© Ann Transplant, 2012; 17(3): 77-84
PMID: 23018259

Original Paper

Received: 2012.01.23
Accepted: 2012.08.15
Published: 2012.09.28

The utility of amylase and lipase as reliable predictive markers for functioning renal graft

Ugur Eser Yilmaz[1ABCDE], **Nevin Yilmaz**[2ABCDEF], **Izzet Titiz**[3F], **Metin Basaranoglu**[2F], **Orhan Tarcin**[4F]

[1] Royal College of Surgeons in Ireland, Dublin, Ireland
[2] Department of Gastroenterology, Transplant Hepatology, Mugla University School of Medicine, Mugla, Turkey
[3] Transplant Clinic, Haydarpasa Research and Trainee Hospital, İstanbul, Turkey
[4] Gastroenterology Clinic, Acibadem Hospital, Kadikoy, Istanbul, Turkey

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: The aim of this study was to evaluate the utility of amylase and lipase as reliable predictive markers for functioning renal grafts, either short- or long-term.

Material/Methods: Serum amylase (Amyl), lipase, creatinine (Cr), creatinine clearance (Cr Cl) and 24-hr proteinuria (Prot) were studied in 190 kidney recipients. The correlation of these outcomes for each parameter was tested. Sensitivity and specificity of the variables were obtained in patients with graft failure (GF) and acute cellular rejection (ACR).

Results: Mean follow-up was 66.7 month. Amyl and lipase were elevated 67% *vs.* 45% in GF (N=23); 60% *vs.* 44% in ACR (N=42) patients and were inversely correlated with Cr Cl (p>.05). Lipase was notably superior to amylase and creatinine; the specificity of lipase (Amyl, Cr) was 87% (59%, 28%). Increases in amylase were more predictive in the presence of mild or moderate kidney failure (33% and 52%, respectively). However, the highest intensity of lipase elevation (39%) was in advanced kidney failure (Cr Cl <30 ml/min).

Conclusions: Serum amylase and lipase should be used as markers monitoring graft function. For early detection of graft dysfunction, amylase seems to be superior to lipase.

Key words: **amylase • graft dysfunction • kidney transplant • lipase**

Full-text PDF: http://www.annalsoftransplantation.com/fulltxt.php?ICID=883461

Word count: 2357
Tables: 4
Figures: 2
References: 29

Author's address: Nevin Yilmaz, Department of Gastroenterology, Transplant Hepatology, Mugla University School of Medicine, Kotekli, 48000, Mugla, Turkey, e-mail: nevinyilmaz@mu.edu.tr

Background

Impairment of renal function after kidney transplantation (KTx) requires specific diagnostic tools and is significantly associated with lower graft survival. For patients with excellent early graft function, both the urine output and serum creatinine (Cr) are useful and simple markers to monitor the occurrence of pathologic events in the allograft. Rapid declines of the serum creatinine within the first transplant week indicate excellent graft function. On the other hand, rise in serum creatinine is a late sign of kidney damage. Likewise, the serum creatinine proteinuria measured at varying stages post-transplant is a valuable predictor of long-term outcome [1–3]. The roles of novel biomarkers – interleukin (IL) -6, IL-1b, cystatin C, kidney injury molecule 1 (KIM-1) and gene polymorphism – on delayed graft function are the most promising topics for studies [4–6]. As an example, the rs5498 ICAM1 GG genotype was found significantly higher in patients with increased risk of ACR [6]. As for imaging, contrast-enhanced ultrasonography in the determination of the early graft dysfunction was reported to be a valuable diagnostic tool in the post-transplant setting [7].

Among healthy individuals, the pancreas and the salivary glands account for almost all serum amylase, up to half from the pancreas and the remaining from the salivary glands. Serum amylase is increased in at least 75% of pancreatitis cases; however, serum amylase measurement in diagnosing pancreatitis results in the lack of specificity due to numerous clinical situations resulting in elevated amylase. Although hyperamylasemia is commonly assumed to be due to the release of amylase into the serum by the diseased organ, amylase (Amyl) is filtered by renal tubules and resorbed (inactivated) by tubular epithelium. Therefore, the kidneys can be assumed to play a major role in amylase metabolism [8–10].

