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Review

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The influence of hemodialysis on FibroTest parameters

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Abstract

Chronic hepatitis C viral infection is an important cause of morbidity and mortality in patients with end-stage renal disease treated with hemodialysis. Liver fibrosis represents a main determinant of liver disease prognosis and clinical management, and its assessment by liver biopsy can decide treatment allocation. Although liver biopsy is the gold standard for staging liver fibrosis, it is an invasive procedure associated with complications that are more prevalent in patients with end-stage renal disease. FibroTest represents a surrogate marker of fibrosis which evaluates the levels of apolipoprotein A1, total bilirubin, haptoglobin, gamma-glutamyltransferase and α2-macroglobulin, generating a score that indicates the level of fibrosis. Discrepancies were observed in clinical practice between FibroTest score and histopathological findings. The aim of this study was to evaluate how hemodialysis influences the level of each FibroTest parameter and the final score. The systematic literature review conducted by us suggests that hemodialysis induces a reduction in apolipoprotein A1, haptoglobin and bilirubin levels, with an increase in gamma-glutamyltransferase and alpha-2-macroglobulin levels. In conclusion, hemodialysis modifies the levels of FibroTest parameters, suggesting that it may also have an impact on the accuracy of liver fibrosis assessment in hemodialysis patients.

Keywords: *hemodialysis, apolipoprotein A1, bilirubin, alpha-2-macroglobulin, haptoglobin, gamma-glutamyltransferase*

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Introduction

Hemodialysis (HD) patients are at high risk of acquiring hepatitis C virus (HCV). The prevalence of chronic viral hepatitis C is high in this population (up to 60%) due to nosocomial spread (1,2).

Patients undergoing HD have a higher prevalence of HCV infection than the general population. Despite the development of effective direct-acting antiviral agents for the treatment of hepatitis C, acquisition of HCV continues to occur in dialysis centers worldwide (3).

In Romania, the most prevalent HCV genotype is genotype 1, 93.46% of patients having the genotype 1B (4).

Among the eligibility criteria, the level of fibrosis is an important factor (5). Liver biopsy is still considered the gold standard for the staging of fibrosis and the evaluation of necroinflammatory activity, despite its limitations: invasive, it does not allow a dynamic evaluation of fibrosis and life-threatening complications (6,7). Also, this reference method is associated with up to 20% diagnostic errors in the staging of the disease (8). In addition, nephrologists hesitate to indicate liver biopsy in patients with end-stage renal disease (ESRD) because of platelet dysfunctions and the significant risk of hemorrhage. The severity of fibrosis can be estimated using biochemical indices such as serum hyaluronic acid (9,10), the aspartate aminotransferase-to-platelet ratio index (APRI), the aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, the Fibrosis 4 (Fib-4) score, FibroTest (11,12), and the measurement of liver stiffness with transient elastography (FibroScan) (13,14).

The novelty of this review consists of evidencing the main variations of each parameter used in calculating the FibroTest score in hemodialysis patients, and how these changes may influence the final score (stage of fibrosis). FibroTest (FT) is a surrogate marker of fibrosis and it combines the determination of serum levels of α_2-macroglobulin (α_2M), haptoglobin, apolipoprotein A1 (ApoA1), total bilirubin (TB), gamma-glutamyltransferase (GGT) to assess the level of liver fibrosis. Total bilirubin, α_2M and GGT concentrations significantly increase with severe fibrosis, whereas haptoglobin and ApoA1 levels decrease (15).

Imbert-Bismut et al. reported that the FT score in HCV patients had a high negative predictive value (100% certainty of absence of significant fibrosis (F2-F4)) for scores $\leq$0.1, and a high positive predictive value (91% certainty of presence of significant fibrosis) for scores $\geq$0.6. In such clear-cut cases, liver biopsy could be definitely avoided (16). However, several questions persist concerning the discrepancies between FT scores and histopathological findings within the HD population.

The accuracy of certain non-invasive procedures to predict the stage of liver fibrosis is significantly different in non-uremic patients versus uremic patients on hemodialysis.

