

# Liver enzymes serum levels in patients with chronic kidney disease on hemodialysis: a comprehensive review

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We reviewed the literature regarding the serum levels of the enzymes aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase in patients with chronic kidney disease on hemodialysis with and without viral hepatitis.

Original articles published up to January 2013 on adult patients with chronic kidney disease on hemodialysis were selected. These articles contained the words "transaminases" "aspartate aminotransferase" "alanine aminotransferase" "gamma glutamyl transferase," "liver enzymes", AND "dialysis" OR "hemodialysis".

A total of 823 articles were retrieved. After applying the inclusion and exclusion criteria, 49 articles were selected. The patients with chronic kidney disease on hemodialysis had reduced serum levels of aminotransferases due to hemodilution, lower pyridoxine levels, or elevated homocysteine levels. The chronic kidney disease patients on hemodialysis infected with the hepatitis C virus also had lower aminotransferase levels compared with the infected patients without chronic kidney disease. This reduction is in part due to decreased viremia caused by the dialysis method, the production of a hepatocyte growth factor and endogenous interferon- $\alpha$ , and lymphocyte activation, which decreases viral action on hepatocytes. Few studies were retrieved on gamma-glutamyl transferase serum levels; those found reported that there were no differences between the patients with or without chronic kidney disease.

The serum aminotransferase levels were lower in the patients with chronic kidney disease on hemodialysis (with or without viral hepatitis) than in the patients with normal renal function; this reduction has a multifactorial origin.

**KEYWORDS:** Transaminases; Aspartate Aminotransferase; Alanine Aminotransferase; Gamma-Glutamyl Transferase; Dialysis.

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## ■ INTRODUCTION

The serum levels of the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) are markers of aggression against hepatocytes (1). Thus, they are elevated in several diseases, such as chronic viral hepatitis (2), non-alcoholic fatty liver disease (3), autoimmune hepatitis (4), hemochromatosis (5), and alcoholic liver disease (6). These enzymes assist in diagnosis and patient follow-up and response to treatment because they reflect inflammatory activity in the parenchyma of the liver (7–9).

The prevalence of hepatitis C virus (HCV) infection is significantly higher in hemodialysis (HD) patients than in the general population (10); this disease is associated with an increased mortality rate primarily due to hepatocellular carcinoma and liver cirrhosis (11,12). The prevalence of HCV infection in HD patients varies greatly between regions of the world and even within the same country (13). The prevalence rates of hepatitis C are 5.5% for dialysis patients in Brazil, 14.4% for those in the United States, and 68% for those in Saudi Arabia (13–15). Although HCV infection results in an increase in ALT, these levels are generally lower in hemodialysis patients.

Interestingly, some studies have shown that patients with chronic kidney disease (CKD) on HD may have lower serum levels of liver enzymes than those with normal renal function for reasons that remain unclear (16,19). This profile may adversely affect the diagnosis, clinical management, and treatment of liver disease in these patients.

The objective of this study was to review the literature to assess the serum levels of GGT and the reasons that favor

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lower levels of ALT and AST in CKD patients undergoing HD. The evaluation of alkaline phosphatase was excluded from this review because this enzyme has a "bone fraction" and is involved in the disturbances of bone mineral metabolism that occur in CKD patients.

## METHODS

A review of the literature was performed using the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Latin American and Caribbean Literature on Health Sciences (LILACS), the Scientific Electronic Library Online (SciELO), and the COCHRANE virtual library. The searches were performed in December 2012 and January 2013.

For each search, a specific strategy was drawn up for crosschecking the Medical Subject Headings (MeSH) terms and the free terms (FTs) that were not found in MeSH but were of relevance to the research.

The following descriptors were used separately: "hemodialysis"[All Fields] AND "liver enzymes"[All Fields] AND "humans"[MeSH Terms]; "hemodialysis"[All Fields] AND "aspartate transaminase"[All Fields] AND "humans"[MeSH Terms]; "hemodialysis"[All Fields] AND "gamma-glutamyltransferase"[All Fields] AND "humans"[MeSH Terms]; "hemodialysis"[All Fields] AND "alanine transaminase"[All Fields] AND "humans"[MeSH Terms]; "dialysis"[All Fields] AND "liver enzymes"[All Fields] AND "humans"[MeSH Terms]; "dialysis"[All Fields] AND "aspartate transaminase"[All Fields] AND "humans"[MeSH Terms]; "dialysis"[All Fields] AND "gamma-glutamyltransferase"[All Fields] AND "humans"[MeSH Terms]; "dialysis"[All Fields] AND "alanine transaminase"[All Fields] AND "humans"[MeSH Terms].