Similarly, lipase is removed from plasma by glomerular filtration and, subsequently, almost totally reabsorbed and metabolized by the renal tubules. Urine of healthy individuals contains essentially no lipase; however, presence of lipase in urine is accompanied by proteinuria and significant amylasuria [11,12].

During the follow-up, serum amylase elevation without underlying disease has been observed in some kidney recipients. Moreover, it was accompanied by a creatinine and, though slight, lipase elevation. In these patients there was not a known condition that could result in hypersecretion. It was thought that a dysfunction of the graft might be present. Therefore, the present study concerning this was planned.

Material and Methods

Patient population

Kidney transplantation has been performed since 1991 at the Institute, with an average of 50 to 60 transplants per year in recent years. The computer database contains patient data beginning from 1996, therefore, medical records of the 190 consecutive patients who underwent living or deceased kidney transplantation (KTx) at the institute between January 1996 and January 2007 were reviewed. Demographic and clinical information was obtained for each patient. Patients were excluded if they had diagnosed pancreatitis, serious infectious diseases, received high-dose (intravenous) steroids. None of the patients in the study group underwent re-transplantation. All patients signed informed consent allowing for data collection prior to undergoing KTx. The complete pre- and post-transplant medical records for all patients were evaluated. Information regarding the donors was also reviewed.

Laboratory data

Post-transplant laboratory studies were collected after an overnight fast at the following minimum intervals: once monthly between 6–12 months after KTx, every 3 months between post-transplant months 12–24, and 6 months thereafter. The routine laboratory work for post-tx follow-up included urinalysis, 24-hour protein urine test (Prot), serum creatinine, creatinine clearance (Cr Cl), blood urea nitrogen levels, electrolyte panel, pancreatic enzymes, hepatic enzyme levels, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), viral status as needed, serum glucose (Glu), and lipid panel.

For the study, serum glucose, Amyl (total amylase), lipase, LDL cholesterol (LDL-Ch), Cr, Cr Cl, and 24-hour protein urine tests were considered. Serum C-reactive protein (CRP) was reviewed as acute phase reactant.In the study, except for serum glucose, LDL chol and CRP, the main variables were named as "outcome variables".

A plasma glucose level >110 mg/dL, LDL –Ch >130 mg/dL, amylase >110 U/L,lipase >78 U/L, creatinine >1.2 mg/dL, CRP >2 mg/dL, Cr Cl

Table 1. Overall characteristics of the study group.

Parameters	Mean, standard deviation or number and %
Recipient age,year (yr)	31.4±10.5, (range 11–63 yr)
Sex, male	138 (72%)
Donor age	48±15.3, (range 9–81 yr)
Sex, male/female	86/97 (46.9 %)
Living donor	164 (86%)
Graft failure, back to dialysis	23 (12%)
Re-transplantation	0 (0%)
Rejection	42 (22%)
Death	5 (0.26%)
Follow-up, months (mo)	66.7±37 (range 1.9–162 mo)
Tacrolimus based Immunosupression	95 (54%)
Cyclosporine	53 (30%)
Rapa	25 (14%)

<90 ml/min and proteinuria> 0.015 gr/24 hour were considered abnormal values. Only test results from blood drawn the same day were reviewed. Amylase and lipase that were elevated for at least 3 consecutive days were enrolled the study. Analyses of the variables were performed at the same laboratory.

Graft failure

Graft failure is signified by return to long-term dialysis or re-transplantation. Graft survival was calculated from the date of transplantation to the date of irreversible graft failure. In the event of death with a functioning graft, the follow-up period was ended at the date of death.

In the institute, protocol biopsies are not performed routinely, and are only done to assess underlying pathology in the evidence of graft dysfunction. The Banff classification is used for diagnosing allograft rejection.