Comparing Transient Elastography (TE), FT, and APRI scores in non-uremic patients based on the area under the ROC curve (AUC) values shows a similar diagnostic performance between them, with a slightly better accuracy of TE and FT compared with APRI score (17). In the case of HD patients, the situation is slightly different, as evidenced by several studies (14,18). TE is superior to APRI, FT, and Fib-4 score in assessing the severity of hepatic fibrosis. Liu et al. further outline that the area under the ROC curve is higher in HD patients evaluated by TE compared with non-uremic patients in predicting a fibrosis stage F2 and F3, and is similar in the case of F4 stage (14).

Furthermore, the APRI score in HD patients has a superior accuracy in evaluating fibrosis stage compared with FT (19). However, in this group of patients the major strength of APRI score is to exclude significant liver fibrosis (9,14).

Although in non-uremic patients FT represents a valuable tool in assessing the stage of liver fibrosis, in HD patients its accuracy is lower compared with other tests such as TE and APRI.

Aim of the study

In the present study, we reviewed the influence of hemodialysis on FT parameters: apolipoprotein A1, total bilirubin, haptoglobin, gamma-glutamyltransferase, and α_2-macroglobulin.

Methods

Search strategy

In the current study, we integrated five different literature reviews evaluating the influence of hemodialysis on each FT parameter.

A systematic web-based literature search of all publications in PubMed was conducted between April and September 2018 using several combinations of keywords ("hemodialysis"[All fields] AND "apolipoprotein A1"[All fields]; "hemodialysis"[All fields] AND "bilirubin"[All fields]; "hemodialysis"[All fields] AND "haptoglobin"[All fields], "hemodialysis"[All fields] AND "gamma-glutamyltransferase"[All fields], "hemodialysis"[All fields] AND "α_2-macroglobulin"[All fields], "hemodialysis"[All fields] AND "fibrotest"[All fields]).

Inclusion and exclusion criteria

The inclusion criteria for primary studies required the following features:

- the studies had to be conducted on adult human patients with chronic kidney disease (CKD) undergoing HD
- published between January 2008 and August 2018
- focused on the impact of HD on each FT parameter or on the effect of HD on the FibroTest score itself
- both prospective and retrospective studies were acceptable.

The following were excluded:

- case reports
- articles that included pediatric patients (under 18 years old)
- articles referring only to peritoneal dialysis
- studies presenting the effect of different substances (drugs, toxins, vitamins) on the level of each FT parameter. Studies in patients undergoing treatments that could influence liver fibrosis stage were excluded (e.g. HCV/HIV co-infected patients undergoing antiretroviral treatment).

A total of 858 articles were retrieved. Five hundred and thirty-five articles were published before January 2008 and were, therefore, excluded. Of the remaining 323 articles, 258 articles used human subjects. After reading the abstracts and the full text of all candidate articles, only 30 articles met all the inclusion and exclusion criteria. Therefore, the effect of HD on ApoA1 was reviewed in 17 articles, on bilirubin in 9 articles, on GGT in 3 articles, on haptoglobin in one article and on α_2M in no article. Nevertheless, there were too few articles referring to α_2M and haptoglobin that met all the inclusion and exclusion criteria, which is why in the case of these substances, all the articles found using the previously mentioned combinations of keywords were included, irrespective of the publication date.

A final number of 31 articles were reviewed and further summarized regarding each FT parameter separately (Figure 1).

Methodological quality assessment

Each of the studies meeting the inclusion criteria was analyzed by two independent reviewers. Data were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[20]. Consensus in disagreements was reached by referral to a third reviewer.

