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Hepatitis C-Related Liver Disease in Dialysis Patients

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Abstract

Hepatitis C virus (HCV) remains the most common cause of liver damage in patients with chronic kidney disease including patients on long-term dialysis. The natural history of HCV infection in patients with chronic kidney disease is not fully elucidated despite the adverse effect of HCV infection on survival in patients receiving long-term dialysis. A recent meta-analysis of seven observational studies (11,589 patients on dialysis) reported that the summary estimate for adjusted relative risk (all-cause mortality) with anti-HCV antibody was 1.34 with a 95% confidence interval of 1.13–1.59. As a cause of death, hepatocellular carcinoma and liver cirrhosis were significantly more frequent among anti-HCV-positive than -seronegative dialysis patients; the summary estimate for unadjusted liver-related mortality risk was 5.89 (95% confidence interval 1.93–17.99). Impairment of quality of life due to HCV has also been suggested to explain the diminished survival in this setting. Recent data also suggest an excess risk of cardiovascular disease in HCV-infected dialysis patients. Recent evidence supports the notion that the progression of HCV-related liver disease is probably slower in the dialysis population than in non-uremic patients despite the immune compromise conferred from chronic uremia; numerous mechanisms have been mentioned to explain it. It appears that the hemodialysis procedure per se reduces the HCV viral load, and the mechanisms by which this phenomenon occurs remain largely speculative – the intradialytic production of interferon- α , hepatocyte growth factor, or other cytokines provided with antiviral activities have been implicated. This is an area of intense investigation, and further studies are indicated.

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The advent of serologic screening of blood by enzyme-linked immunoassays, routine use of erythropoietin for patients with anemia and chronic kidney disease (CKD), and compliance with infection control procedures to prevent the

spread of hepatitis C virus (HCV) within dialysis units have helped to reduce the transmission of HCV infection among patients on maintenance dialysis in developed countries [1]. However, HCV infection continues to be the most frequently recognized cause of liver damage in patients with CKD. The aim of this chapter is to review the recent and available evidence on HCV-related liver disease in patients undergoing long-term dialysis.

HCV-Related Liver Disease in Dialysis: Biochemical and Clinical Manifestation

HCV-related liver disease is mostly asymptomatic in patients on long-term dialysis. Some symptoms which typically occur in non-dialysis patients with HCV (i.e. asthenia, fatigue, and cognitive impairment) are frequently in the dialysis population irrespective their HCV serologic status. HCV infection can be evident at biochemical level, as some enzyme levels (serum transaminase and gamma glutamyl transpeptidase, GGTP) are frequently elevated in HCV-infected patients on long-term dialysis. In a large cohort of patients undergoing long-term dialysis in the US (13,664 patients), after adjustment for several covariates including surrogates of MCS (malnutrition-inflammatory complex syndrome), an independent relationship between anti-HCV seropositive status and serum alkaline phosphatase activity was found, OR, 1.01 (95% confidence interval, CI, 1.0–1.02), $p = 0.001$ [2]. Among HCV-infected patients, higher serum intact parathormone levels have been detected, 422 ± 423 vs. 338 ± 356 pg/ml ($p = 0.0001$), which persisted even among African-American patients [3]. These observations have been linked to ‘hepatic osteodystrophy’ that has been described in non-dialysis subjects with hepatitis [4]. However, dialysis patients have multiple comorbidities (arterial hypertension, gastrointestinal bleeding, anemia, and failure of the vascular access, among others), and clinicians frequently neglect these biochemical alterations in the everyday clinical practice. Cirrhosis is an infrequent event among dialysis patients in western world as it ranges between 1.5 and 2%, according to some international registries [5].

Natural History of HCV in Dialysis Population

The natural history of HCV in patients on maintenance dialysis remains incompletely appreciated. HCV infection in dialysis patients is usually asymptomatic with an apparently indolent course. Because the natural history of HCV extends over decades rather than years even in patients with normal renal function, adverse consequences of chronic HCV infection may not be obvious in patients followed for shorter periods of time. Patients with CKD have higher

morbidity and mortality rates than the general population because their average age is higher and because of their frequent comorbidities. The long-term consequences of HCV infection are therefore difficult to assess in this population.

Factors modifying progression of liver disease in patients with CKD include alcohol abuse and coinfection with HBV, HCV, and HIV. Antiviral therapy of HCV in patients on long-term dialysis and elimination of post-transfusion HCV hepatitis hamper the implementation of observational studies with appropriate follow-up. Posttransfusion HCV hepatitis is, in fact, a form of hepatitis in which the timing of acquisition of the virus is likely to be unequivocal.