Immunosupression

Immunosuppressive regimen of the institute consisted of calcineurin inhibitors, mycophenolate mofetil (MMF) and steroids. Antithymocyte globulin (ATG) or IL-2 receptor mAB (daclizumab or basiliximab) are used for induction in the days immediately after transplant. The immunosuppression is then switched to calcineurin inhibitors. Steroid was tapered within 2 months of transplantation and lifetime maintenance with 5 mg Prednisolone/day.

Statistical analysis

Data were obtained from the unit database. Statistical analysis was performed using SPSS 17. Demographic and clinical characteristics are presented as mean ± standard deviation or as percentages. The correlation of these outcomes for each parameter was questioned by using the Pearson's correlation. Sensitivity and specificity of the variables were obtained in patients with graft failure continuing hemodialysis (HD) treatment and rejection-experienced patients (ACR; acute cellular rejection) separately. Missing data were excluded case-wise. A P-value less than 0.05 was considered as appropriate.

Results

Patient characteristics

The clinical characteristics of the patients and their donors are summarized in Table 1. The mean age of the entire study population was 31 years (11–63 years), 72% of recipients were male, and all were Caucasian. Mean donor age was 48 years (range 9–81 years), and 86% of donors were living donors.

Mean follow-up was 66.7 months (range 1.9 to 162 mo). Five recipients died during the follow-up. Mortality was attributed to graft failure in 4 of the patients. Twenty-three recipients underwent graft failure and returned to hemodialysis treatment. Nineteen (82%) of these patients experienced at least one episode of rejection. The 1- and 3-year graft survival rates for overall patients were 96% and 93%, respectively.

Glomerulonephritis was one of the most frequent underlying diseases within the known etiologies in the group.

Metabolic assessment

Serum amylase and the other test results are shown in Table 2. In the post-transplant follow-up, Cr-Cl, proteinuria, creatinine and amylase levels became abnormal in 90%, 84%, 75% and 44% of the patients, respectively. These were followed by elevation in serum LDL-chol (29%), lipase (16%) glucose (11%) and CRP (0.7%) levels.

Table 2. Post -transplant outcome variables of the study group.

Parameters	Number of recipients	Abnormal results, N	Mean ±SD, range	Reference range
Glucose, mg/dl	181	21, (11%)	93.4±26.7, (58–330)	74–110
Ldl Cholesterol, mg/dl	182	53, (29%)	110.5±39.5, (24–254)	<130
Amylase,U/L	182	81, **(44%)**	109±42.0, (37–239)	<110
Lipase, U/L	145	23, (16%)	52±29.7, (7–196)	<78
Creatinine, mg/dl	189	142, **(75%)**	2.8±2.8, (0.62–16.1)	0.40–1.20
Cr Cl, ml/min	119	107, **(90%)**	51±25.5, (6–117)	>90
CRP, mg/dl	155	12, (0.7%)	0.96±2.1, (0–17)	<2
Proteinuria, gr/24 hour	118	99, **(84%)**	1.47±2.3, (0.03–12.7)	0–0.15

Cr – creatinine; Cr Cl – 24 hour creatinine clearance; CRP – serum C reactive protein; N – number of patients.

Table 3. Correlation among the outcome variables in the study.

		Amylase	Cr	Cr Cl	CRP	Lipase	24-h Proteinuria
Amylase	Pearson Correlation	1.000	.105	–.214*	.019	.497**	.103
	Sig. (2-tailed)		.158	**.021**	.817	**.000**	.278
	N	182.000	181.000	115.000	150.000	144.000	113.000
Lipase	Pearson Correlation	.497**	.340**	–.321**	.138	1.000	.404**
	Sig. (2-tailed)	**.000**	**.000**	**.001**	.120		**.000**
	N	144.000	144.000	98.000	129.000	145.000	99.000

Cr – creatinine; Cr Cl – 24 hour creatinine clearance; CRP – serum C reactive protein; * correlation is significant at the 0.05 level (2-tailed); ** correlation is significant at the 0.01 level (2-tailed).