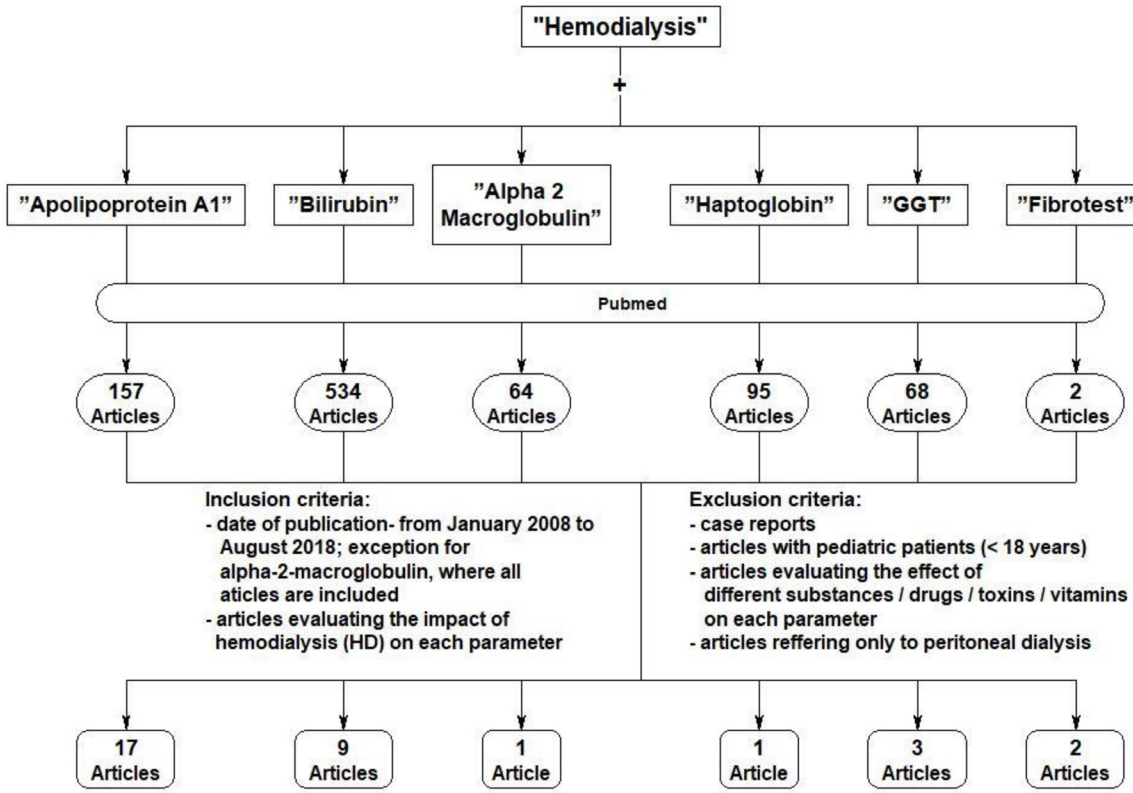

Fig. 1. Flow diagram of the potential articles. Inclusion and exclusion criteria. Apart from evaluating the effects of HD on each FT parameter, the study also aimed to analyze the effect of HD on the final score indicated by FT. Therefore, we extended our literature search in PubMed using the terms "hemodialysis"[All fields] and "fibrotest"[All fields]. Only two articles were identified.

Results

Apolipoprotein A1

ApoA1 is synthesized in the liver and the gut, representing approximately 70% of the high-density lipoprotein (HDL) content (21,22).

The main functions of ApoA1 include reverse cholesterol transport (22-24), anti-inflammatory and antioxidant effects due to its binding to paraoxonase 1 (PON1) – the enzyme that prevents the formation of oxidized low-density lipoprotein (LDL).

HDL metabolism is initiated in the liver and intestine by the secretion of ApoA1, which attaches to macrophages in the arterial wall via ATP-binding cassette transporter (ABCA1), a receptor that initiates the flux of free cholesterol and phospholipids into the surface of HDL (25), forming nascent pre-β-HDL. Once in the circulation, pre-β-HDL particles interact with lecithin-cholesterol acyltransferase (LCAT))(24). LCAT is a key constituent of HDL, which serves a dual function as phospholipase 2 and acyl-CoA cholesterol acyltrasferase, playing a crucial role in reverse cholesterol transport and HDL maturation (26).

