The reduction of serum aminotransferase levels is proportional to the decline of the glomerular filtration rate in patients with chronic kidney disease

Luís Henrique Bezerra Cavalcanti Sette,* Edmundo Pessoa de Almeida Lopes

Universidade Federal de Pernambuco (UFPE), Department of Internal Medicine, Recife/PE, Brazil.

OBJECTIVE: This study sought to determine the serum aminotransferase levels of patients with predialysis chronic kidney disease and establish their relationships with serum creatinine levels and glomerular filtration rate.

METHODS: Patients with chronic kidney disease were evaluated between September 2011 and May 2012. Aminotransferase and creatinine serum levels were measured using an automated kinetic method, and glomerular filtration rates were estimated using the Cockroft-Gault and Modification of Diet in Renal Disease formulas to classify patients into chronic kidney disease stages.

RESULTS: Exactly 142 patients were evaluated (mean age: 64 ± 16 years). The mean creatinine serum level and glomerular filtration rate were 3.3 ± 1.2 mg/dL and 29.1 ± 13 mL/min/1.73 m^2, respectively. Patients were distributed according to their chronic kidney disease stages as follows: 3 (2.1%) patients were Stage 2; 54 (38%) were Stage 3; 70 (49.3%) were Stage 4; and 15 (10.5%) were Stage 5. The mean aspartate aminotransferase and alanine aminotransferase serum levels showed a reduction in proportion to the increase in creatinine levels ($p=0.001$ and $p=0.05$, respectively) and the decrease in glomerular filtration rate ($p=0.007$ and $p=0.028$, respectively). Alanine aminotransferase and aspartate aminotransferase serum levels tended to be higher among patients classified as stage 2 or 3 compared with those classified as stage 4 or 5 ($p=0.08$ and $p=0.06$, respectively).

CONCLUSIONS: The aspartate aminotransferase and alanine aminotransferase serum levels of patients with predialysis chronic kidney disease decreased in proportion to the progression of the disease; they were negatively correlated with creatinine levels and directly correlated with glomerular filtration rate.

KEYWORDS: Aspartate aminotransferase; Alanine aminotransferase; Creatinine; Chronic kidney disease; Glomerular filtration rate.

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E-mail: setteluis@hotmail.com

*Corresponding author

INTRODUCTION

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are markers of aggression to hepatocytes and aid in the diagnosis, monitoring and treatment of liver diseases because they reflect the inflammatory activity of the liver (1–3). However, patients with chronic kidney disease (CKD) on hemodialysis (HD) have lower aminotransferase serum levels than those with preserved renal function, which

might adversely affect the assessment of liver injury among these patients (4,5).

Some factors are implicated in the reduction of AST and ALT serum levels among patients with CKD on HD such as lower pyridoxine serum levels, higher homocysteine levels and hemodilution due to fluid retention (6–8). In patients on HD infected with the hepatitis B (HBV) or hepatitis C viruses (HCV), other factors also contribute to the decrease in aminotransferases, such as the lower viremia caused by the dialysis procedure through the sequestration of the virus by the dialyzer; the higher production of hepatocyte growth factor (HGF), which is induced via dialysis and accelerates liver regeneration; and the increased endogenous α-interferon serum levels and lymphocyte activation that fight the viral agent together (9–11).

However, most studies evaluating serum aminotransferase levels have involved patients with CKD on HD, and only one article has described a reduction in serum aminotransferase

levels among patients with predialysis CKD (12). In that study, only the AST serum levels were correlated with the creatinine concentration, whereas the relationship between the aminotransferases and the glomerular filtration rate (GFR) was not assessed; furthermore, this analysis was not conducted according to CKD stage (12,13). In fact, the behavior of AST and ALT serum levels during CKD progression is still not fully known.

Therefore, this study aimed to determine the AST and ALT serum levels of patients with predialysis CKD and correlate them with their creatinine serum levels and GFRs.

■ PATIENTS AND METHODS

A cross-sectional study was conducted from September 2011 to May 2012 that included all of the patients older than 18 years who attended the CKD outpatient clinic of the Nephrology Service, Hospital das Clínicas (UFPE) and who were diagnosed with CKD at least 3 months previously.

The patients were consecutively selected using the following criteria during their arrival at the clinic. Those with positive serological markers for HBV, HCV, HIV or a chronic liver disease were excluded, as were those who consumed more than 210 g of alcohol/week, those with a manifest infectious disease, and pregnant or postpartum women.