## Selection criteria

The inclusion criteria required that the studies utilized adult human patients with CKD on HD; that they had a publication date prior to January 2013; and that they were written in Portuguese, English or Spanish. Relevant articles cited in the references of those initially selected were also included. The exclusion criteria included articles that involved patients with acute kidney injury; articles that primarily described the prevalence, routes of transmission, and treatment of hepatitis; articles reporting medicamentous or exogenous toxicity or those involving transplant patients. Articles with a primary focus on the treatment of viral hepatitis were excluded because this treatment could influence the aminotransferase serum levels and, therefore, the physiopathological "non-elevation" of the relevant enzymes.

## RESULTS

A total of 823 articles were retrieved. After reading the title, 215 were excluded for not fitting the inclusion criteria. Another 472 articles matched the exclusion criteria and were removed from the analysis. Of the remaining 136 articles, another 41 articles were excluded after reading the abstracts (Figure 1). After this step, another 46 articles that were repeated within databases were identified and excluded. A total of 49 complete original articles were then analyzed. Of these, 6 matched the exclusion criteria and were excluded, leaving a total of 43 articles. Subsequently, 6 articles were

selected from the references of those already included because they were considered relevant. This left a total of 49 articles.

Due to the heterogeneity of the studies and the predominance of articles involving liver enzymes in patients with viral hepatitis, the results were didactically divided into two topics to enhance the understanding of the analysis. One topic was on liver enzymes in CKD patients on HD without hepatitis virus infection, and the other was on the serum levels of the liver enzymes in patients with such an infection.

## DISCUSSION

### Liver enzymes in CKD patients on hemodialysis

**Aminotransferases.** Since the 1970s, studies have shown that AST and ALT serum levels were decreased in CKD patients undergoing HD. It was hypothesized that this reduction could be caused by factors such as the withdrawal of aminotransferases during the HD session; the high lactate serum levels, which, during biochemical dosages, would rapidly consume Nicotinamide Adenine Dinucleotide Phosphate (NADPH) and result in low levels of aminotransferases; the presence of uremic factors that would inhibit the activity of these enzymes; and, finally, the deficiency of pyridoxine, a cofactor for the synthesis of the aminotransferases (20,21).

In assessing the possibility of this pyridoxine deficit, in the 1980s, Jung et al. evaluated the levels of aminotransferases in CKD patients on HD and did not observe differences between the values prior to and after the addition of pyridoxal 5'-phosphate (PLP), an active form of pyridoxine, to the chemical reaction for the dosage of these enzymes (18). Similarly, Gressner et al. evaluated 26 patients undergoing HD and found no relationship between the fluctuations of the plasma levels of PLP (pPLP) and ALT or AST serum levels (19).

Later, in the 1990s, Ono et al. performed a prospective study in which they administered pyridoxine (30 mg/day) to 52 CKD patients on HD for 5 weeks. Prior to supplementation (Day 0), 17 patients (33%) had deficient pPLP levels (Group 1), and the other 35 patients had normal pPLP values (Group 2). There were positive correlations between pPLP and AST levels ( $r=0.57$ ;  $p<0.01$ ) and between pPLP and ALT levels ( $r=0.68$ ;  $p<0.01$ ). The mean serum levels of AST ( $9.2 \pm 0.3$  vs.  $13.4 \pm 0.7$  U/L) and ALT ( $8.6 \pm 0.6$  vs.  $11.4 \pm 0.9$  U/L) were significantly lower in Group 1 than in Group 2. These researchers concluded that the low AST and ALT levels in patients on HD were partly due to a deficiency in pyridoxine, which serves as a coenzyme in the synthesis of the aminotransferases (20).

However, Yasuda et al. did not find a serum deficiency of pyridoxine in a group of 305 CKD patients on HD when compared with 556 healthy individuals, thereby putting the role of pyridoxine as a factor in the reduction of aminotransferase serum levels to question. Nevertheless, the average respective AST and ALT serum levels were  $9.2 \pm 2.4$  and  $7.4 \pm 1.7$  IU/L in those undergoing HD and  $22.7 \pm 5.4$  and  $18.0 \pm 4.0$  IU/L in healthy subjects ( $p<0.001$  in both comparisons).