Apart from LCAT and ABCA1, there are other enzymes that control the levels of ApoA1 and HDL, such as cholesteryl-ester transfer protein (CETP) and phospholipid transfer protein (PTLP) (26,27). PTLP transfers phospholipids

and free cholesterol from triglyceride-rich lipoproteins to HDL, phospholipids between HDL particles, and facilitates cholesterol efflux from cells (26). CETP catalyzes the transfer of cholesteryl esters from HDL to LDL in exchange for triglycerides (26).

In patients with CKD or ESRD, the metabolism of HDL and ApoA1 is changed, their decreased levels being caused by increased catabolism and decreased production (21,25). Some studies (28-30) suggest that an explanation for the reduced levels of HDL and ApoA1 can be attributed to the levels of enzymes involved in their metabolism, such as decreased levels of ABCA1, LCAT, PON1 and unchanged levels of PTLP and CETP. As a consequence, the reverse cholesterol transport is inhibited and the interaction of ApoA1 with macrophages via ABCA1 is altered.

The main effect of hemodialysis on the level of ApoA1 is to lower it (21,22,24,28,30-34).

In vivo kinetic studies revealed that ApoA1, the main apolipoprotein of HDL, is catabolized at a faster rate in hemodialyzed patients, leading to a decreased ApoA1 level. A study (33) suggested that decreased LCAT and increased CETP may, at least in part, account for the increased catabolism of ApoA1.

Another explanation can be the presence of anti-ApoA1-IgG that tends to correlate with dialysis vintage. In one study (22), a significant association was found between dialysis vintage and anti-ApoA1-IgG positivity. Moreover, dialysis vintage was found to be significantly longer in anti-ApoA1-IgG negative patients (22).

Along with a lower level of ApoA1, some studies have highlighted certain abnormalities in the HDL profile of hemodialysis patients. These include: lower HDL apolipoprotein levels, a lower content of lipoprotein A1, A2 and a high content of pre-β-HDL compared with healthy patients (24). This abnormal HDL profile mirrors the profile found in individuals with genetic LCAT deficiency and probably reflects the plasma accumulation of the cholesteryl-ester-poor ApoA1 containing discoidal HDL particles which cannot mature into spherical HDL particles of cholesterol (24).

Uremic plasma also tends to reduce the level of ApoA1. Hemodialysis, instead of eliminating the previously mentioned effect, has a tendency to perpetuate it, although its main role is to clear uremic toxins (21,35).

In a study of Moradi et al. (36), compared with normal plasma, both pre-dialysis and post-dialysis plasma lowered ApoA1 mitochondrial ribonucleic acid (mRNA) abundance in HepG2 human liver cancer cell line to the same extent. This finding suggests that the toxins responsible for the inhibition of ApoA1 expression are not removed by hemodialysis. The authors also observed that the molecules responsible for this effect are larger than 30 kDa and cannot be removed by hemodialysis (36).

Another effect of hemodialysis on lipid metabolism would lead to moderate hypertriglyceridemia, lower HDL-cholesterol, ApoA1 and HDL particle concentrations, as well as PON1 activity, and increased oxidized LDL levels (37). Wu et al. reported that dyslipidemia and the cholesterol efflux role in ESRD patients were not improved by HD, this being contrary to what HD is supposed to induce throughout the clearance of uremic toxins (35). The same study demonstrated a decreased serum triglyceride level and an increased HDL level in ESRD patients dialyzed with high-flux polysulfone membranes, but not in patients dialyzed with cellulose ester membranes (35) (Table 1).

Bilirubin

Bilirubin is produced in the reticuloendothelial system, as the end product of heme catabolism, derived from the oxidation of heme from hemeproteins (38).