Biochemical evaluation of HCV infection in patients with CKD is inaccurate. Serum aminotransferase values are typically lower in dialysis patients than the non-uremic populations. Dialysis patients who are HCV viremic have aminotransferase levels greater than those without, although values are still within the 'normal' range. In a series of 394 chronic hemodialysis (HD) patients, serum aspartate aminotransferase activity in bDNA-positive versus -negative patients was 23.8 (95% CI, 60.8–9.3) vs. 17.1 (95% CI, 50.4–5.8), $p = 0.009$, and serum alanine aminotransferase (ALT) activity, 14.4 (95% CI, 48.9–4.3) vs. 9.8 (95% CI, 37.3–2.5) IU/l, $p = 0.008$. Logistic regression analysis showed an association between HCV viremia and ALT activity ($p = 0.01$) [6].

Serum GGTP levels are greater in dialysis patients with HCV and/or HBV infection compared to non-infected patients, but the increase was rather small (85.1 ± 184 vs. 25.8 ± 24 IU/l, $p = 0.001$) and occurred in a minority of patients ($41/184 = 22\%$). Multivariate analysis established a significant and independent relationship between serum GGTP and positive anti-HCV antibody ($p = 0.001$) in a large population of patients on long-term dialysis in northern Italy ($n = 757$) [7].

Clinicians are frequently reluctant to perform liver biopsy in dialysis patients because of concerns about platelet function in chronic uremia. The recent implementation of guidelines recommending antiviral therapy for HCV infection in patients with CKD makes difficult the conduction of longitudinal clinical trials on the natural history of HCV infection in patients with CKD [1].

HCV: Survival and Hemodialysis

Mortality is an unequivocal end point in the natural history of HCV, but data concerning the relationship between HCV infection and risk for death among HCV-infected patients are not abundant. However, longitudinal studies with an appropriate size and follow-up have found an independent and significant relationship between anti-HCV antibody positivity and reduced patient survival [8–11]. A recent meta-analysis of seven observational studies about the effect of anti-HCV serologic status on survival in dialysis patients demonstrated an independent and significant impact of HCV on mortality among patients

receiving long-term dialysis (11,589 patients); the summary estimate for relative risk was 1.34 (95% CI, 1.33–1.86) [12]. In all these studies, hepatocellular carcinoma (HCC) and liver cirrhosis were significantly more frequent causes of death in anti-HCV antibody-positive patients on dialysis than in anti-HCV antibody-negative patients on dialysis. The unadjusted overall estimate for the relative risk of liver-related mortality was 5.89 (95% CI, 1.93–17.99, $p < 0.001$) in anti-HCV antibody-positive patients on dialysis relative to their anti-HCV antibody-negative counterparts [12].

A recent study from Australia and New Zealand ($n = 23,046$) also reported an independent and significant association between anti-HCV-positive serologic status and all-cause mortality over a 10-year follow-up (HR, 1.25, 95% CI 1.07–1.46, $p = 0.004$) [13]. Hepatic failure was a more common cause of death in the anti-HCV-positive group (adjusted hazard ratio, aHR, 5.79, 95% CI 1.99–16.83, $p = 0.001$), but this was still infrequent (rate = 0.34 deaths per 100 patients per year). In the anti-HCV-positive group, one of the 9 deaths due to malignancy was to primary liver cancer compared with 12 of 583 deaths due to malignancy in the anti-HCV-negative group. These authors suggested that the majority of dialysis patients who are infected with HCV may not live long enough to die of long-term complications of HCV-related liver disease (i.e. HCC and cirrhosis).

Another population-based survey has been reported by Johnson et al. [14] in dialysis patients (HD and peritoneal dialysis, PD) from Asia-Pacific countries. Analysis of the Japanese cohort (76,201 patients) showed that the presence of anti-HCV antibody was an independent predictor of all-cause mortality (RR, 1.37; 95% CI, 1.15–1.62, $p = 0.003$). Similarly, in the cohort from Australia and New Zealand (21,487 patients), all-cause mortality was linked to the presence of anti-HCV at baseline (aHR, 1.29; 95% CI, 1.05–1.58, $p = 0.016$) and acquisition of anti-HCV antibody during the course of dialysis (aHR, 1.27; 95% CI, 1.05–1.55, $p = 0.017$) [14]. Unfortunately, no information on liver-related or cardiovascular death risk was provided.

These findings are consistent with accumulating evidence from other sources [15, 16]. The Dialysis Outcomes and Practice Patterns Study on patients undergoing regular dialysis in three continents had reported an independent and significant association between positive anti-HCV antibody and mortality risk (adjusted relative risk, aRR, 1.17; $p < 0.0159$) [16].