The patients who agreed to participate signed an informed term of consent and completed a questionnaire regarding their demographic, socioeconomic, anthropometric and clinical data. Thereafter, approximately 5 mL of blood was collected to perform biochemical testing using an automated kinetic method (COBAS C501 ROCHE, Roche Diagnostics, Indianapolis, Indiana, U.S.A.), which included evaluations of their ALT, AST and creatinine levels.

When indicated, the test results were standardized for gender by calculating the ratio of the value found by the method and the upper limit of normal (ULN). Patients presenting ALT and AST values greater than 5 times the ULN were excluded from the analyses. Renal function was assessed using the creatinine serum levels and by estimating the GFR with the Cockcroft-Gault (CG) formula (13) corrected for body surface area (14) and the abbreviated Modification of Diet in Renal Disease (MDRD) equation (15).

The patients were classified into different CKD stages based on the GFR (mL/min/1.73 m^2) defined by the guidelines of the Kidney Disease Outcomes Quality Initiative, such that GFR >90=Stage 1; between 60–89=Stage 2; between 30–59=Stage 3; between 15–29=Stage 4; and <15 or under dialysis=Stage 5 (16). The early CKD stages were defined as Stages 2 or 3, and the advanced stages were categorized as Stages 4 and 5.

Initially, the population was described using a frequency distribution when the variable was categorical; means and standard deviations were calculated when the variable was quantitative.

The Kolmogorov-Smirnov normality test was applied; when the distribution was not normal, a logarithmic transformation was applied to normalize the data. Student's t test (up to 2 levels) and ANOVA followed by a Bonferroni post hoc test (>2 levels) were applied to compare means. Pearson's chi-square test was applied to evaluate the association between the CKD stages and the categorical variables. A linear regression model was applied to analyze the association with the GFR, and significant associations were adjusted for BMI. All of the tests were conducted using a significance threshold of 5% (p < 0.05). STATA version 12.0 was used for all data analyses.
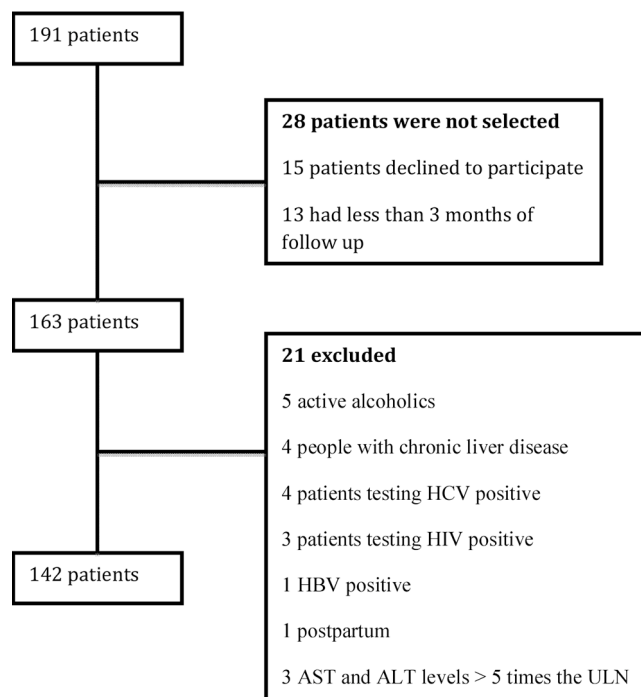

Figure 1 - A flow chart of the patients who met the inclusion/exclusion criteria for the study. ULN, AST and ALT.

Table 1 - The major medications used among the 142 patients with predialysis CKD.

Major Medications in Use	N	%
ACE (angiotensin converting enzyme) inhibitors and ARBS (angiotensin II receptor blockers)	77	54.2
Aspirin	61	43
Calcium channel blockers	63	44.3
B-Blockers	52	36.6
Diuretics	90	63.3
Erythropoietin-stimulation agents	13	9.1
Insulin	42	29.5
Alpha blockers	19	13.4

The Research Ethics Committee of the Universidade Federal de Pernambuco Health Sciences Center approved this study under registration number 335/11, CAAE 0314.0.172.000-11. This study follows the precepts set forth in Resolution No. 196/96 of the (Brazilian) National Health Council.