Therefore, the only study that demonstrated an association between pyridoxine and aminotransferase levels was performed by Ono et al; this study was prospective and interventional (20). However, the influence of pyridoxine in

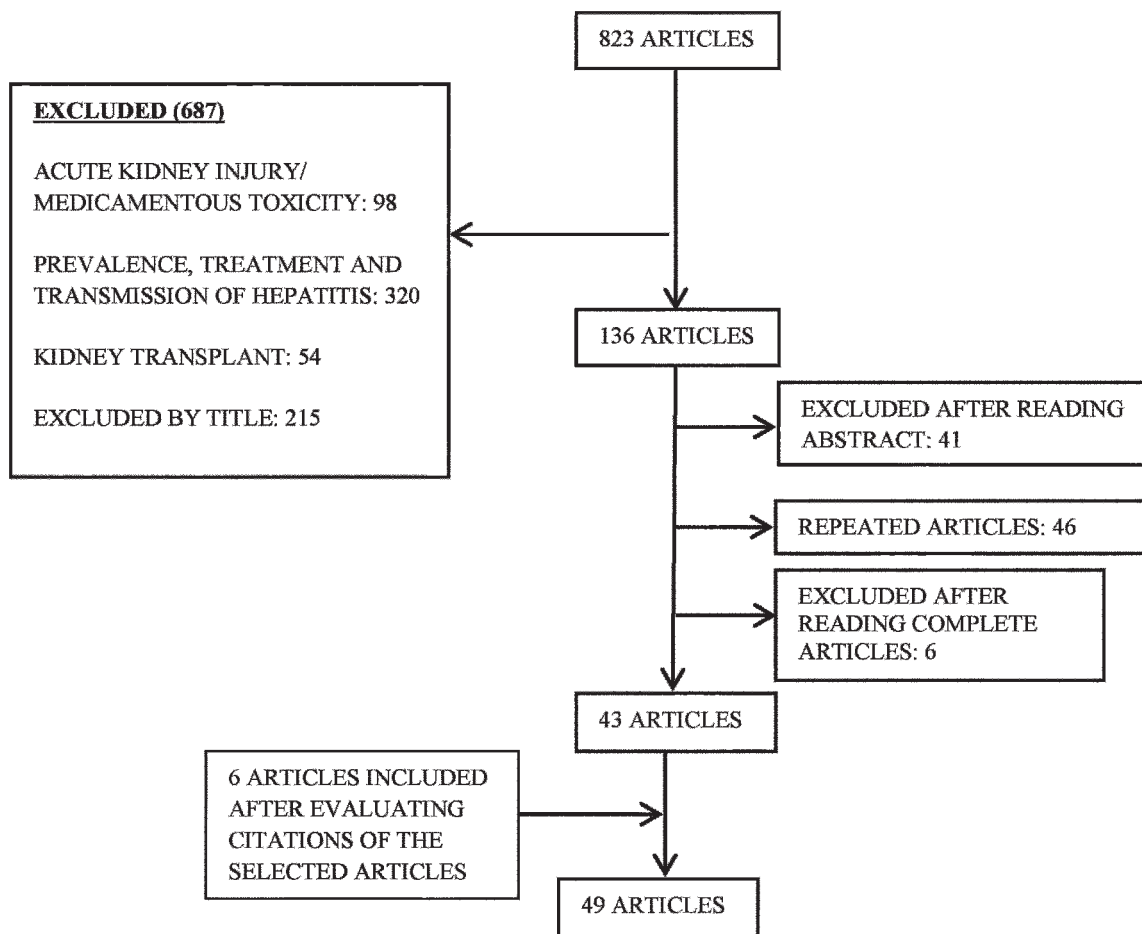


Figure 1 - Flow chart of article selection performed for the systematic review, 2013.

low serum aminotransferase levels remains uncertain, and the largest and most recent study found no such association (22). Therefore, a prospective double-blind randomized trial has been proposed to evaluate the supplementation of pyridoxine as a factor that influences the aminotransferase levels in HD patients.

In this same study, Yasuda et al. collected serum aminotransferases prior to and after HD sessions and observed a 15-35% increase after dialysis, which supports the hypothesis of hemoconcentration for the rise in aminotransferases observed after the dialysis procedure (22).

We have described an association between weight loss (ultrafiltration) during HD and increased serum ALT levels in 146 patients with CKD. The average weight loss in these patients was 5.3%, and the mean ALT levels prior to and after HD were 18.8 and 23.9 IU/L, respectively, an increase of 28.1%. The weight loss was inversely correlated with the increase in the ALT level ( $r=0.3$ ;  $p<0.001$ ) (23). Subsequently, this hypothesis was also corroborated by Liberato et al., who found lower serum levels of ALT but also of AST and GGT prior to HD compared with after HD (16).