HCV: Survival and Peritoneal Dialysis

Evidence on the relationship between HCV and survival among patients on PD is even more limited. Wang et al. [17] retrospectively reviewed 538 PD patients from 1996 to 2005. Of these patients, 75 (13.9%) were anti-HCV positive at the beginning of PD. Cox regression analysis suggested that chronic HCV

Table 1. Impact of HCV on survival in dialysis patients: aRR of all-cause mortality

First author	Patients	aRR	Reference year	Country
B. Pereira	496	1.41	1998	US
C. Stehman-Breen	200	1.97	1998	US
E. Nakayama	1,470	1.57	2000	Japan
M. Espinosa	175	1.62	2001	Spain
K. Kalantar-Zadeh	2,778	1.28	2005	US
A. Di Napoli	6,412	1.29	2006	Italy
S.M. Wang	538	2.19	2008	Taiwan

infection was associated with increased 10-year mortality. The adjusted HR of HCV infection was 2.195 (95% CI, 1.486–3.243, $p = 0.001$). The incidence of liver cirrhosis-related mortality was higher in patients with HCV infection than in those without; however, it was not statistically significant ($p = 0.146$). HCV infection was not significantly associated with any specific cause of death. The frequency of the three most frequent causes of death (CVD, infection and cancer) was not significantly different in patients with and without HCV ($p = 0.597$). Serum levels of albumin (3.1 ± 1 vs. 3.4 ± 0.8 mg/dl), cholesterol (178 ± 44 vs. 198 ± 52 mg/dl), and triglyceride (194 ± 12 vs. 212 ± 17 mg/dl) were lower in anti-HCV-positive patients, suggesting that HCV infection might result in increased mortality due to impaired nutritional status.

HCV: Survival and Cardiovascular Disease

Kalantar-Zadeh et al. [3] were the first investigators to establish a relationship between anti-HCV antibody serologic status and cardiovascular mortality. In a population-based survey (2,778 patients undergoing long-term dialysis at DaVita system), the HR for all-cause mortality and cardiovascular death was 1.28 (95% CI, 1.02–1.62, $p = 0.03$) and 1.48 (95% CI, 1.05–2.08, $p = 0.02$), respectively, after adjustment for several case-mix parameters. The link between anti-HCV antibody positivity and cardiovascular death was partially mitigated after adjustment for available surrogates of malnutrition-inflammation syndrome, HR, 1.43 (95% CI, 1.00–2.06, $p = 0.05$). However, the association between anti-HCV positive serologic status and CVD mortality did persist after adjustment for case-mix and MICS covariates, HR = 1.80 (95% CI, 1.1–2.95, $p = 0.02$), in the subgroup of dialysis patients younger than 65 years ($n = 1,551$).

In their subsequent survey (13,664 patients on regular dialysis followed during 3 years), the HR of 3-year all-cause mortality related to HCV antibody

positivity was 1.25 (95% CI, 1.12–1.39, $p = 0.001$) [2]. The relative risk of cardiovascular disease mortality associated with HCV infection persisted across almost all group of patients, although it did not reach statistical significance.

Interestingly, Scott et al. [13] in another population-based study reached similar conclusions. The predominant cause of death in their cohort was cardiovascular: also, having taken into account patient characteristics including age and pre-existing cardiovascular disease, a significantly increased risk of cardiovascular death among the anti-HCV positive cohort persisted (HR, 1.34, 95% CI, 1.08–1.67, $p = 0.007$). This study differed from other studies as the authors censored their data at the time of transplant in order to remove the potential for confounding by post-transplant outcomes [12]. However, their observation was valid as follow-up of the dialysis cohort continued through the transplantation period (aHR = 1.27, 95% CI, 1.10–1.48).

Another observation is that HCV-infected dialysis patients have a higher prevalence of hypoalbuminemia when compared to non-HCV-infected counterparts. A survey from the US reported a significant difference in serum levels of albumin in their cohort of patients on long-term dialysis ($n = 69,294$), 3.68 ± 0.45 vs. 3.76 ± 0.41 g/dl ($p = 0.0001$) [2]. They suggested that the impact of HCV infection on nutritional status and inflammation may be a main cause of cardiovascular mortality in this population. Inflammation associated with chronic infections may contribute to the increased CVD death risk in dialysis individuals. In addition, multiple studies have shown that HCV is associated with liver steatosis, insulin resistance, and hypoadiponectinemia [18]. In addition to conventional cardiovascular risk factors in dialysis population such as hypertension, hypercholesterolemia, and hyperhomocysteinemia, HCV infection may be an important factor. This view is supported by the notion that traditional risk factors only partially explain the mortality excess in dialysis population [19].