Bilirubin is a water-insoluble compound that requires glucuronidation by a microsomal enzyme,

Table 1. The effect of hemodialysis on the level of ApoA1

Authors	Study type	Number of patients	Results
Moradi et al., 2012 (21)	Analytical prospective cohort study	Cellular cultures	Uremia lowers ApoA1 production by reducing RNA stability.
Pruijm et al., 2012 (22)	Cross-sectional study	66	The prevalence of anti-ApoA1-IgG is high (20%) in patients on maintenance hemodialysis. The antibody titer is associated with dialysis vintage.
Rolla et al., 2015 (23)	Prospective study	142	ApoA1 levels were significantly lower in hemodialysis patients than in controls.
Calabresi et al., 2014 (24)	Analytical transversal study	288	ApoA1 levels were lower in hemodialysis patients than in controls.
Moradi et al., 2008 (25)	Analytical transversal study	45	End-stage renal disease patients on hemodialysis exhibited significant reductions in ApoA1 levels compared to the control population.
Pahl M V et al., 2009 (26)	Analytical transversal study	42	Patients with end-stage renal disease on maintenance hemodialysis had significantly reduced plasma ApoA1 concentrations compared to the control population.
Kaysen G A et al., 2014 (27)	Prospective cohort study	266	During one year of observation, ApoA1 levels decreased from baseline in patients initiated on hemodialysis in the first two quarters and then returned to baseline values by the end of the observation year.
Honda H et al., 2015 (28)	Prospective cohort study	111	The levels of ApoA1 decreased according to the chronic kidney disease severity. The levels of ApoA1 were similarly decreased in patients with CKD5 and CKD5 on hemodialysis compared to those having CKD stage 2 or 3.
Ribeiro S et al., 2012 (29)	Prospective cohort study	205	Patients on hemodialysis presented lower levels of ApoA1 than controls.
Kimak E et al., 2011 (30)	Prospective cohort study	193	Hemodialyzed patients had lower levels of ApoA1.
Lokesh S et al., 2016 (31)	Comparative cross-sectional study	80	The mean level of ApoA1 was significantly lower in patients receiving hemodialysis.
Ikewaki K, 2014 (32)	Analytical study	-	ApoA1 levels were significantly decreased in hemodialysis patients comparative to controls. The decreased levels of ApoA1 in patients with end-stage renal disease on hemodialysis were primarily due to the increased rate of catabolism.
Yeo Y et al., 2009 (33)	Retrospective case-control study	252	Chronic dialysis patients showed significantly lower levels of ApoA1 than controls.
Samouilidou EC et al., 2008 (34)	Prospective cohort study	51	ApoA1 concentrations were higher after hemodialysis than before hemodialysis.
Wu S et al., 2015 (35)	Prospective cohort study	79	ApoA1 significantly decreased in end-stage renal disease patients. After hemodialysis, the levels of ApoA1 were significantly reduced.
Holzer M et al., 2011 (37)	Prospective cohort study	46	The reduced cholesterol efflux of uremic HDL is linked to the depletion of HDL-associated ApoA1.

ApoA1 – apolipoprotein A1; CKD – chronic kidney disease; HDL – high-density lipoprotein; IgG – immunoglobulin G; RNA – ribonucleic acid

uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), in order to be excreted.

The most important properties of bilirubin include: antioxidant effects, cytoprotective effects, anti-inflammatory effects, lipid-lowering properties and also antiatherogenic properties (38,39).

Apart from the association with lower oxidative stress, elevated bilirubin levels can augment endothelial function/endothelial-dependent vasodilatation (38). A study (38) indicated that serum total bilirubin concentrations were positively related to collateral development, by increasing NO (nitric oxide) bioavailability, which is known to play a crucial role in the development of collateral vessels.

The immunomodulatory effects of unconjugated bilirubin may explain its availability to restrain inflammation. It has also been suggested that serum bilirubin concentration is associated with lower CRP levels via reduction of blood lipid concentration and increased HDL availability and not by direct inhibition of inflammation (38).

There is still debate about the effect of hemodialysis on the level of total bilirubin, some studies reporting that after HD the level of total bilirubin (TB) decreases (38,40-43), while others show that it actually remains the same, due to the total bilirubin level (39).

The effects of HD include the removal of circulating antioxidants from the aqueous phase of plasma, leaving proteins vulnerable to oxidation. Although water soluble antioxidants are dialyzed, unconjugated bilirubin, due to its affinity for circulating albumin, is retained in the vascular compartment, therefore being free to react with radicals from the plasma (38). In this context, some studies (38) have suggested that the reduced bilirubin concentration is due to the fact that bilirubin may represent a sacrificial antioxidant.