More recently, Sombolos et al. evaluated 53 CKD patients on HD and divided them into three groups: HD, isolated ultrafiltration, and euvolemic HD (without the removal of fluids) and verified the effects of hemodilution in the serum

levels of the aminotransferases. In the patients who underwent euvolemic HD, there were no differences between the ALT and AST levels prior to and after the procedure. However, when an isolated ultrafiltration or HD was performed, there was an increase in the aminotransferase levels when compared with the values prior to and after the procedure (24). The authors concluded that the rise in the aminotransferase serum levels after HD should primarily occur due to the hemoconcentration induced by the ultrafiltration; they indicated that this increase could not be attributed to the removal of inhibitors of the enzymatic activity of aminotransferases, as previously hypothesized (17,21). Multicenter studies could potentially confirm the hypothesis of hemodilution.

Huang et al. evaluated the homocysteine serum levels in 145 patients on HD. All patients had elevated homocysteine levels, which were inversely related to the AST levels ( $r=0.4$ ;  $p<0.001$ ). There was no relationship between serum homocysteine and ALT levels. Thus, the AST serum levels may reflect the high metabolic activity of homocysteine (25). To further explore this possibility, a larger group of patients should be tested.

Some authors raised the possibility that the aminotransferase serum levels were not related to the dialysis method. Hung et al. evaluated 90 patients on peritoneal dialysis and 526 healthy adults and reported an average ALT concentration of 15 IU/L in the peritoneal dialysis patients compared



with 22 IU/L in the control group ( $p < 0.0001$ ) (26). These data support the hypothesis that CKD patients have lower levels of ALT regardless of the dialysis method.

Subsequently, some researchers have suggested that the aminotransferase serum levels could be reduced even during conservative treatment at earlier stages of CKD. Fabrizi et al. evaluated 407 patients with CKD before they initiated dialysis, 171 patients on dialysis, and 431 healthy controls and observed that the CKD patients on dialysis had decreased AST ( $19.7 \pm 11.2$  IU/L vs.  $20.4 \pm 6.8$  IU/L;  $p = 0.00001$ ) and ALT ( $19.5 \pm 15.1$  IU/L vs.  $21.7 \pm 11.3$  IU/L;  $p = 0.00001$ ) serum levels compared with the healthy controls. Similarly, patients on dialysis had lower aminotransferase serum levels than CKD patients under conservative treatment (AST,  $17.9 \pm 8$  IU/L vs.  $16.6 \pm 11.6$  IU/L;  $p = 0.01$ , and ALT  $17.9 \pm 8$  IU/L vs.  $16.3 \pm 9.4$  IU/L;  $p = 0.04$ , respectively) (27).

Therefore, CKD patients have reduced aminotransferase serum levels, and this reduction appears to occur prior to dialytic treatment.

**Gamma glutamyl transferase.** Between 1975 and 2012, we found only three articles about GGT serum levels in CKD patients on HD without viral hepatitis. In 1975, for the first time, Fine et al. evaluated GGT serum levels in 32 CKD patients and reported high levels of this enzyme in 37% of cases (28).

However, in more recent studies, other authors have shown that GGT serum levels in CKD patients on HD are similar to those of patients with normal renal function (29,30). Fabrizi et al. evaluated GGT serum levels in 573 dialysis patients and 343 healthy patients and reported average values of 25.8 and 23.3 IU/L, respectively ( $p = 0.081$ ). After correcting for sex, race, and age, no significant difference in GGT levels was observed between the two groups (30).

In contrast, in light of the hypothesis of hemodilution, our group evaluated 40 CKD patients on HD and performed GGT serum dosage immediately prior to and after the dialysis procedure. When divided by the upper limit of normal (ULN), the GGT serum levels were 0.88 IU/L prior to HD and 1.14 after HD ( $p = 0.001$ ), which is compatible with the increase in the hematocrit serum levels, thus characterizing hemoconcentration (Ht before HD, 36.7%; after HD, 41.3%,  $p < 0.001$ ) (16). Therefore, after the dialysis procedure, the mean GGT values were higher than those of the ULN, suggesting that the serum levels of this enzyme could be reduced in CKD patients prior to the HD session.

Ultimately, GGT serum levels in CKD patients on HD are not as reduced as the aminotransferase serum levels but are possibly also influenced by hemodilution due to the liquid retention of CKD patients.