The link between cardiovascular mortality and HCV infection in patients on long-term dialysis has been studied by Oyake et al. [20] using pulse-wave velocimeter measurements. They prospectively evaluated 94 dialysis patients (17 being HCV positive) by measurements of aortic stiffness (by carotid-femoral pulse wave velocity). Multiple logistic regression analysis found that mean blood pressure and HCV viremia (OR, 9.7, 95% CI, 1.18–81.19, $p < 0.05$) were significantly and independently associated with high PWV (≥ 10.0 m/s, mean). Kaplan-Meier survival curves for cerebrovascular and cardiovascular event-free rates indicated a highly significant difference between HCV RNA-positive or -negative patients on dialysis (log-rank test, $p < 0.05$). They suggested that HCV infection plays an atherogenic role through aggravation of metabolic syndrome and dyslipidemia.

According to the meta-analysis of observational studies reported above [12], the summary estimate for unadjusted RR of cardiovascular-related mortality was 0.95 (95% CI, 0.76–1.18), NS.

HCV: Survival and Quality of Life

It has been recently suggested that one of the mechanisms of increased mortality in HCV-positive patients is due to an impairment of quality of life (QOL). Several authors have noted that the QOL is diminished in dialysis population; also, HCV-infected individuals with intact kidney function have an impairment of QOL scores. However, the relationship between HCV infection and QOL among patients receiving long-term dialysis has been to date analyzed only by Afsar et al. [21]. They studied 165 patients on regular dialysis, 83 of whom being anti-HCV positive. They evaluated QOL by SF-36, a test which consists of 36 items, assigned to eight subscales, that can be summarized by a physical component summary score and mental component score (MCS). SF-36 has been commonly used and validated in CKD patients. There was an independent relationship between anti-HCV-positive status and reduced mental component summary score (B, -3.423, $p = 0.016$). No association with the physical component summary score was noted (NS). The presence of symptoms of depression might be one explanation – depression is frequent in patients with HCV as a reactive phenomenon related to the diagnosis ('labeling' effect) and concerns over long-term health. Depression may be secondary to symptoms such as fatigue and cognitive impairment that can be frequently observed in HCV-infected individuals. In addition, HD treatment is independently associated with an increased prevalence of depression, which in turn negatively affects health-related QOL. It remains unclear whether treatment of HCV in HD population can decrease mortality by improving QOL, irrespective of biological markers (i.e. liver histology or virologic features); thus, dialysis patients with advanced liver disease could still benefit from antiviral therapy in terms of QOL and therefore lowered mortality.

Natural History of HCV: Dialysis versus Non-Uremic Controls

Despite these data showing the adverse impact of anti-HCV serologic status on survival in the dialysis population, the course of HCV infection the dialysis population has not been fully characterized, although there is evidence promoting the notion of a difference in the natural history of chronic hepatitis C between dialysis and non-uremic populations. A severe clinical course of HCV-related liver disease seems unusual in most HD patients. Another distinctive feature is that antiviral therapy can be very effective in the minority of patients requiring such treatment. In a case-control study, Okuda and Yokosuka [22] gave the most important information to date. 189 patients with anti-HCV antibody were followed up for more than 4 years and compared with twice as many gender- and age-matched controls with chronic hepatitis C diagnosed in the same month as the case and followed up for comparable periods. The longest

follow-up was 23 years in dialysis cases. No dialysis patients with chronic hepatitis C progressed to cirrhosis, whereas the disease progressed to cirrhosis in more than one quarter of the controls (62/228). These differences were highly significant ($p < 0.0001$).

Ishida et al. [23] found an incidence rate of HCC and cirrhosis of 1.8% (114/6,222) and 8.6% (536/6,242), respectively, in 314 dialysis units from Japan. These incidence rates appear much lower than those they attributed to normal adults, according to the medical literature (cirrhosis in 15–20%; HCC in 5–28%). Furthermore, the incidence rates of HCC and cirrhosis in patients who underwent HD therapy for more than 10 years were lower than in patients who had been on HD for less than 10 years: 0.5% (17/3,533) vs. 4.2% (79/1,870) and 6% (211/3,533) versus 13% (243/1,870), respectively. In view of the high risk of cancer in patients on maintenance HD, a very high incidence rate of HCC in dialysis patients with HCV had been postulated. The authors did not clarify the paradoxical phenomenon they found.