■ RESULTS

During the study period, 191 patients were assessed, but only 142 were included. The non-enrollment reasons for these screened patients are shown in Figure 1.

The mean age of participants was 64 ± 16 years, and 72 patients (51%) were male. The mean serum creatinine level was 3.3 ± 1.2 mg/dL, and the mean GFRs, as estimated using the CG and MDRD equations, were 28.9 ± 13 mL/min/1.73 m^2 and 25.5 ± 12.9 mL/min/1.73 m^2, respectively. The major drug groups that the patients used are listed in Table 1. The patients were distributed across the CKD stages according to the CG equation thusly: 3 (2.1%) patients were classified as Stage 2; 54 (38%) were Stage 3; 70 (49.3%) were Stage 4; and 15 (10.5%) were Stage 5. In addition, when the

Table 2 - The distribution of clinical and epidemiological characteristics according to the CKD stages of the 142 patients with predialysis CKD.

Characteristic	Stages of CKD			p-value
	Stages 2 & 3	Stage 4	Stage 5	
N	57	70	15	
Age[*]	65.3 ± 12.9	63.2 ± 17.4	60.2 ± 22.1	0.506
BMI[*]	27.6 ± 4.4	25.7 ± 4.8	23.6 ± 2.4	0.007[a]
Diabetic				
Yes (%)	27 (47.3)	24 (34.2)	7 (46.7)	0.400
No (%)	30 (52.7)	46 (65.8)	8 (53.3)	
Use of statin				
Yes (%)	37 (64.9)	38 (54.2)	8 (53.3)	0.601
No (%)	20 (35.1)	32 (45.8)	7 (46.7)	
N° of medications	4.4 ± 2.1	4.4 ± 2.2	4.6 ± 2.2	0.926

* ANOVA, post hoc Bonferroni test
** Pearson's chi-squared test
[a] Difference between the patients with Stage 2 and 3 versus those with Stage 4

MDRD equation was used, the following distribution was noted: 3 (2.1%) patients were classified as Stage 2; 48 (33.8%) were Stage 3; 73 (51.4%) were Stage 4; and 18 (12.6%) were Stage 5. Because the number of Stage 2 patients was small and their GFRs approximated those of the Stage 3 patients, these patients were reclassified as Stage 3 for the purpose of statistical analysis. The clinical and epidemiological characteristic distributions are shown in Table 2.

The means of patients with regard to stage distribution as evaluated using the CG and MDRD formulas were not significantly different; therefore, we used the CG formula to evaluate the variables.

The mean serum level divided by the AST or ALT ULNs were 0.55 and 0.29, respectively. AST and ALT serum levels above the ULN (>1) were found in 6 (4.2%) and 2 (1.4%) patients, respectively.

The AST and ALT serum level means reduced in proportion to the increase in creatinine levels ($p=0.001$, $r=-0.27$; and $p=0.05$, $r=-0.17$, respectively). In addition, the mean ALT and AST serum levels were also reduced in proportion to the descent in GFR ($p=0.007$ and $p=0.028$, respectively; see Table 3).

Female patients had higher GFR levels, and significant associations were observed with regard to the BMI and aminotransferase measurements. The associations among AST, ALT, and GFR remained significant after adjusting for BMI ($p=0.008$ and $p=0.039$, respectively; see Table 3).

A significant difference was not detected when the association of the AST and ALT serum levels were evaluated for each CKD stage ($p=0.16$ and $p=0.18$, respectively). When the earlier CKD stages (2 and 3) were combined and compared with the more advanced stages (4 and 5), significant trends in the ALT ($p=0.08$) and AST ($p=0.06$) serum levels were observed, as described in Table 4. Reductions of approximately 12% and 10% were observed in the ALT and AST serum levels, respectively, when Stages 2 and 3 were compared with Stages 4 and 5.

DISCUSSION

Serum aminotransferase levels decrease in patients with CKD who undergo HD (17); however, little is known with regard to how the levels of these enzymes behave during the

Table 3 - A linear regression of the clinical and laboratory characteristics according to the GFRs of the 142 patients with predialysis CKD.