### Liver enzymes in CKD patients on hemodialysis with viral hepatitis

**Aminotransferases.** As expected, the CKD patients on HD infected with HCV have higher aminotransferase serum levels than those on HD who are not infected (31,35), e.g., CKD patients on HD who are also infected with HCV have lower aminotransferase levels than infected patients who do not have CKD (36–39).

Cotler et al. evaluated the histological and laboratory data of 92 patients with HCV (46 renal transplant candidates on HD and 46 control subjects with normal renal function) and

found that the ALT serum levels were lower ( $p < 0.001$ ) in the CKD patients on HD than in the controls (40).

The lower aminotransferase levels complicate the proper assessment and clinical management of HD patients infected with HCV and hepatitis B virus (HBV) (41,42).

The lower elevation of aminotransferase serum levels in CKD patients on HD with viral hepatitis could be due to other factors in addition to those related to CKD alone, as previously discussed (Figure 2).

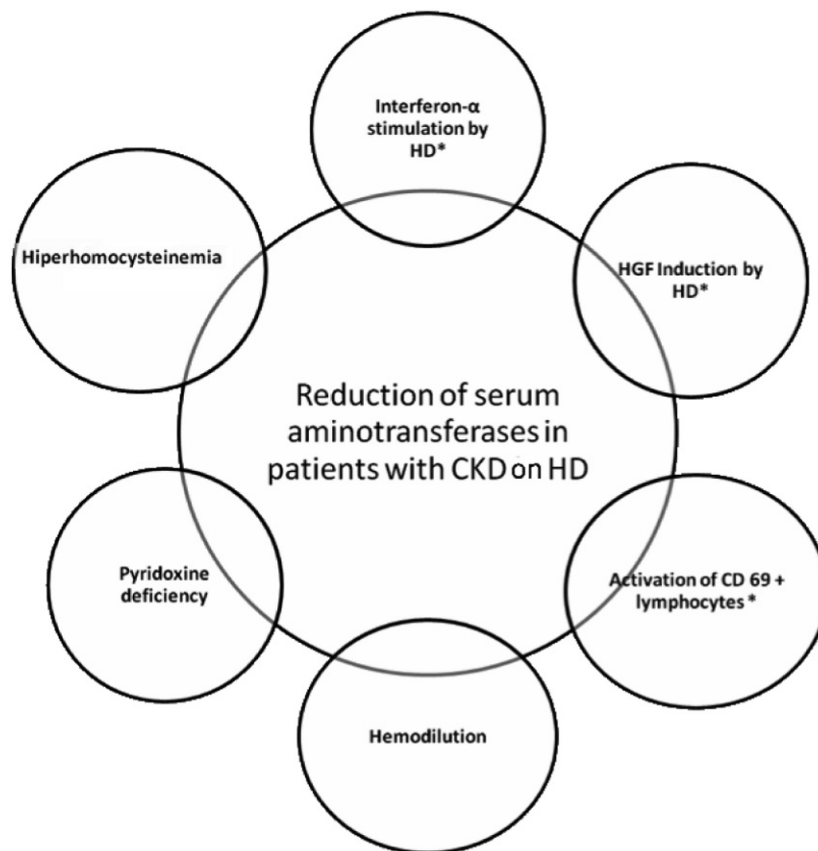
One possible factor could be the reduction of viremia as a result of the dialysis procedure. Tseng et al. evaluated 30 patients infected with the HBV and quantified the viremia (HBV-DNA) immediately prior to and after the dialysis session. The average levels of HBV-DNA were higher prior to the HD session ( $3.823 \pm 1.130$  Log<sub>10</sub> copies/mL) than after it ( $3.686 \pm 1.114$  Log<sub>10</sub> copies/mL) ( $p = 0.004$ ) (42).

Similarly, Baedalamnti et al. evaluated viremia in 11 CKD patients on HD with HCV infection. The dosages were taken before, immediately after, and 24 and 48 hours after the end of the HD session. HCV-RNA levels decreased in all patients after dialysis (range 3% to 95%,  $p = 0.001$ ); thereafter, they increased progressively and returned to baseline at 48 hours after dialysis (before HD session,  $824 \pm 234$ ; immediately after,  $633 \pm 178$ ; 24 hours after,  $758 \pm 213$ ; and 48 hours after,  $776 \pm 226$  copies/mL  $\times 10^3$ ). Immediately after HD, the viral load levels were lower than those prior to the procedure ( $p = 0.005$ ) (43).