Thirty-nine percent (37/95) and 49% (26/53) of the patients with hyperamylasemia received tacrolimus- and CYC-based immunosuppression, respectively. It was present in 40% of living donor and 16% in deceased donor recipients.

The maximum increase in serum amylase and lipase were up to 2.5 times the upper limits.

Looking at the correlation within the outcome variables, negative correlations were detected between the creatinine clearance amylase, and lipase (p=0.021 and 0.001, respectively) (Table 3).

When CrCl has fallen under 30 ml/min, increase in serum amylase and lipase was detected in 68% and 39% of the patients; in patients with moderate-level kidney dysfunction (CrCl range 30–60 ml/min) it was 52% and 11%, and the elevations were detected in 33% and 3% of the patients with mild kidney dysfunction (Cr Cl range 60–90 ml/min), respectively (Figure 1).

Unlike serum amylase, there was a positive correlation between the serum lipase, creatinine and 24-h proteinuria (p<0.001). These findings were observed independently from CRP (p>0.05) (Table 3).

The sensitivity and specificity of amylase and lipase measurement for the diagnosis of graft failure were evaluated in 23 patients undergoing regular hemodialysis treatment. Creatinine was used as a control variable. Of the group, 21 patients' amylase levels and 11 patients' serum lipase levels were accessible in the database. In these, hyperamylasemia was detected in 67% (14/21) and lipase in 45% (5/11). Lipase, however, was notably superior to amylase and creatinine – the specificity of lipase was 87%, while specificity of amylase and creatinine were 59% and 28%, respectively (Table 4A).

Additional sensitivity and specificity tests were applied to ACR patients (n=42). In this group the

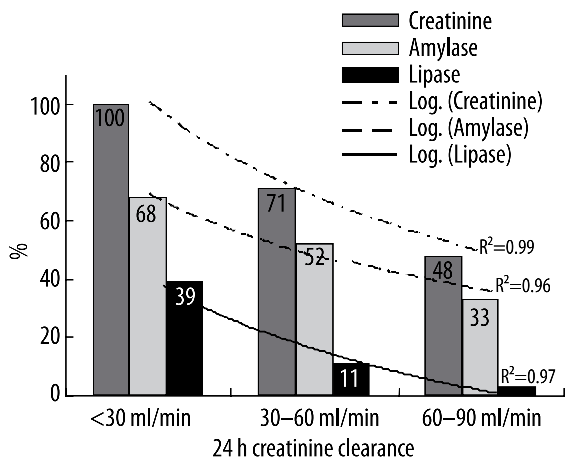

Figure 1. Deterioration of the tests in the presence of graft dysfunction according to creatinine clearance.

amylase levels of 40 patients and the lipase levels of 25 patients were obtained. In the group, an elevation of amylase was in itself as valuable as creatinine at confirming ACR (positive predictive value =30%). Besides the sensitivity of the amylase (60%) being lower than the creatinine (98%), it was found to be 2 times more specific than creatinine for the presence of ACR (59% *vs.* 31%, respectively). However, lipase was found to be the most specific test in the ACR evaluation (specificity was 90%) (Table 4B). In the overall consideration, positive predictive value and specificity of amylase and lipase were superior to creatinine in the groups (Figure 2A, B).

Discussion

In many of the previous reports, the elevation in serum amylase when coupled with increases in serum lipase was usually attributed to a pancreatic origin [13,14]. Extremely high enzyme levels may be associated with radiologic evidence of pancreatitis, or, if found to be of non-pancreatic origin, likely to be multiple organ failure [15,16]. In the study group, increases in both enzymes were less than 3 times their upper normal limit, being higher in lipase. It was seen through literature review that hyperamylasemia in transplant patients was first mentioned in studies from the 1970s. Penn et al evaluated hyperamylasemia developed secondary to pancreatitis in kidney recipients [17]. The reported factors causing pancreatitis in the KTx patients included uremia, pancreatic injury by drugs, infections resulting from chronic immunosuppression, and hyperparathyroidism [17]. Other studies found pancreatitis that developed after renal transplantation was accompanied by hyperamylasemia [18,19].

