

## CLINICAL SCIENCE

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### SERUM ALANINE AMINOTRANSFERASE LEVELS, HEMATOCRIT RATE AND BODY WEIGHT CORRELATIONS BEFORE AND AFTER HEMODIALYSIS SESSION

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**PURPOSE:** To evaluate alanine aminotransferase levels before and after a hemodialysis session and to correlate these values with the hematocrit rate and weight loss during hemodialysis.

**PATIENTS AND METHODS:** The serum alanine aminotransferase levels, hematocrit rate and body weight were measured and correlated before and after a single hemodialysis session for 146 patients with chronic renal failure. An receiver operating characteristic (ROC) curve for the serum alanine aminotransferase levels collected before and after hemodialysis was plotted to identify hepatitis C virus-infected patients.

**RESULTS:** The mean weight loss of the 146 patients during hemodialysis was 5.3% ( $p < 0.001$ ). The mean alanine aminotransferase levels before and after hemodialysis were 18.8 and 23.9 IU/, respectively, denoting a significant 28.1% increase. An equally significant increase of 16.4% in the hematocrit rate also occurred after hemodialysis. The weight loss was inversely correlated with the rise in both the alanine aminotransferase level ( $r = 0.3$ ;  $p < 0.001$ ) and hematocrit rate ( $r = 0.5$ ;  $p < 0.001$ ). A direct correlation was found between the rise in alanine aminotransferase levels and the hematocrit during the hemodialysis session ( $r = 0.4$ ;  $p < 0.001$ ). Based on the ROC curve, the upper limit of the normal alanine aminotransferase level should be reduced by 40% relative to the upper limit of normal if the blood samples are collected before the hemodialysis session or by 60% if blood samples are collected after the session.

**CONCLUSION:** In the present study, significant elevations in the serum alanine aminotransferase levels and hematocrit rates occurred in parallel to a reduction in body weight after the hemodialysis session. These findings suggest that one of the factors for low alanine aminotransferase levels prior to hemodialysis could be hemodilution in patients with chronic renal failure.

**KEYWORDS:** Alanine aminotransferase; Hemodialysis; Hepatitis C; Chronic renal failure.

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#### INTRODUCTION

The frequency of raised serum alanine aminotransferase (ALT) concentrations in patients who are infected with

the hepatitis C virus (HCV) and have chronic renal failure (CRF) that requires hemodialysis (HD) therapy has been reported to be between 4 and 67%.<sup>1-3</sup> On the other hand, between 54 and 75% of patients with HCV antibodies (anti-HCV) without CRF have increased ALT levels.<sup>4</sup> On the basis of these considerations, the ALT levels are assumed to be poor predictors of hepatocellular damage in the chronic HD population.<sup>1,2</sup>

A number of factors may explain the reduction in the ALT levels in HD patients, such as low or fluctuating serum viral load due to adsorption in the dialyzer membrane; non-

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virulent HCV strains; intermittent increases in the serum ALT concentration; or decreased levels of vitamin B6, a coenzyme of ALT.<sup>5-8</sup> The ALT levels may also be lower before the HD session due to hemodilution and may increase after the session, depending on how much liquid is lost during dialysis.

Other studies have found that the ALT levels – even those not exceeding the upper limit of normal (ULN) – are higher in the anti-HCV positive patients in comparison to the anti-HCV negative patients. Indeed, new criteria for the ULN of the ALT have been proposed for patients on HD.<sup>5, 7, 9</sup>

A new ULN for the serum levels of ALT has also been proposed, corresponding to around 70% of the present ULN, for screening for liver damage not only in patients with CRF but also for the general population. One argument for this decrease is that sub-clinical conditions such as fatty liver disease and HCV infection had not yet been identified when the last ULN was established about 20 years ago. With the new ULN criteria, the ALT sensitivity should improve from 55 to 76% for the detection of patients with minimal to mild histological lesions, despite a reduction in specificity from 97 to 89%.<sup>9</sup> Recently, a population-based study carried out in Korea revealed that the risk of death from liver disease was higher among patients with ALT levels closer to the ULN in comparison to patients with lower ALT levels. Thus, a reduction to below 75% of the current normal cutoff values was suggested.<sup>11</sup>

Likewise, in trials using peginterferon and ribavirin for the treatment of patients with HCV infection and “normal” ALT concentrations, cases with a sustained virological response exhibited a greater decrease in ALT values than cases that did not respond. These results suggest that, in this group of patients, the “normal” ALT levels before therapy may be higher than in individuals without chronic hepatitis and that viremia clearance after treatment induces a subsequent reduction towards “true normal” ALT levels.<sup>12</sup> Considering the clinical importance of these differences in ALT normality, a reduction of approximately 30% has been suggested for the conventional ULN serum ALT levels.<sup>13</sup>

The aim of the present study was to evaluate the ALT levels in patients with CRF and correlate those values with the hematocrit rate and weight loss before and after a single HD session. On the basis of these data, a more appropriate ALT cutoff value was established in order to better identify biochemical activity due to HCV infection in HD patients with CRF.