Additionally, Kaiser et al. evaluated the viremia and serology of HCV-infected patients during 20 HD sessions and demonstrated both anti-HCV and HCV-RNA decline during the dialysis procedure. They also observed that there was a linear 77% reduction in anti-HCV titers during the HD session and a 73% reduction of HCV-RNA at the end of the HD session. However, the reduction in viremia was observed only in the last two hours of dialysis. These authors suggested that the serum levels of HCV-RNA and anti-HCV titers should be regulated or removed independently during dialysis and that HD could be a beneficial therapy when combined with antiviral therapy (44).

Although the dialysis procedure reduces the viral load, patients on HD infected with HCV may not present lower viral loads than those with normal renal function. In evaluating 66 patients on HD infected with HCV and 264 patients also infected but with normal renal function, Azevedo et al. did not observe any differences in viremia levels between the two groups ( $5.3 \times 10^5$  IU/mL in the group on HD and  $6.6 \times 10^5$  IU/mL in the group with normal renal function,  $p = 0.23$ ) (45). Perhaps, the fact that the samples were collected before hemodialysis session, where the viral load is higher, has contributed to these findings.

Another factor involved in the reduction of aminotransferase serum levels could be the increased production of hepatocyte growth factor (HGF) induced by HD; this substance stimulates hepatocyte mitogenesis, accelerates liver regeneration, and protects the liver from toxins (46). Rampino et al. evaluated 10 HD patients with HCV and measured HGF before, during (15 min), immediately after, and 24 hours after the end of dialysis and compared the results with those from HCV-infected patients who were not on HD. The HGF serum levels were similar in both groups prior to the procedure (mean, 0.17 ng/mL). However, after dialysis, the HGF serum levels increased significantly in the HD patients compared with patients not on dialysis (5.51 and 2.67 ng/mL during and after de HD session,



**Figure 2** - Factors involved in aminotransferase reduction in patients with chronic kidney disease on hemodialysis, 2013. \*Patients infected with viral hepatitis. HGF: hepatocyte growth factor; CKD: chronic kidney disease; HD: hemodialysis.

respectively;  $p < 0.001$ ). It should be noted that even 24 hours following the procedure, the HGF serum levels of the patients on HD were higher than those of the patients who were not on HD (0.41 ng/mL,  $p < 0.05$ ) (46).

Similarly, Baedalamnti et al. evaluated the serum levels of alpha interferon (IFN- $\alpha$ ), a cytokine with antiviral and immunomodulatory properties, in 11 CKD patients on HD who had been infected with HCV. The dosages were performed prior to, immediately after, and 24 and 48 hours after the end of the HD session. There was a significant rise in the serum levels of IFN- $\alpha$  in 10 of 11 patients; the values returned to baseline levels after 48 hours (43). This behavior suggests that a hemodialysis session induces IFN- $\alpha$  production, which could reduce HCV viremia and, consequently, aminotransferase levels in the serum.

Maia et al. evaluated lymphocyte activation by measuring the percentages of CD69+ lymphocytes of patients infected with HCV and on HD; they observed a negative relationship between ALT levels and lymphocyte activation in those infected with HCV ( $r = 0.56$ ;  $p = 0.05$ ). These authors suggested that lymphocyte activation could be a protective factor against HCV and, therefore, against liver injury (43).

Thus, the increase in IFN- $\alpha$  serum levels and lymphocyte activation arising from the HD session indicate that CKD patients on HD who are infected with HCV present a more pronounced viremia reduction immediately after the session. Associated with the HGF induction, these patients present an indolent course of the disease and less severe histological lesions compared with patients not on HD (38,47,48).

Although biochemical tests are not cost-effective compared with virological tests in detecting new cases of acute hepatitis C (49), aminotransferases are predictors of the acute form of hepatitis due to the large increases in their serum levels in this context (50,51). However, ALT serum levels are not accurate in the diagnosis of chronic HCV infection (50). After evaluating 2,440 CKD patients on HD, Saab et al. demonstrated that a recent rise in ALT serum levels provided neither sensitivity (21%) nor an adequate positive predictive value (16%) to diagnose “chronic” HCV infection (50).

Due to the reduced accuracy of ALT in the diagnosis of chronic hepatitis in CKD patients on HD, several authors have sought new cut-off values to improve sensitivity and specificity and to establish more reliable ALT serum level values that could be related to histological and virological activity responses (52,55). To do so, reductions of the ULN of ALT have been tested to improve their accuracy in diagnosing aggression against hepatocytes.