There are various types of hemodialysis that can impact the final level of bilirubin: intermittent hemodialysis (IHD), continuous venovenous hemofiltration (CVVH), high-volume hemofiltration (HVHF) and plasma exchange (PE) (40,42).

IHD relies on the passive diffusion of the solutes through a semi-permeable membrane, while CVVH is an alternative technique that provides continuous blood purification based on convection driven by a hydrostatic pressure gradient. HVHF is a form of CVVH that has an ultrafiltration flow rate >50 mL/kg/h (40).

HVHF followed by IHD appears to have an advantage over IHD alone, evidenced by an earlier decline in the bilirubin level. In the same study (40), total bilirubin, direct and indirect, improved significantly in the HVHF group compared to the IHD group.

Zhang et al. demonstrated that the total bilirubin level decreased at a faster rate in patients treated with CVVH+PE rather than CVVH alone (42).

When comparing the level of TB between people with chronic kidney disease and those on dialysis, the decrease in bilirubin concentration was 65% lower according to Tbahriti et al. (41) (Table 2).

Alpha-2-macroglobulin and haptoglobin

Alpha-2-macroglobulin belongs to the group of acute phase proteins and its production is related to inflammation and liver fibrosis. Alpha-2-macroglobulin is also a proteinase inhibitor and its increased synthesis can inhibit the catabolism of matrix proteins and enhance fibrotic processes (44). Haptoglobin decreases when fibrosis increases. This may be a response to the increased hepatocyte growth factor seen in liver damage (45). The positive correlation between fibrosis and α_2M and the negative correlation between fibrosis and haptoglobin could be explained by the different roles of cytokines such as hepatocyte growth factor (HGF) during fibrogenesis. HGF stimulates α_2M synthesis and decreases haptoglobin synthesis (16). Furthermore, in HD patients, the same correlations can be explained

Table 2. The effect of hemodialysis on the level of bilirubin

Authors	Study type	Number of patients	Results
Boon A C et al., 2014 (38)	Review	-	Bilirubin concentrations are reduced in hemodialysis patients.
Mekki K et al., 2010 (39)	Cohort study	60	Bilirubin levels were similar in end-stage liver failure patients, hemodialysis patients and peritoneal dialysis patients.
Si X et al., 2015 (40)	Prospective cohort study	36	Total, direct and indirect bilirubin levels were significantly lower in patients treated with HVHF than those treated with IHD alone.
Tbahriti HF et al., 2013 (41)	Cohort study	167	Bilirubin levels were diminished (around 65%) in patients on hemodialysis compared to chronic kidney disease patients.
Zhang L et al. (42)	Retrospective study	81	Serum levels of total bilirubin decreased steadily in the first 7 days of dialysis. The total bilirubin level decreased more in the CVVH+ PE than in the CVVH group.
Cheng YC et al.(43)	Retrospective study	327	The total bilirubin levels were lower in hemodialysis patients than in patients with ischemic heart disease or normal subjects.

CVVH - continuous venovenous hemofiltration; HVHF – high-volume hemofiltration; IHD – intermittent hemodialysis; PE – plasma exchange

by acute phase reaction induced by the dialysis procedure (46,47). Different variables that formulate the FT scores may be influenced by non-hepatic conditions such as hematoma and immunological factors, which are frequently seen in the hemodialysis population. These conditions may result from high α_2M levels and low haptoglobin levels (49).

Canbakan et al. demonstrated that in HCV hemodialysis patients, the certainty of absence of significant fibrosis (F2-F4) for scores ≤0.1 was only 60% (19) compared with 100% in HCV patients with normal renal function (16), and the accuracy of the presence of significant fibrosis for scores ≥0.6 was only 20% (19) compared with a PPV ≥90% in HCV patients with normal renal function (16).

A possible reason for the lower diagnostic accuracy may be due to variations in the biochemical components of the FT/AT scores among patients with renal failure. Renal dysfunction may affect results concerning the proteins included in FibroTest. The levels of α_2M may rise in the context of renal insufficiency because of the inflammatory response induced by the dialysis procedure (46,47).