HCV Viral Load: Uremic versus Non-Uremic Controls

The relationship between HCV viral load and liver disease progression is currently a matter of debate. An increase in HCV RNA load by 8-fold or more compared with natural infection has been observed in various immunosuppressed populations, including liver or renal transplant recipients, and patients with HCV/HIV coinfection. The accelerated progression of HCV-related liver disease in these groups has been related, at least in part, to a high viral load. It remains unclear if these findings apply to dialysis patients with immune compromise due to chronic uremia. At least 5 cross-sectional studies [reviewed in 24] have concluded that the HCV load is lower in HCV-infected dialysis patients than in patients with chronic hepatitis C and intact kidney function, whereas at least 3 other studies [reviewed in 24] have failed to find any significant difference in the viral load between dialysis patients and non-uremic controls. Overall, the available information does not support an increase in HCV load in patients on maintenance HD despite the immune abnormalities related to uremia and the HD procedure per se.

There is a paucity of longitudinal studies of HCV virology during natural infection in chronic dialysis patients with HCV. Two prospective studies [24] have not reported differences in HCV viremia over time in patients on maintenance dialysis, but the short follow-up precluded definitive conclusions. In contrast, two prospective controlled trials with appropriate follow-up have given contrasting findings [24]. Furusyo et al. [25] found that HCV RNA levels were significantly lower in 98 HD patients (median, 0.4 mEq/ml) than in 228 non-uremic individuals (median, 3.0 mEq/ml; $p < 0.05$). Their prospective observations over 3 years revealed a significant decrease in HCV RNA levels in 47 HD

patients with HCV genotype 1b (2.6 ± 0.7 vs. 1.8 ± 0.6 mEq/ml, $p = 0.0082$), whereas levels in 155 non-uremic subjects with genotype 1b did not decrease (5.7 ± 0.7 vs. 5.8 ± 0.6 mEq/ml, NS).

Histopathology of HCV-Related Liver Disease in Dialysis and Non-Uremic Controls

Evidence comparing liver biopsy findings between dialysis patients and non-uremic controls infected with HCV is limited. A large controlled study conducted by Cotler et al. [26] compared histology findings between renal transplant candidates ($n = 46$) and non-uremic individuals ($n = 46$) with chronic HCV. Study and control patients were well matched for age, gender, and race. All study patients with CKD had been on long-term dialysis. As already reported by other authors, aspartate aminotransferase and ALT were significantly lower in CKD patients than in the non-uremic controls. Patients with CKD had less inflammation, 3.5 (2.0–7.0) versus 6 (3.0–9.0), $p = 0.033$, and less bridging fibrosis or cirrhosis, 13% (6/46) versus 30% (14/46), $p = 0.043$, than controls. Similar observations were noted by other authors in another controlled study, although the small number of patients included ($n = 20$) prevented definitive conclusions [27]. Alric et al. [28] observed that Knodell score was similar between HCV-infected dialysis patients ($n = 30$) and control (non-transplanted and non-hemodialyzed) patients ($n = 30$), 5.14 ± 0.54 vs. 5.1 ± 0.3 (NS), although fibrosis progression/year was lower in HCV-infected HD patients than in controls, 0.11 (0.04–0.17) versus 0.17 (0.14–0.20), $p < 0.05$.

Kinetics of HCV Load during Hemodialysis

According to the data reported above, the question is why there is such a distinct difference in the natural history of chronic hepatitis C between dialysis and non-uremic patients. It is well known that liver injury caused by HCV is mainly through immunologic processes rather than due to a direct cytopathic activity of the virus. Current data suggest that many different immune disturbances occur in HD patients, and the lower immune competence of HD patients has been considered a possible cause of attenuated inflammatory reactions and reduced hepatocyte destruction caused by HCV.

It appears that the HD procedure per se can protect patients from a more aggressive course of HCV by reduction in the viral load. The mechanisms by which the HD procedure lowers HCV viremia remain largely speculative: the passage of viral particles into the dialysate [29, 30], the trapping of HCV on the surface of the dialysis membrane [31, 32], and an indirect host-mediated phenomenon have been cited. The latter hypothesis implicates the production of

interferon- α [33], hepatocyte growth factors [27], or other cytokines with anti-viral activities during the HD sessions.

Conclusions

HCV-related liver disease remains frequent in patients on long-term dialysis with an impact upon survival. Several lines of evidence support the concept that progression of HCV-related liver disease is probably slower than in HCV-infected individuals with intact kidney function, despite immune compromise due to uremia. Numerous mechanisms have been suggested to explain it, and it is possible that an indirect host-mediated mechanism could be involved. Clinical trials and experimental studies aimed at clarifying this issue are needed.

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