After evaluating 202 CKD patients on HD, 15 (7.4%) of whom were anti-HCV-positive, our group determined that the cut-off value for ALT stood at 60% of ULN, with a sensitivity of 67% and specificity of 75% in identifying anti-HCV-positive patients (54). We observed a similar reduction when evaluating 217 patients on HD, 18 (8.3%) of whom were anti-HCV-positive, and 17 (7.8%) of whom were also HCV-RNA-positive. The cut-off value of ALT to distinguish the anti-HCV-positive from negative patients was 50% of the ULN (sensitivity = 67%; specificity = 83%). According to



the HCV-RNA, the cut-off value for ALT was 45% of ULN with a sensitivity of 71% and a specificity of 80% (53). Therefore, we concluded that the reduction of the ULN of ALT could increase the accuracy for the diagnosis of chronic HCV infection in CKD patients on HD.

Guh et al. performed a study in Taiwan with 217 patients on HD (including patients with HBV and HCV) and 804 controls and showed that the serum levels of the aminotransferases could not be used to detect patients with positive hepatitis B surface antigen (HBsAg). However, the best cut-off values for detecting the presence of anti-HCV were 18 IU (40% of the ULN) for AST (sensitivity = 73.8% and specificity = 55.4%) and 16 IU for ALT (40% of the ULN) (sensitivity = 61.2% and specificity = 73%). The authors proposed reductions of 45% for the ULN of AST and 34% for the ULN of ALT to improve the diagnostic accuracy of anti-HCV (52).

Caramelo et al. evaluated 22 patients with CKD on HD with negative anti-HCV and positive HCV-RNA by PCR and showed that the ALT and AST serum levels may be useful in the diagnosis of HCV infection in places where the HCV-RNA survey is not available. These authors used second-generation enzyme-linked immunosorbent assay (ELISA) and detected HCV-RNA in 28.2% of the patients who were negative for anti-HCV. Within the group of negative anti-HCV patients, the average AST and ALT values were higher ( $p < 0.001$  and  $p < 0.001$ ) in the cases of positive HCV-RNA than in those with negative HCV-RNA (56).

Other authors investigated the correlation between aminotransferases and viremia and demonstrated an association between HCV-RNA and AST and ALT serum levels (31,37,55,57). Fabrizi et al. demonstrated that patients with positive HCV-RNA presented higher AST ( $p < 0.008$ ) and ALT ( $p < 0.0001$ ) serum levels than those observed in HCV-RNA-negative patients (31). Likewise, Espinosa et al. demonstrated that ALT serum levels could be predictors of viremia in CKD patients on HD who are anti-HCV-positive. In this study, ALT serum levels above 27 IU showed 50% sensitivity and 100% specificity in the detection of viremia (57). When Milotic et al. used this same ALT value, they found differences ( $p < 0.05$ ) between patients with positive HCV-RNA (40%) and negative HCV-RNA (9.6%). However, 60% of the patients with positive HCV-RNA also presented ALT serum levels below 27 IU (55).

Likewise, Fabrizi et al. found that patients infected with HBV and with positive HBV-DNA presented aminotransferase serum levels that were higher than the negative HBV DNA levels: AST  $22.8 \pm 31.3$  IU/L *vs.*  $14.2 \pm 9.7$  IU/L ( $p = 0.00001$ ); ALT  $25.0 \pm 41.6$  IU/L *vs.*  $13.9 \pm 41.6$  IU/L ( $p = 0.00001$ ) (39).

In contrast, Li et al. evaluated 32 CKD patients on HD who were anti-HCV-positive. Of these, 12 patients (37.5%) were HCV-RNA-positive and 20 (62.5%) were negative. The average ALT serum levels were  $15.4 \pm 6.4$  IU/L in patients positive for HCV-RNA and  $14.8 \pm 6.4$  IU/L in patients negative for HCV-RNA ( $p = 0.793$ ), i.e., the presence or absence of viremia did not affect the ALT serum levels in CKD patients on HD with anti-HCV (58). The number of patients in each subgroup of this study was potentially insufficient to reveal any differences.