Argiles et al. demonstrated that serum α_2M levels significantly increased from the third hour after initiation of HD, continued to increase for at least 2 h after the end of dialysis ($P<0.01$) and remained elevated at 12 h, independently of the membrane used (AN69 or cuprophane). Since α_2M is related to acute phase reactant proteins, its variations during the dialysis session could represent an inflammatory-like response to the dialysis procedure (47,48).

Decreased serum levels of haptoglobin were observed in the plasma of long-term HD patients. Haptoglobin is a heme-binding glycoprotein that protects the body from hemoglobin-induced oxidative damage, nitric oxide toxicity and pro-inflammatory effects induced by intravascular hemolysis. Haptoglobin also functions as a chaperone that inhibits oxidation-induced

misfolding of extracellular proteins and thus exerts anti-inflammatory effects. Based on these beliefs, Lin et al. postulated that downregulation of haptoglobin might reflect an exhausted antioxidant reserve in long-term HD patients, while counteracting the persistent deranged redox state and inflammatory stresses (50) (Table 3).

Gamma-glutamyltransferase

In CKD on HD, serum GGT levels may be a useful and low-cost marker, similar to aminotransferases, for the diagnosis of chronic HCV infection (1).

Fabrizi et al. identified an association between serum GGT levels and chronic viral hepatitis C. After analyzing the ROC curve, these authors determined that the best cut-off values to predict positive anti-HCV would be 18 IU/L (sensitivity = 61%; specificity = 50%). These GGT values represent the upper limit of normal (ULN) reductions of 64% (50 IU/L) for the detection of anti-HCV positive patients (51). Souza et al. also reported higher serum GGT levels in HD patients with HCV infection than in those negative for anti-HCV (49.8±56.6 IU/L and 94.8±105 IU/L, respectively) (p = 0.05). Both authors suggested the use of serum GGT levels as an indirect marker to detect liver disease in HD patients, which should be measured monthly for these patients (52).

Liberato et al. evaluated 40 CKD patients on HD and performed serum GGT dosage immediately prior to and after the dialysis procedure. When divided by the ULN, serum GGT levels were 0.88 IU/L prior to HD and 1.14 IU/L after HD (p = 0.001), which is compatible with the increase in serum hematocrit levels, thus characterizing hemoconcentration (hematocrit before HD, 36.7%; after HD, 41.3%, p = 0.001) (53). Therefore, after the dialysis procedure, the mean GGT values were higher than the mean ULN values, suggesting that the serum levels of this enzyme could be reduced in CKD patients prior to the HD session. Ultimately, serum GGT levels in CKD patients on HD are possibly influenced by hemodilution due to the liquid retention of CKD patients (Table 4).

The effect of HD on FibroTest accuracy in predicting the stage of fibrosis

There are very scarce data regarding the influence of HD on the accuracy of FT in predicting the stage of liver fibrosis.

Although the areas under the ROC curves for the diagnosis of significant fibrosis were similar in the studies of Varaut et al. (0.46) and Canbakan

Table 3. The effect of hemodialysis on the serum levels of a2-macroglobulin and haptoglobin

Study	Study type	Influenced parameter(s)	Number of patients	Results
Argiles et al., 1993 (47)	Prospective	α_2M	30	Serum α_2M levels significantly increased from the third hour after initiation of HD, continued to increase for at least 2 h after the end of dialysis ($p<0.01$) and remained elevated at 12 h.
Canbakan et al., 2011 (19)	Prospective	Fibrosis (α_2M, haptoglobin, TB, GGT, ApoA1)	33	The absence and the presence of significant fibrosis (F2–F4), determined by FibroTest, are underestimated in HCV HD patients compared to HCV patients with normal renal function.
Lin et al., 2012 (50)	Prospective	Haptoglobin	12	The protein profile of long-term HD patients includes decreased serum haptoglobin levels.