## PATIENTS AND METHODS

In a dialysis unit in northeastern Brazil, 146 patients with CRF undergoing HD treatment were studied after giving

informed consent. All patients over 16 years of age who fulfilled the following criteria were included: regular hemodialysis for at least 6 months and no history of alcohol intake (> 40 g/day). The study protocol was approved by the Research Ethics Committee of the University Federal de Pernambuco (Brazil).

The serum ALT was determined by an automated kinetic method (Abbott®) in blood samples that were obtained immediately prior to and at the end of a single HD session. The serum concentration for each patient was divided by the ULN of the ALT according to gender (40 IU/L for women and 43 IU/L for men). The hematocrit rate was determined before and after the same HD session using a CELL-DYN 4000 analyzer. The antibody against hepatitis C virus (anti-HCV), hepatitis B virus surface antigen (HBsAg) and antibody against hepatitis B virus surface antigen (anti-HBs) levels were determined through enzyme immunoassays (Abbott®).

For each analyzed variable, differences before and after the HD session were established as a gradient (after – before).

The statistical analysis was carried out using SPSS v8.0. The chi-squared test was used to determine the frequency difference, and Student’s t-test was used to evaluate the mean differences. The degree of correlation between measurements before and after the HD session was assessed using the Pearson’s correlation test. A significance level of  $p < 0.05$  was chosen.

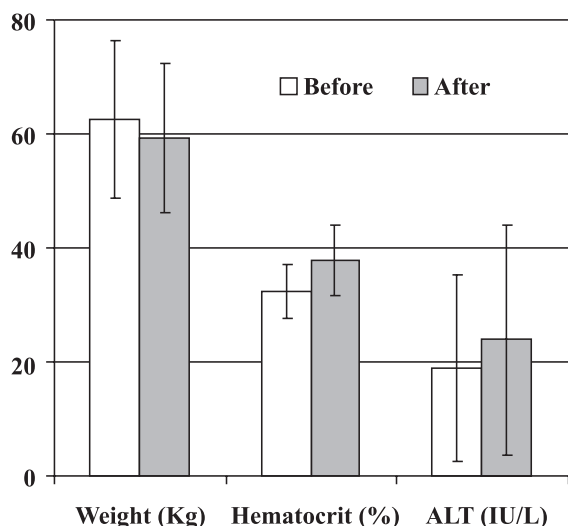
The best cutoff value for the ALT was established from a receiver operating characteristic (ROC) curve, which is the value that maximizes the sum of the sensitivity and specificity to identify the biochemical activity in HD patients with HCV antibodies.

## RESULTS

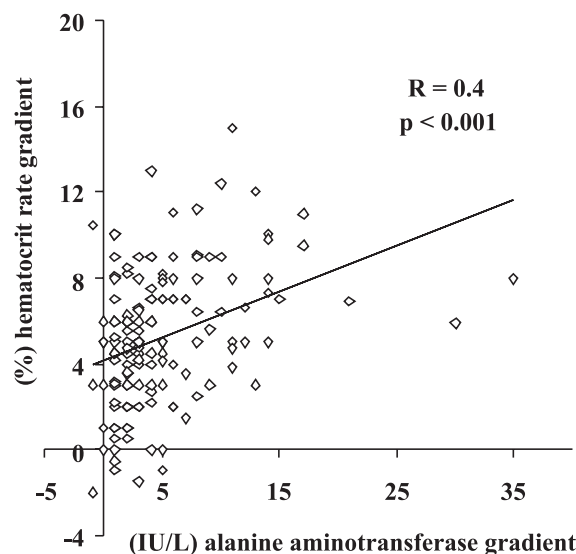
Among the 146 patients, 88 (60%) were men and 58 (40%) were women; the average age was  $48 \pm 15$  years (range 16-84 years). HCV antibodies were detected in 13 (8.9%) patients; 11 patients (7.5%) tested positive for HBsAg; and 95 patients (65%) tested positive for anti-HBs.