In contrast, Takagi et al. reported that asymptomatic transient hyperamylasemia was accompanied by hyperamylasuria after a large intravenous dose of methylprednisolone in patients with renal allograft [20]. None of the patients in the group were on large dose of steroids.

The study by Dardaman is was one of the first emphasizing hyperamylasemia rather then pancreatitis in kidney recipients. In this study,

Table 4. Sensitivity and Specificity of the tests for determining graft failure (**A**) and acute cellular rejection (**B**). PPV; positive predictive value, NPV; negative predictive value.

A

Tests	Graft Failure			
	PPV	NPV	Sensitivity	Specificity
Amylase	18%	93%	67%	59%
Lipase	22%	95%	45%	87%
Creatinine	16%	100%	100%	28%

B

Tests	Acute Cellular Rejection			
	PPV	NPV	Sensitivity	Specificity
Amylase	30%	84%	60%	59%
Lipase	33%	88.5%	44%	90%
Creatinine	28%	98%	98%	31%

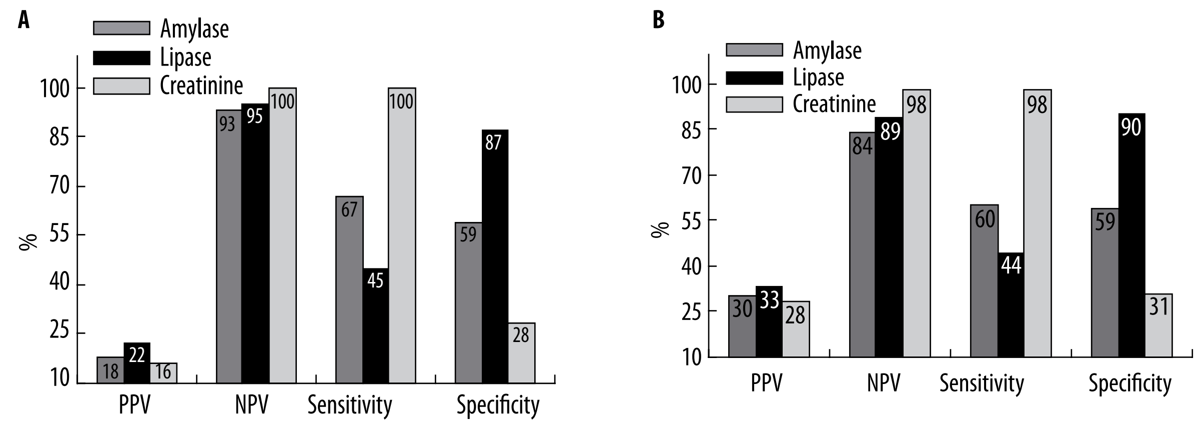

Figure 2. Diagnostic value of the variables in the graft failure (**A**) and acute cellular rejection (**B**) cases.

hyperamylasemia was evaluated within 3 groups: in patients with kidney failure, patients undergoing hemodialysis (HD), and kidney recipients. They found that kidney recipients had serum amylases up to 3 times higher than the upper normal limit, without exhibiting any clinical sign of acute pancreatitis [21]. In contrast to serum amylase, the absence of correlation between urine amylase and serum creatinine was found only in the recipient group. It was thought that disturbed amylase catabolism or reabsorption could play a role in the increased serum amylase. Findings of this study support our hypothesis. However, hyperamylasemia was detected in 92% of the recipients in that study, and no data has been noted by us concerning the condition of that recipient graft function. In the present study, only 40% of recipients had experienced hyperamylasemia, and the correlation was between the serum amylase and Cr Cl. The increased hyperamylasemia was detected in 100% of the hemodialysis patients and 98% of patients with varying degrees of renal insufficiency [21].