Characteristic	GFR			
	Univariate analysis		Adjusted by BMI	
	β coefficient	p-value	β coefficient	p-value
Clinics				
Age (years old)	0.03	0.625		
Gender (F > M)	6.9	0.001	6.1	0.005
BMI[*]	24.1	0.000		
Diabetes (Yes > No)	1.4	0.546		
Use of a statin (Yes > No)	3.0	0.171	2.9	0.183
Number of medication	0.43	0.408		
Laboratory				
AST/ULN[*]	8.87	0.007	8.40	0.008
ALT/ULN[*]	5.06	0.028	4.58	0.039

ULN: upper limit of normal
* Logarithmic transformation

Table 4 - The mean serum aminotransferase levels, divided by the ULN for the early (2 and 3) and advanced (4 and 5) stages of CKD among the 142 patients undergoing conservative treatment.

Aminotransferase	Stages of CKD		p-value*
	Early (2 & 3)	Advanced (4 & 5)	
N	57	85	
AST/ULN	0.586 ± 0.211	0.530 ± 0.201	0.061
ALT/ULN	0.311 ± 0.156	0.274 ± 0.162	0.084

ULN: upper limit of normal
* Student's t-test; measures with logarithmic transformation

earliest stages of CKD under predialysis treatment. This study is the first to find a direct correlation between a reduction in GFR and a decrease in aminotransferases.

In fact, we observed that AST and ALT serum levels tended to be higher during the initial stages (2 and 3) of CKD compared with the later stages (4 and 5). The possible increases in the number of patients within each CKD stage might reveal a more gradual and significant decrease in serum aminotransferases levels; this finding is in line with the reduction in the GFR. Importantly, the sample size must be regarded as one of the limitations of this study.

Some hypotheses have been offered to explain the reduction of serum aminotransferase levels among patients with CKD on HD: a deficiency of pyridoxine, hemodilution and hyperhomocysteinemia (6–8). In fact, Ono et al. reported that patients with CKD on HD with pyridoxine deficiencies have lower serum aminotransferase levels than those without vitamin deficiencies (7). Lopes et al. observed hemodilution and found that weight loss during HD was associated with a rise in ALT serum levels ($r=0.3$, $p<0.001$) (6). Huang et al. evaluated the serum homocysteine levels of 145 patients undergoing HD and found that they were negatively related to AST ($r=0.4$, $p<0.001$). Thus, AST serum levels might reflect the high metabolic activity of homocysteine and influence its serum levels (8). Importantly, these hypotheses concern patients with CKD under HD; however, they cannot be rejected with regard to

patients during predialysis. Therefore, another limitation of this study is that it did not measure homocysteine or pyridoxine.

Interestingly, this study found that almost all of the patients had aminotransferase levels below the ULN, even when they were using several potentially hepatotoxic drugs (4 per patient on average) such as statins, which were used by approximately 60% of the patients (18). Moreover, a considerable number of patients had diabetes mellitus, which might lead to liver inflammation (steatohepatitis) and a consequent rise in liver enzymes (19).

Another interesting finding of this study concerns the significant reduction in BMI based on CKD progression. This behavior is explained not only by the fact that patient weight is included in the calculation of the GFR but also given the malnutrition associated with CKD (13,20,21). In fact, the progressive decrease of BMI might reduce dyslipidemia or glucose levels, thereby promoting a regression of underlying fatty liver disease that contributes to decreased aminotransferase levels (22). To reduce this possible confound, the association between GFR and aminotransferases was adjusted for BMI; however, it remained significant. Moreover, malnutrition might reduce the stocks of B-complex vitamins, especially pyridoxine, which act as a co-factor in the synthesis of aminotransferases by reducing their production (23).

Male patients presented lower GFRs than their female counterparts. This finding might be related to the CKD progression rate, which occurs more rapidly in males, thereby increasing the chances that these patients are at more advanced stages of the disease (24).

This preliminary study revealed that the decrease in AST and ALT serum levels among patients with CKD occurs before the start of dialysis, and these enzymes are independently decreasing factors associated with HD. Future studies, should collect larger samples of patients with CKD to evaluate the evidence of aminotransferase reduction in these patients, such as pyridoxine and homocysteine serum levels.

In conclusion, the AST and ALT serum levels of patients with pre-dialysis CKD tended to decrease in proportion to their CKD progression, and these levels were negatively correlated with their creatinine serum levels and directly correlated with the GFR.

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■ AUTHOR CONTRIBUTIONS

Lopes EP was responsible for the conception and design of this paper as well as the data analysis and interpretation. Sette LH was responsible for the data collection, patient interviews, laboratory analyses, text preparation and data analysis. Both authors contributed to, read and approved the final manuscript.

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