The mean patient weight was  $62.4 \pm 13.8$  kg (range 37-119 kg) before the HD session and  $59.2 \pm 13.3$  kg (range 36-113 kg) after the session. The mean weight reduction was  $3.3 \pm 1.3$  kg ( $p < 0.001$ ), denoting a 5.3% loss during each session (range 0-12.5%).

The mean serum ALT levels before and after the HD session were  $18.8 \pm 16.3$  IU/L and  $23.9 \pm 20.2$  IU/L, respectively, denoting an increase of 5.1 IU/L or 28.1% ( $p < 0.001$ ). The mean hematocrit rates before and after the HD were  $32.4\% \pm 4.7$  and  $37.7\% \pm 6.1$ , respectively, denoting a 5.3% increase in the hematocrit rate ( $p < 0.001$ ). This corresponded to an increase of 16.4% (Figure 1).



**Figure 1** - Mean body weight ( $p < 0.001$ ), hematocrit rate ( $p < 0.001$ ) and serum levels of alanine aminotransferase (ALT;  $p < 0.001$ ) measured before and after a hemodialysis session in 146 patients with chronic renal failure, Recife, PE, Brazil



**Figure 2** - Correlation between the serum alanine aminotransferase gradient and hematocrit rate gradient before and after a hemodialysis session in 146 patients with chronic renal failure, Recife, PE, Brazil

At the end of the HD session, 137 of the 146 patients (94%) had raised ALT levels; on the other hand, 6 patients (4%) maintained the same level, and 3 patients (2%) had decreased levels. Regarding the hematocrit rates, 137 (94%) patients had an increased hematocrit rate after the HD session; meanwhile, 4 patients (2.7%) maintained their rate, and the rate dropped in 5 patients (3.4%). Only one patient maintained the same body weight, in the other 145 patients (99.3%) the weight dropped at the end of the HD session.

The weight loss that occurred throughout the HD session exhibited an inverse correlation with the increase in both the ALT serum levels ( $r = 0.3$ ;  $p < 0.001$ ) and the hematocrit rate ( $r = 0.5$ ;  $p < 0.001$ ). A direct correlation was found for the parallel increase in the ALT and hematocrit rate ( $r = 0.4$ ;  $p < 0.001$ ) throughout the HD session (Figure 2).

To determine the ROC curves for the mean ALT values before and after the HD session, the 11 HBsAg-positive patients were excluded from the analysis (one of these was also anti-HCV positive). Among the 135 remaining patients, 80 (59%) were men, and the average age was 48 years. Among the 123 anti-HCV-negative patients, 6 (4.9%) exhibited high ALT levels before the HD session; among the 12 anti-HCV positive patients, only 1 (8.3%) exhibited high ALT levels before the HD session ( $p = 0.86$ ). After the HD session, 9 (7.3%) of the 123 anti-HCV negative patients had higher ALT levels, and 2 (16.6%) of the 12 anti-HCV-positive patients had higher ALT levels ( $p = 0.56$ ).

Among the 12 anti-HCV-positive patients, the mean ALT divided by the ULN (ALT/ULN) before and after the HD session was  $0.54 \pm 0.29$  and  $0.67 \pm 0.34$ , respectively ( $p = 0.32$ ). Among the 123 anti-HCV-negative patients, the ALT/

ULN before and after the HD session was  $0.44 \pm 0.39$  and  $0.56 \pm 0.48$ , respectively ( $p = 0.03$ ).

The best serum ALT concentration cutoff value for identifying biochemical activity in the anti-HCV positive patients before the HD session was 0.40, or 40% of the ULN. This value corresponded to 75% sensitivity, 59% specificity, and positive and negative predictive values of 15 and 96%, respectively. After the HD session, the best serum ALT concentration cutoff value for identifying biochemical activity in the anti-HCV positive patients was 0.60, or 60% of the ULN. This value corresponded to 66% sensitivity, 65% specificity, and positive and negative predictive values of 16 and 95%, respectively.

In clinical practice, we recommend that the ULN for women decreases from 40 IU/L to 16 IU/L if the ALT was collected before the HD session or to 24 IU/L if the ALT was collected after the HD session. For men, the ULN of the ALT would then decrease from 43 IU/L to 17 IU/L if collected before the HD session or to 28 IU/L if collected after the HD session (Table 1).