It was earlier concluded that amylase clearance was a function of glomerular filtration and tubular reabsorption [22,23]. Loss of tubular function would explain why amylase/creatinine clearance ratios are sometimes elevated in renal diseases [24]. In the study, urine amylase and lipase were not studied. However, the decrease in the increasing rate of hyperamylasemia in recipients with developing advanced level kidney failure could be explained by loss through tubular reabsorption.

There are several similar studies, but they were performed in ESRD patients [25–28]. From these, Jiang et al reported that the ESRD patients had elevated serum amylase and lipase levels in 60% and 57% of the cases respectively, which were within 3-fold of the upper normal limits [25]. In contrast, Colen et al concluded that serum amylase levels remained in the normal range when creatinine clearance was greater than 50 ml/min and became elevated when Cr Cl was less then 50 ml/min within the kidney patients [26]. In our study, only lipase levels stayed close to normal limits in recipients (3%) whose Cr Cl was 60 ml/min or higher. In contrast, amylase was elevated in 33% of the same group. This may mean that amylase can increase before renal filtration has failed sufficiently. This suggests that it could be due to disturbed tubular function. In this study, the PPV and NPV values of amylase in ACR cases were similar to creatinine, but its specificity has been found to be up to 28% greater. Within the documentation in the database, this elevation is accompanied by an elevation in serum creatinine, followed by lipase elevation. This could be explained by the different rates of renal handling of the enzymes [12,25,28,29]. All of these factors suggest that amylase, too, might have importance in the early spotting of tubulitis in ACR events or any type of tubular dysfunction, regardless of the cause. These approaches are also valid for lipase. Sensitivity and specificity tests show that lipase acts more specifically in the cases of graft failure or rejection than amylase or creatinine. However the increase in lipase starts after the increase in amylase.

Conclusions

In conclusion, results of more recent studies of non-invasive biomarkers for the detection of early graft dysfunction are encouraging. However, some of these biomarkers were developed in non-transplant settings and are expensive [5]. As in gene tests, some of these tests need to be studied pre-transplantation [4].Therefore, along with cost effectiveness and practicality, amylase and lipase are seen as more beneficial at this stage. As such, if there is any elevation of serum amylase and lipase levels of less than 3-fold their upper limits during the follow-up, it is recommended to evaluate patients for possible graft dysfunction in the setting of kidney transplantation.

This is a retrospective study and prospective studies would be beneficial.

Declared

No funding and no conflict of interest.

References:

