic disease did not resemble to changes seen in pancreatitis from non-renal

Table 3 Cox regression analysis for predicting mortality in ESRD patients (−2 log likelihood: 204.366, χ^2: 42.59, $p < 0.0001$)

Variable	β value	Hazard ratio	Confidence interval (95 %)	p value
Amylase/10 (IU/L)	−0.11	0.89	0.81–0.98	0.021
Lipase (IU/L)	0	1	0.98–1.01	0.954
Age (years)	0.02	1.02	0.99–1.05	0.072
Gender	0.35	1.42	0.61–3.31	0.405
Presence of diabetes	0.24	1.27	0.51–3.20	0.738
Creatinine (mg/dL)	0.01	1.01	0.87–1.16	0.871
Phosphorus (mg/dL)	0.22	1.24	0.99–1.56	0.053
Albumin (g/dL)	−0.80	0.44	0.27–0.72	0.001
CRP (Log)	0.75	2.13	0.59–7.72	0.248

subjects. The morphological and biochemical changes in early uremic pancreatic disease were quite distinct, correspond to toxic damage of the pancreas, and were dominated by functional impairment. In the study investigating pancreatic exocrine insufficiency in HD patients, a statistically significant decrease in amylase and lipase levels in the duodenal aspirate and increased basal and stimulated serum amylase levels were observed [4]. It was concluded that deficiencies in pancreatic functions may have important roles in the etiology of the CKD-associated wasting syndrome, and supplementation of pancreatic enzymes was suggested to improve nutritional status in these patients.

Relatively low levels of pancreatic enzymes in CKD may be caused by uremic medium and increased inflammation. This hypothesis was supported in our study by the fact that serum amylase and lipase levels were significantly inversely correlated with serum CRP levels. Also loss of pancreatic stimulation due to decreased appetite and PEW may result in decreased levels of pancreatic enzyme activities. Eventually, this may constitute a vicious circle that the PEW aggravates pancreatic insufficiency and pancreatic insufficiency accentuates PEW. Significant positive correlation of serum pancreatic enzyme activities with serum albumin levels may reflect a putative relationship between amylase and PEW.

ESRD patients with higher serum amylase and lipase levels seemed to have survival benefits compared to relatively lower serum enzyme levels. Only serum amylase activity was found to be an independent predictor of mortality in CKD patients in regression analyses. However, survival advantage of higher serum amylase or lipase levels was not detected in non-ESRD CKD patients. This discrepancy in survival analysis may be explained by quite different pathophysiological mechanisms in ESRD patients involving higher inflammation and PEW compared to earlier CKD stages.

Clinical implications of relatively low levels of serum amylase levels have been recently investigated in non-uremic population. Low serum amylase is also known to be associated with insulin deficiency in patients with diabetes [16, 17]. In the recent epidemiological study performed on 2425 asymptomatic non-uremic subjects, low serum amylase was found to be associated with increased risk of metabolic syndrome and diabetes [18]. This relationship between serum amylase levels and diabetes in non-uremic population may also be valid for CKD patients. Bastani et al. [2] reported that diabetic HD patients had significantly lower levels of serum amylase than non-diabetic patients consistent with our results showing lower serum amylase levels in diabetic CKD patients.

Furthermore, we found that patients with IHD had significantly lower serum amylase and lipase levels compared to the patients without IHD despite similar serum creatinine levels. Serum pancreatic enzyme levels may also be related to atherosclerosis component of the MIA syndrome in CKD patients.

In conclusion, serum amylase activity was found to be an independent predictor of mortality in ESRD patients. Relatively low serum pancreatic enzyme levels in CKD may be regarded as a novel component of MIA syndrome. Further studies are warranted to delineate the pathophysiological mechanisms involved in the clinical implications of relatively low serum pancreatic enzyme levels in CKD patients.

Conflict of interest None.

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