**Table 1** - Mean body weight (kg), serum levels of alanine aminotransferase (IU/L), and hematocrit rate (%) measured before and after a hemodialysis session in 146 patients with chronic renal failure at Recife, PE, Brazil

	Hemodialysis session		p
	Before	After	
Body weight (kg)	62.4 ± 13.8	59.2 ± 13.3	0.001
Alanine aminotransferase (IU/L)	18.8 ± 16.3	23.9 ± 20.2	0.001
Hematocrit rate (%)	32.4 ± 4.7	37.7 ± 6.1	0.001

## DISCUSSION

The serum ALT concentration is lower in patients with CRF submitted for HD treatment and is a poor predictor of HCV infection in this population. Evaluating the laboratory and histological data from 92 patients with HCV-related liver disease (46 renal transplant candidates and 46 control subjects with normal renal function), Cotler et al.<sup>13</sup> found that the serum ALT levels were significantly lower in patients with CRF. The exact reason for the lower ALT in patients with CRF needs to be fully elucidated. One possibility is due to liver cells protection by hepatocyte growth factor (HGF), which is higher concentration in patients with CRF for whom HD is recommended.<sup>14</sup> The lower ALT activity in HD patients may also be a consequence of a smaller serum HCV viral load, due to the adsorption of the virus genome in the dialyzer membrane or to the induction of endogenous interferon caused by the HD.<sup>15</sup> On the other hand, a recent article reported that HCV-infected patients with CRF submitted for HD have lower ALT levels, but the viral load and the genotype distribution are similar to those found in HCV-infected patients with normal renal function.<sup>16</sup>

Another hypothesis to explain the lower serum levels of ALT in patients with CRF could be the severity of the impairment of renal function induced by glomerular damage. In fact, Fabrizi et al.<sup>7</sup> found significantly lower serum ALT activity in patients on chronic HD than in pre-dialysis patients with CRF, and they reported a correlation between the reduced ALT activity and the degree of renal function in these patients. In a large cohort of pre-dialysis patients,<sup>17</sup> the HCV-infected patients had significantly higher ALT levels compared to the non-infected patients, and the accuracy of the ALT in detecting the HCV infection was 92%. Thus, Lemos et al.<sup>17</sup> have suggested that the serum ALT level in pre-dialysis patients may be a good marker of HCV infection.

Hung et al.<sup>18</sup> evaluated 90 patients on continuous ambulatory peritoneal dialysis (CAPD) and 526 healthy adults and found a mean ALT concentration of 15 IU/L in the CAPD patients as opposed to 22 IU/L in the control group ( $p < 0.0001$ ). Such data support the fact that patients with CRF have lower levels of ALT, regardless of HD.

In the present study, the ALT levels also increased significantly after the HD session in both patient groups (with and without anti-HCV). This increase may be a

consequence of the loss of liquid during the session, thereby correcting the prior hemodilution. This premise is reinforced by the direct correlation found between the ALT gradient and the hematocrit rate throughout HD and the inverse correlation between the ALT gradient and the weight loss during the HD session. Furthermore, Conway et al.<sup>19</sup> evaluated the serum cardiac troponin levels in patients undergoing chronic HD and found that the concentration of this enzyme was significantly higher after the HD session as compared to before the session. The authors suggested that this rise in troponin levels following HD was probably due to hemoconcentration, as was also detected with the hematocrit rate in the same study.

The possibility that the rise in the ALT levels is due to hemodilution correction following the HD sessions does not explain the reduced ALT levels in the CAPD patients, who theoretically would not have hemodilution. Another possibility to explain the lower serum levels of ALT in patients with CRF could be hypotension-induced liver cell injury during the HD session. However, ischemic hepatitis is generally related to hepatocyte necrosis and these patients exhibit a higher serum ALT concentration than that found in our patients. Perhaps hemodilution also contributes to the reduction in the ALT levels before the session in patients with CRF requiring regular HD therapy. In the present study, we detected an approximately 25% increase in the serum ALT levels after the HD session, but this increase was not sufficient to exceed the conventional ULN value. In fact, after HD, only 2 of the 12 patients (16.6%) with chronic HCV infection had ALT concentrations above the conventional ULN, thereby supporting the need for a lower ALT cutoff value.

In conclusion, the present study has revealed that most of the CRF patients submitted to chronic HD treatment had serum ALT concentrations below the ULN, even though these levels were higher than in patients on HD without HCV infection. The ALT levels, however, underwent a significant increase after the HD session, probably due to the correction in hemodilution, as was also observed with the hematocrit rate. Therefore, by reducing the ALT cutoff value to about 60% of the previously established value and collecting the blood sample after the HD session, it is possible to better identify patients with hepatocellular damage. Further studies, however, are needed in order to validate the reduced ULN for the serum ALT concentration in clinical practice.

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