1. Sahadevan M, Kasiske BL: Long-Term post transplant management and complications. In: Danovitch GM (ed.), Handbook of Kidney Transplantation, Lippincott Williams &Wilkins, Philadelphia; 2005; 147
2. Hariharan S, Mcbride SA, Cherikh WS et al: Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney International, 2002; 62: 311–18
3. Fresnedo FG, Rodrigo E, DeFrancisco AL et al: Change in Serum Creatinine Levels between 6 and 12 Months and Kidney Graft Survival: Influence of Proteinuria. Transplant Proceedings, 2005; 37: 1433–34
4. Caban A, Brudzinski G, Oczkowicz G et al: Factors determining chances in concentrations of pro-inflamatory markers in blood serum in the initial period after kidney transplantation from dead donor. Ann Transplant, 2009; 14: 10–13
5. Halawa A: The early diagnosis of acute renal graft dysfunction: a challenge we face.The role of novel biomarkers. Ann Transplant, 2011; 16: 90–98
6. Kloda K, Domanski L, Pawlik A et al: Effect of the ICAM1 and VCAM1 gene polymorphisms on delayed graft function and acute kidney allograft rejection. Ann Transplant, 2010; 15: 15–20
7. Grzelak P, Szymczyk K, Strzelczyk J et al: Perfusion of kidney graft pyramids and cortex in contras-enhanced ultrasonography in the determination of the cause of delayed graft function. Ann Transplant, 2011; 16: 48–53
8. Mathew A, Chiemprabha AF, Donelson S: Hyperamylasemia. *http://emedicine.medscape.com/article/186389-overview* 2009
9. Pieper BC, Strocchi AL: Where does serum amylase come from and where does it go? Gastroenterol Clin North Am, 1990; (4): 793–810
10. Ravel R: Clinical Laboratory Medicine, 6th ed, Mosby, Missouri, 1995; 447–49
11. Tietz NW, Shuey DF: Lipase in serum – the Elusive Enzyme: An overview. Clin Chem, 1993; (5): 746–56
12. Waller SI, Ralston AJ: The hourly rate of urinary amylase excretion, serum amylase, and serum lipase. Part I. In control subjects and patients with renal disease. Gut, 1971; 12: 878–83
13. Agarwal N, Pitchumoni CS, Sivaprasad AV: Evaluating tests for acute pancreatitis. Am J Gastroenterol, 1990; 85(4): 356–66
14. Malfertheiner P, Kemmer TP: Clinical picture and diagnosis of acute pancreatitis.Hepatogastroenterology. 1991; 38(2): 97–100
15. Manjuck J, Zein J, Carpati C, Astiz M: Clinical significance of increased lipase levels on admission to the ICU. Chest, 2005; 127: 246–50
16. Rattner DW, Gu ZY, Vlahakes GJ, Warshaw AL: Hyperamylasemia after cardiac surgery. Incidence, significance, and management. Ann Surg, 1989; 209: 273–83
17. Penn I, Durst AL, Machado M et al: Acute pancreatitis and hyperamylasemia in renal homograft recipients. Arch Surg, 1972; (105): 167–72
18. Frick TW, Fryd DS, Sutherland DE et al: Hypercalcemia associated with pancreatitis and hyperamylasemia in renal transplant recipients: Data from the Minnesota randomized trial of cyclosporine versus antilymphoblast azathioprine. Am J Surg, 1987; (154): 487–89
19. Johnson WC, Nabseth DC: Pancreatitis in renal transplantation. Ann Surg, 1970; 171: 309–14
20. Tagagi H, Yasue M, Morimoto T et al: Asymtomatictransienthyperamylasemia after a large intravenous dose of steroid hormone. Am J Surg, 1977; 133: 322–25
21. Dardamanis MA, Elisaf MS, Vasakos SA et al: alpha-Amylase and isoamylase levels in renal transplant recipients compared touremicpatients. Ren Fail, 1995; (17): 715–19
22. Frederickson A, Jacobson G: Influence of renal function on the urinary excretion of amylase: An experimental study in the rat. Scandinavian J Clini Lab Invest, 1974; 33: 313–21
23. Johnson SG, Ellis CJ, Levitt MD: Mechanism of increased renal clearance of amylase/creatinine in acute pancreatitis. N Engl J Med, 1976; 295: 1214–17
24. Keogh JB, McGeeney KF, Drury MI et al: Renal clearance of pancreatic and salivary amylase relative to creatinine in patients with chronic renal insufficiency. Gut, 1978; 19: 1125–30
25. Jiang CF, Ng KW, Tan SW et al: Serum level of amylase and lipase in various stages of chronic renal insufficiency. Zhonghua Yi Xue Za Zhi (Taipei), 2002; (2): 49–54 (abstract)

26. Colen MJ, Ansher AF, Chapman AB et al: Serum amylase in patients with renal insufficiency and renal failure. Am J Gastroenterology, 1990; 85: 1377–80
27. Ventrucci M, Campieri C, Di Stefano M et al: Alterations of exocrine pancreas in end-stage renal disease.Do they reflect a clinically relevant uremic pancreopathy? Dig Dis Sci, 1995; 40: 2576–81
28. Caruana RJ, Altman R, Fowler B et al: Correlates of amylase and lipase levels in chronic dialysis patients. Int J Artif Organs, 1988; 11: 454–58
29. Junge W: The role of the kidney in the elimination of pancreatic lipase and amylase from blood. J Clin Chem Clin Biochem, 1985; 23: 387–92