As in patients with preserved renal function, aminotransferases alone did not present any relationship to liver histology in patients on HD who were infected with HCV

(59,60). However, the degree of hepatic fibrosis can be estimated using the ratio between the AST serum levels and the number of platelets (AST-to-Platelet Ratio Index or APRI). Schiavon et al. evaluated 203 CKD patients on HD with chronic HCV and found advanced liver fibrosis (F2, F3, or F4) via the METAVIR classification in 24% of these patients. The area under the receiver operating characteristic (ROC) curve for the APRI was 0.81. In patients with an APRI of less than 0.40, it was reliably possible to identify the patients with no or mild liver fibrosis (F0 or F1). These authors stated that, according to the APRI score, approximately half of the biopsies could have been avoided (61). These results were also corroborated in a study with 279 patients conducted by Liu et al. in which the APRI could be used to correctly predict the fibrosis level in 60% of the patients (62).

**Gamma glutamyl transferase.** In CKD patients on HD, GGT serum levels may be a useful and low-cost marker, similar to aminotransferases, in the diagnosis of chronic HCV infection (63). However, four articles were found in the literature regarding GGT serum levels in CKD patients on HD with viral hepatitis.

Fabrizi et al. identified an association by performing a multivariate analysis between GGT serum levels and hepatitis via HBV or HCV. After analyzing the ROC curve, these authors determined that the best cut-off values to predict positive HBsAg and anti-HCV would be 23 IU/L (sensitivity = 62%; specificity = 62%) and 18 IU/L (sensitivity = 61%; specificity = 50%), respectively. These GGT values represent ULN reductions of 54% and 64% (50 IU/L) for the detection of HBsAg and anti-HCV, respectively. The authors suggested that GGT levels should be measured monthly for HD patients, as is performed for ALT (30).

Souza et al. also reported higher GGT serum levels in HD patients with HCV infection than in those negative for anti-HCV ( $49.8 \pm 56.6$  IU/L and  $94.8 \pm 105$  IU/L, respectively) ( $p < 0.05$ ). These authors suggested the use of GGT serum levels as an indirect marker to detect liver disease in these patients (64).

In conclusion, patients with CKD on HD have reduced serum aminotransferase levels. The reasons for this reduction remain unclear; however, they likely begin before dialysis and are due in part to hemodilution in patients before dialysis, lower pyridoxine serum levels, and higher homocysteine levels.

CKD patients who are on HD and infected with HBV or HCV also present reduced aminotransferase levels compared with patients with these infections who do not have CKD. This reduction is due to factors related to CKD and the reduced viremia caused by dialysis, the production of HGF and endogenous INF- $\alpha$ , and the lymphocyte activation induced by HD, which together could decrease viral action in the liver tissue. However, due to both the small number of patients evaluated and the specificity of HGF, endogenous INF- $\alpha$ , and lymphocyte activation, further studies are needed to confirm these hypotheses. Reducing the ULN of ALT to levels that are approximately 60% of current levels could more accurately indicate the CKD patients on HD with viral hepatitis.

There are few studies on GGT serum levels in patients with CKD undergoing HD, which makes it difficult to draw further conclusions. The GGT serum levels in CKD patients on HD are apparently similar to those of patients with preserved renal function. However, the GGT serum levels



may be elevated due to the increased oxidative stress induced by CKD or the use of medications. This increase would not be as significant due to the reduction in GGT serum levels induced by hemodilution. As with aminotransferases, GGT serum levels appear to be useful in the identification of viral hepatitis during the follow-up of CKD patients on HD. Nonetheless, further studies are necessary to better evaluate GGT serum levels in CKD patients on HD.

Finally, it was confirmed that, with or without HCV infection, serum aminotransferases are reduced in patients with CKD on HD. Hemodilution is involved in this reduction; other factors, such as pyridoxine deficiency or increased homocysteine, may also be involved. In HCV-infected patients, the serum levels of these enzymes are potentially decreased due to the reduction of the viral load that results from the induction of endogenous HGF and interferons (and the activation of lymphocytes). Further studies are required to investigate the reduction of HCV viremia and the involvement of pyridoxine and homocysteine in patients with CKD on HD.

The serum aminotransferase levels of are lower in CKD patients on HD (with or without viral hepatitis) than in individuals with normal renal function; this difference is related to factors such as hemodilution, pyridoxine deficiency and hyperhomocysteinemia and, in patients with viral hepatitis, is associated with HGF elevation, CD69+ lymphocyte induction, and increased interferon- $\alpha$  production.

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## AUTHOR CONTRIBUTIONS

The work presented here was performed in collaboration between all authors. Dr. Sette and Lopes were responsible for the conception, design, and acquisition of data, along with their analysis and interpretation. Both authors performed a literature review separately, and the articles were selected jointly.

Both authors have contributed to, seen, and approved the final manuscript.

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