α_2M – alpha-2-macroglobulin; GGT- gamma-glutamyltransferase; HCV – hepatitis C virus; HD – hemodialysis; TB – total bilirubin

Table 4. The effect of hemodialysis on the serum levels of GGT

Study	Study type	Number of patients	Results
Fabrizi et al., 2007 (51)	Retrospective	333	The best cut-off values to predict positive anti-HCV would be 18 IU/L (Se = 61%; Sp = 50%). These GGT values represent ULN reductions of 64% (50 IU/L) for the detection of anti-HCV positive patients.
Souza et al., 2008 (52)	Prospective	87	The mean GGT values were higher in patients with HCV infection than in those without HCV, suggesting that serum GGT levels could be used as an indirect marker for detecting liver disease in HD patients.
Liberato et al., 2012 (53)	Prospective	40	The levels of serum GGT collected before the dialysis session were significantly lower than the values observed after dialysis. Also, the hematocrit rates were significantly lower before dialysis than after the HD session.

anti-HCV – anti-hepatitis C virus antibodies; GGT – gamma-glutamyltransferase; HD – hemodialysis; ULN – upper limit of normal

et al. (0.47), the negative predictive value (NPV) of an FT score <0.2 and the positive predictive value (PPV) of a score >0.6 were significantly different (15,19).

In the first study by Varaut et al., in the analysis of the entire cohort of HD patients, 72% were correctly classified and the use of FT instead of liver biopsy (LB) meant that 32% of the LBs could have been avoided. Furthermore, the PPV of a score >0.6 was 75% while the NPV of a score <0.2 was 71% (15).

In contrast, in the study conducted by Canbakan et al., fibrosis was correctly classified in only 33.3% of all included patients, while LB could have been prevented in 15.15% of patients with a FT score <0.2 and in 3% of patients with a score >0.6. The PPV of a score >0.6 was only 20%, while the NPV of a score <0.2 was 45.45% (19).

However, both studies illustrate the idea that the accuracy of FT in HD patients is lower than in the general population and it may reflect the effect of renal disturbances induced by either CKD and/or HD on the biochemical parameters of FT (15,19).

A major strength of the current study is that, to our knowledge, this is the first systematic literature review which evaluates the influence of hemodialysis on FibroTest.

The limitation of this review consists of the relatively small number of studies which reported data regarding the influence of hemodialysis on FibroTest parameters. There are also few papers about FibroTest efficiency in predicting liver fibrosis as compared with other non-invasive methods in hemodialysis patients with hepatitis C virus infection.

Discussions

The effect of uremic plasma, and, to a greater extent, of hemodialysis on the level of ApoA1 is to decrease it through increased catabolism and the presence of anti-ApoA1-IgG antibodies. Furthermore, the failure of HD to eliminate the toxins responsible for the inhibition of ApoA1 expression is also responsible for the decreased level of ApoA1.

Although still debatable, most of the studies analyzed in our review suggest that HD tends to decrease the level of TB either by a reduction of the retained TB through the reaction with dialyzed plasma radicals or by the different types of HD utilized: HVHF, IHD and CVVH+PE.

Serum α_2-macroglobulin levels may rise in HD patients because of the inflammatory response induced by the dialysis procedure. Increased serum α_2M levels were described from the third hour after initiation of HD until at least 2 hours after the end of dialysis and remained elevated at 12 hours.

Hemolysis and inflammatory status seen in long-term HD patients are the main conditions that lead to decreased levels of haptoglobin in these patients.

In HD patients, serum GGT levels could be influenced by hemodilution due to hypervolemia seen in CKD patients.

Conclusions

Hemodialysis induces a reduction in ApoA1, haptoglobin and bilirubin levels, but increases GGT and α_2-macroglobulin levels. These changes could alter the estimation of the fibrosis level indicated by FibroTest in patients undergoing hemodialysis.

Author Contributions

OHO - Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

IB, AMS - Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – original draft, Writing – review & editing

AST, SCC, IAM, TA - Formal analysis, Investigation, Resources, Writing – review & editing

AC - Data curation, Formal analysis, Investigation, Resources, Software, Visualization, Writing – original draft, Writing – review & editing

LU, RAO - Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing

Conflicts of Interest

The authors declare that they have no conflicts of interests.

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